The Stroke Care Continuum and Patient Pathway

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Received – 26 June 2018; Accepted – 19 July 2018

A B S T R A C T

This article summarizes a Medtronic-sponsored symposium held on May 17th 2018 at the 4th European Stroke Organisation Conference (ESOC) in Gothenburg, Sweden. This symposium was introduced and moderated by Professor Antoni Dávalos. He explained the content of the four speakers' presentations, collectively, cover important aspects of the total continuum of care and management required for the stroke patient. These presentations covered insights into the acute phase, with a focus on diagnostic imaging methods for the improved selection of those patients with salvageable brain tissue likely to benefit most from endovascular treatment, first year clinical experience and outcomes achieved with with Medtronic's SolitaireTM Platinum stent-retriever device, secondary prevention considerations, and the importance of identifying patients with or at risk of atrial fibrillation, and finally, the rehabilitation process for disabled stroke patients, highlighting an important potential contribution of intrathecal baclofen therapy (ITB) for post-stroke spasticity. Medtronic are committed to improving care and outcomes for stroke patients at all stages of the care continuum in their patient pathway.

Key words: stroke, perfusion imaging, Solitaire PlatinumTM, insertable cardiac monitor, post-stroke spasticity, intrathecal baclofen.

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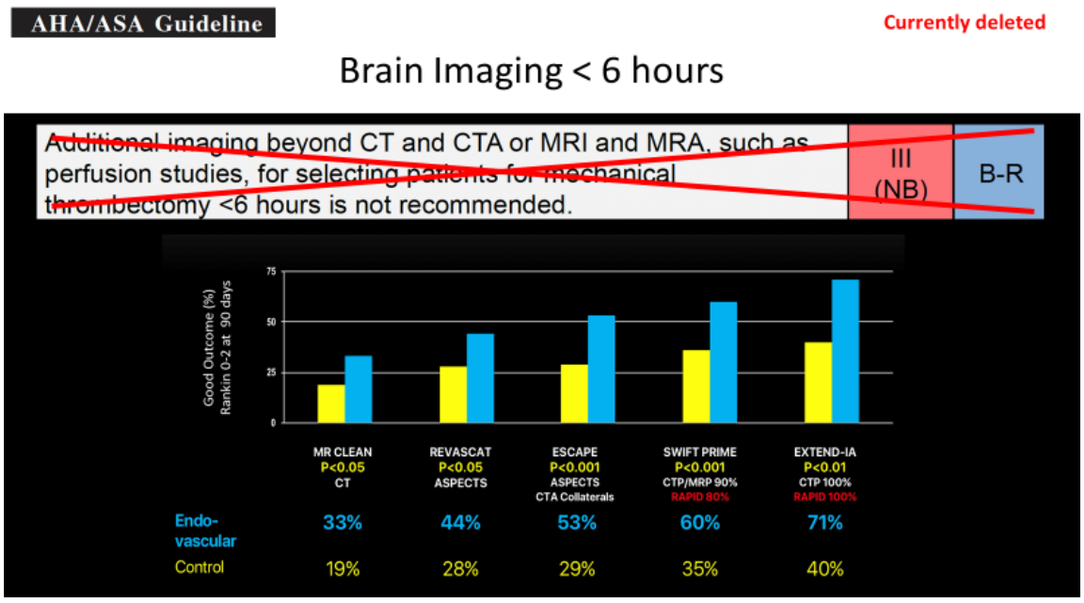
Acknowledgements: The editorial assistance of Mr Rob Goodwin, Oruen Ltd, in the preparation of this article is acknowledged with thanks.

ADVANCED IMAGING IN PATIENT SELECTION FOR MECHANICAL THROMBECTOMY. PROFESSOR GREGORY ALBERS.

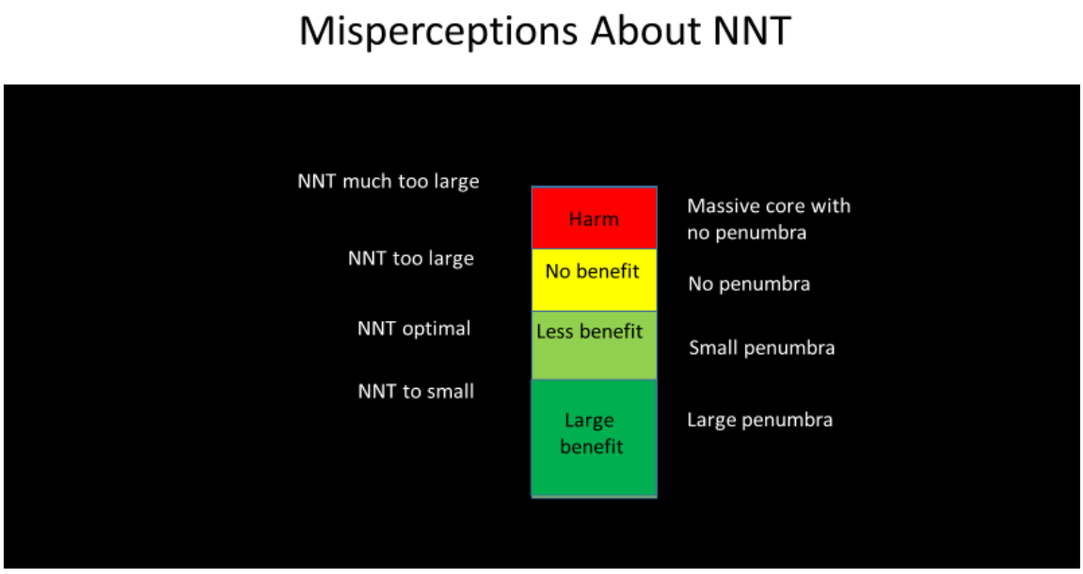
Professor Albers highlighted recent important changes in the treatment guidelines for endovascular therapy. In 2015, new guidance covering the first six hours since symptom onset has emerged, followed by guidance for late-window presenting patients in 2018. These changes have been largely driven by clinical trial outcomes achieved with stent-retriever devices in conjunction with more advanced imaging techniques.

The first six hours

Professor Albers explained there have been very recent developments (January 2018) in the AHA/ASA guidelines for the early management of patients with acute ischemic stroke. Some guidelines have been temporarily rescinded in the light of feedback from the stroke community and further clarification is ongoing. Professor Albers noted the guideline stating that advanced perfusion imaging should not be used for selecting patients for mechanical thrombectomy within the 6-hour time window had been withdrawn.

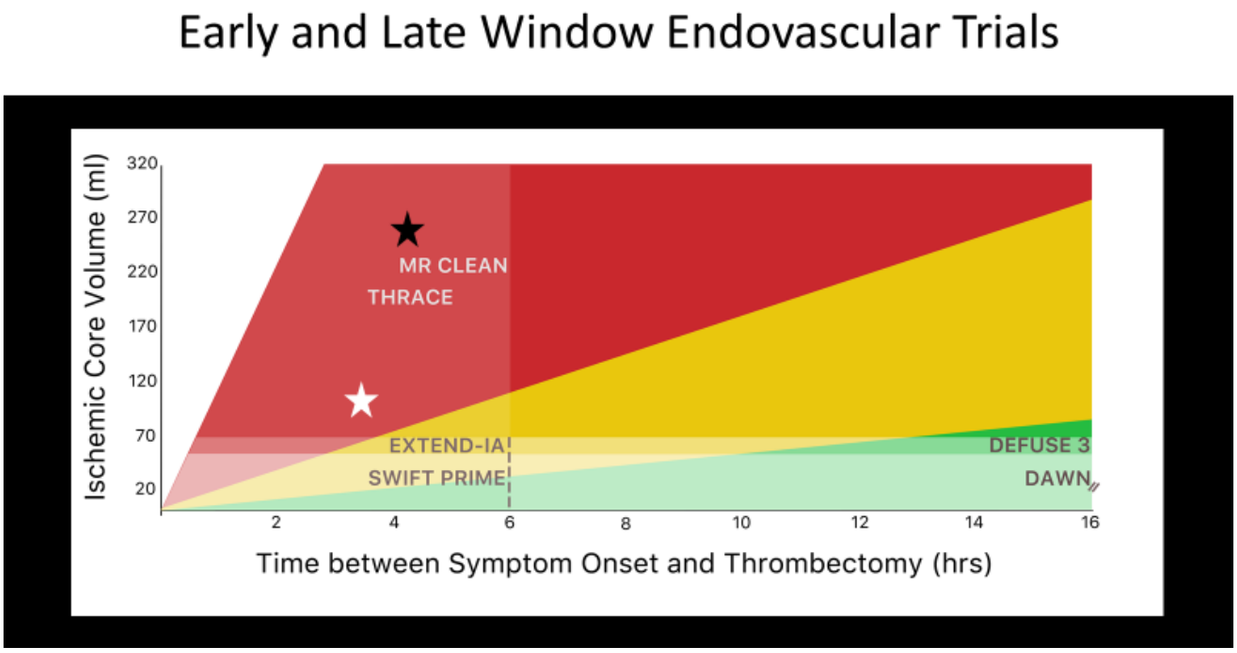


A potential reason for this withdrawal may be that if perfusion imaging can be done quickly, valuable Computed Tomography (CT) perfusion or Magnetic Resonance (MR) diffusion/perfusion data can be obtained. Notably, the EXTEND-IA and SWIFT PRIME studies, with patient selection techniques based on RAPID imaging software, resulted in larger treatment benefits in both the endovascular and control (i.v. thrombolysis) treatment arms compared with the MR CLEAN, REVASCAT, and ESCAPE studies. Having a favourable imaging pattern therefore indicates that treatment, especially endovascular therapy, is likely to result in a good outcome for the patient; however, a potential downside is that use of perfusion data may be encouraging "over-selection" of patients. Professor Albers questioned whether the number needed to treat (NNT) was too low when you look at the advanced imaging studies; he also raised some misperceptions relating to NNT. The type of stroke patients who can benefit from acute stroke therapies are patients with a penumbra, and those with a large penumbra will benefit the most, although patients with a small penumbra are likely to have some benefit. Some adjustment of selection criteria may therefore be warranted; however, Professor Albers warned that the adjustment should not include patients with no penumbra, and certainly not patients with a very large ischemic core and no penumbra, as this could result in patient harm and a corresponding NNT that is too high. The relationship between penumbra size and NNT and potential benefit of endovascular treatment is shown in the following illustration.



Professor Albers explained that in studies such as THRACE and MR CLEAN, which accepted patients with any size of ischemic core, the NNT in these study populations was probably too large. Conversely, with more restrictive trials e.g. SWIFT PRIME, the NNT, arguably, may have been too small. This raises the question: how should interventional neurologists deal with these considerations in their patient selection decisions?

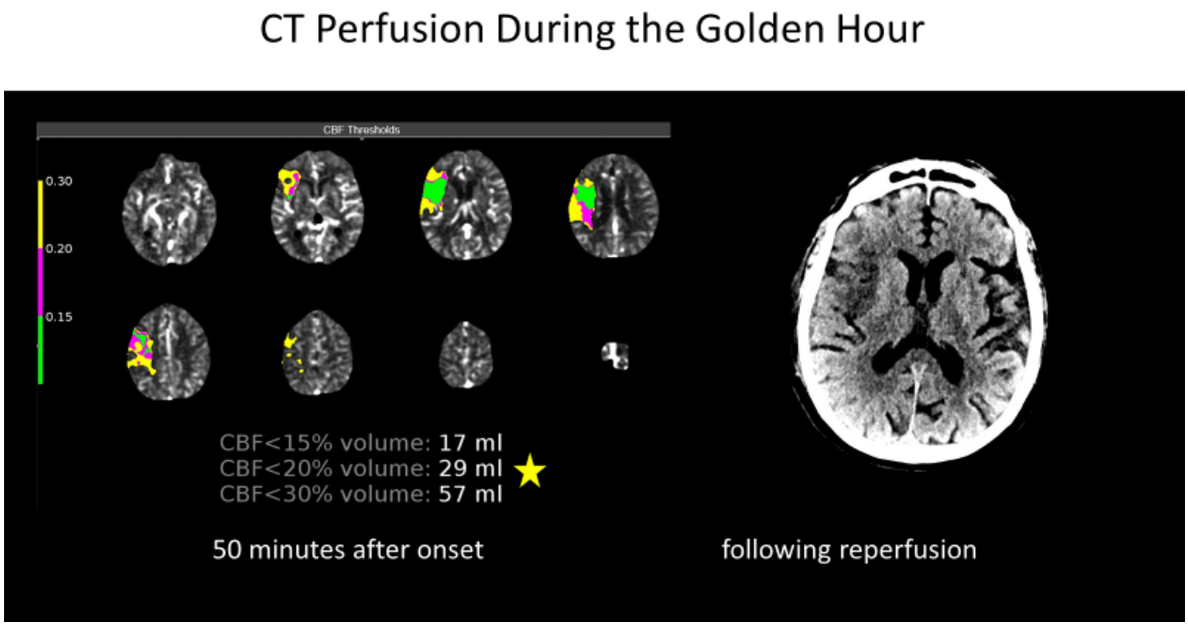
Professor Albers presented two example patients who would have been eligible for inclusion in the MR CLEAN or the THRACE trials; these are represented by the black and white stars in the following illustration.



The white star patient would have been excluded from EXTEND-IA and SWIFT PRIME because their infarct core is 100 mL; however, this patient would probably benefit from endovascular treatment because their early infarct volume is substantially smaller than the volume of tissue that is typically hypoperfused in a proximal MCA occlusion. With the black star patient, with an ischemic core significantly greater than 200 mL and growing rapidly, after around 1.5 hours when reperfusion has been established, the patient will have completed their infarct. Professor Albers emphasized this is the type of patient who should not be selected for endovascular treatment; such patients make the NNT too large and, in all probability, would not benefit from treatment. Hence, the goal for future trials is to try and optimize the NNT by treating the patients who can benefit, but don't treat the patients who cannot.

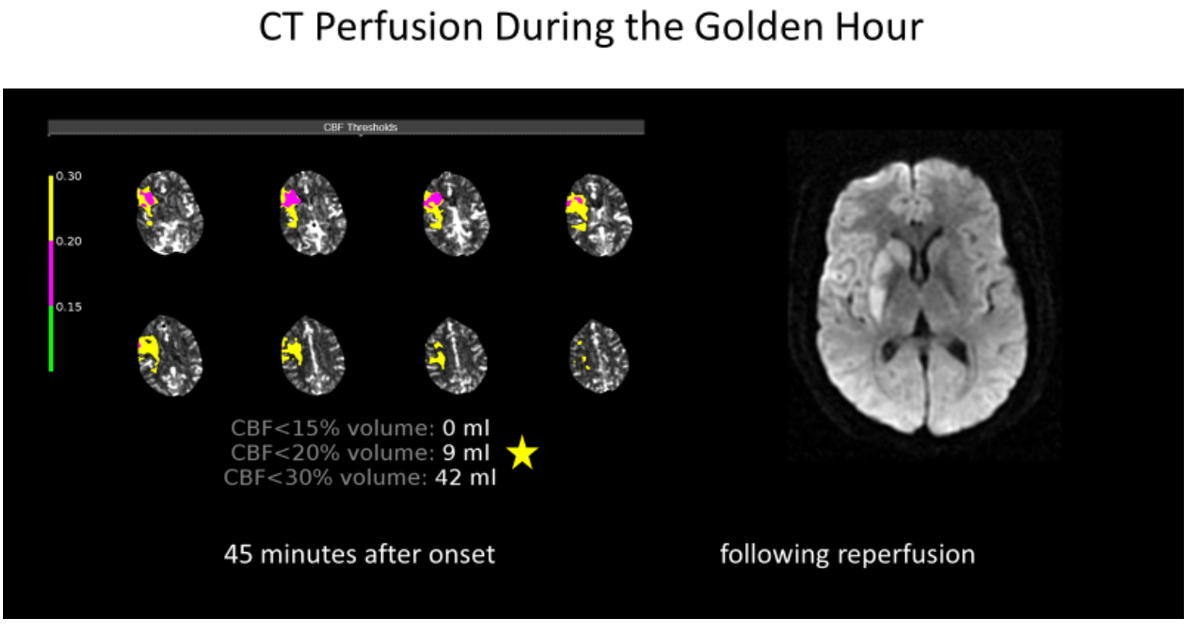
CT Perfusion thresholds

Professor Albers highlighted important newly emergent information related to Computerised Tomography (CT) Perfusion in acute stroke patients in the early window. A recent Canadian publication[1] has stressed that CT Perfusion thresholds for an ultra-early patient scan should be adjusted. CT Perfusion does not show dead brain; it shows tissue with very low blood flow and the low flow has to persist to cause the death of brain tissue. This is an important consideration when analysing CT Perfusion studies. Najm and co-workers argue that relative cerebral blood flow (rCBF) thresholds of 15-20% should be used for patients imaged within 60 minutes of symptom onset rather than the typical 30% CBF threshold that has been used in clinical trials.



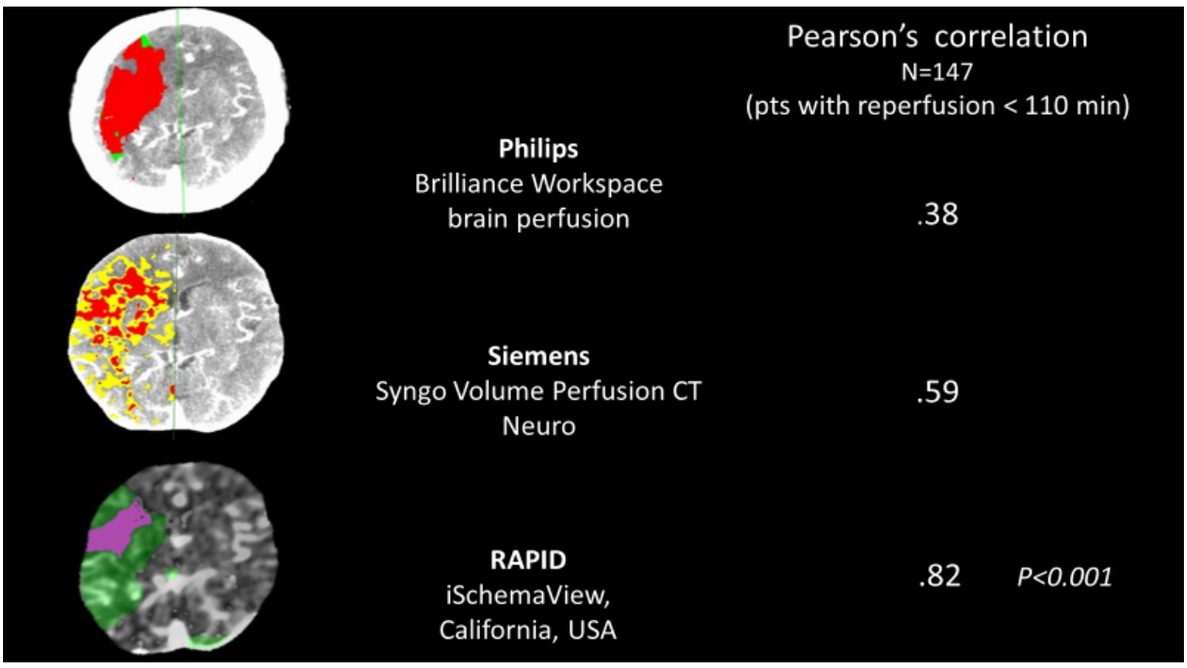
The estimated ischemic core volumes on CT perfusion after reperfusion at three different CBF thresholds are presented and the <20% threshold most accurately predicted the final infarct volume following reperfusion. In the DAWN, DEFFUSE 3, SWIFT PRIME, and EXTEND-IA trials a ≤30% cut off criterion was applied i.e. if the CBF was 30% or less of normal flow, the tissue was considered to be ischemic core. This threshold performed extremely well in these trials, however these trials typically did not include ultra-early patients. In patients imaged within an hour of symptom onset, Professor Albers explained that his team has seen number of patients where 30% is not the optimal threshold.

In a second example, where the patient was imaged 45 minutes after symptom onset, based on the standard threshold, the predicted infarct volume would be about 40 mL if reperfusion is obtained promptly; however, the Diffusion Weighted Imaging (DWI) following reperfusion showed a volume that was closer to 15 mL, and this is a better fit with the <20% CBF threshold. This is illustrated in the following images.



Professor Albers noted that the new version of RAPID software now includes an additional threshold pre-programmed to show the <20% CBF threshold that can be used should the patient be fortunate enough to undergo ultra-early CT Perfusion. There are a number of companies providing software for CT Perfusion infarct core analysis, and this raises the question of their validation in terms of predicting infarct volume and clinical outcome.

Professor Albers presented summary data from a study that evaluated how accurately different CT-perfusion software predicts the final infarct volume (FIV) in patients with acute stroke after thrombectomy.[2] In this study (Austen et al. 2016), identical perfusion data sets from successfully recanalized patients were analyzed with three different software packages from Philips, Siemens, and RAPID. Philips and Siemens are semi-automatic software tools, whereas RAPID is a fully automatic software. In the following illustration, in the same patient, the Phillips software indicated a very large ischemic core (that probably should not be treated), the Siemens software indicated an intermediate core, and RAPID indicated a small core and a large penumbra. The patient had a successful thrombectomy and a small final infarct volume was observed.



The study then examined the correlation between how these volumes matched with FIV if reperfusion was obtained within 110 minutes. A substantial difference in the accuracy of these packages was evident. This study demonstrated best accuracy for predicting final infarct volumes using the fully automated RAPID software and FIV, especially in patients who are rapidly and fully recanalized

Treating Acute Ischemic Stroke patients beyond the 6-hour window

Currently, the ASA guidelines for mechanical thrombectomy are very specific; they state: "DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from these trials should be used for patient selection". Accordingly, DAWN and DEFUSE 3 eligibility criteria should be strictly adhered to in clinical practice. In the DAWN study, most patients had CT Perfusion that provided perfusion penumbral and ischemic core volumes; however, the clinical-core mismatch was the main focus of the study. Professor Albers explained that subsequent analyses have shown that 95% of patients who meet this clinical-core mismatch also had a penumbra or perfusion core mismatch similar to that used in the DEFUSE 3 study. In DEFUSE 3, the critically hypo-perfused tissue that was likely going to die needed to be around twice the size of the core, and this allowed the target mismatch profile in DEFUSE 3 to increase core size values to 70 ml, so in this respect, DEFUSE 3 was a more inclusive study. Both studies showed dramatic benefits and improvements in patient outcomes, and Professor Albers emphasized the importance of developing systems to treat these late-window patients with thrombectomy.

Imaging at primary stroke centers

For primary centers, Professor Albers outlined two approaches. An increasingly popular approach in the US is for primary centers to establish CT Perfusion and MR capabilities, so these centers can apply the DAWN or DEFUSE 3 study criteria. Over 350 centers in the US are now using RAPID software in this respect. This allows these centers to retain those patients who do not meet DAWN or DEFUSE 3 criteria, rather than transferring them to a comprehensive center. The other approach is for centers to perform CT and CTA (computed tomographic angiography) and an ASPECTS assessment, then transfer all MCA / ICA occlusions with a NIHSS >6 and a favourable ASPECTS. An FDA-cleared automated RAPID CTA angiography system is now available from IschemaView; it provides 3D images of vessels to help neurologists to identify where the occlusion is. In addition, a colour-coded area over the MCA territory shows the reduction in blood vessel density giving an objective collateral assessment. This software is expected to help those centers following this latter approach. Automated ASPECTS programmes are also becoming increasingly available and validation studies with the RAPID ASPECTS programme have demonstrated excellent accuracy. Preliminary indications suggest these automated programmes are going to be very helpful. The prospect of a fast ASPECTS assessment with increased consistency, and accuracy, heralds a major step forward in the assessment of acute stroke patients.

Imaging at comprehensive stroke centers

At comprehensive stroke centers, key decisions are: (1) whether the acute stroke patient should receive an MRI scan, or undergo CT Perfusion imaging, and (2), does any imaging performed at a primary center have to be repeated after transfer to a thrombectomy center? Professor Albers presented summary data from clinical studies where both MRI scans and CT Perfusion were used. Both imaging methods performed well in these studies; however, use of MRI imaging was associated with numerical improvements in the percentages of patients with good outcomes (modified Rankin Scale 0-2 assessments) and absolute benefits. These data are summarized in the following table.

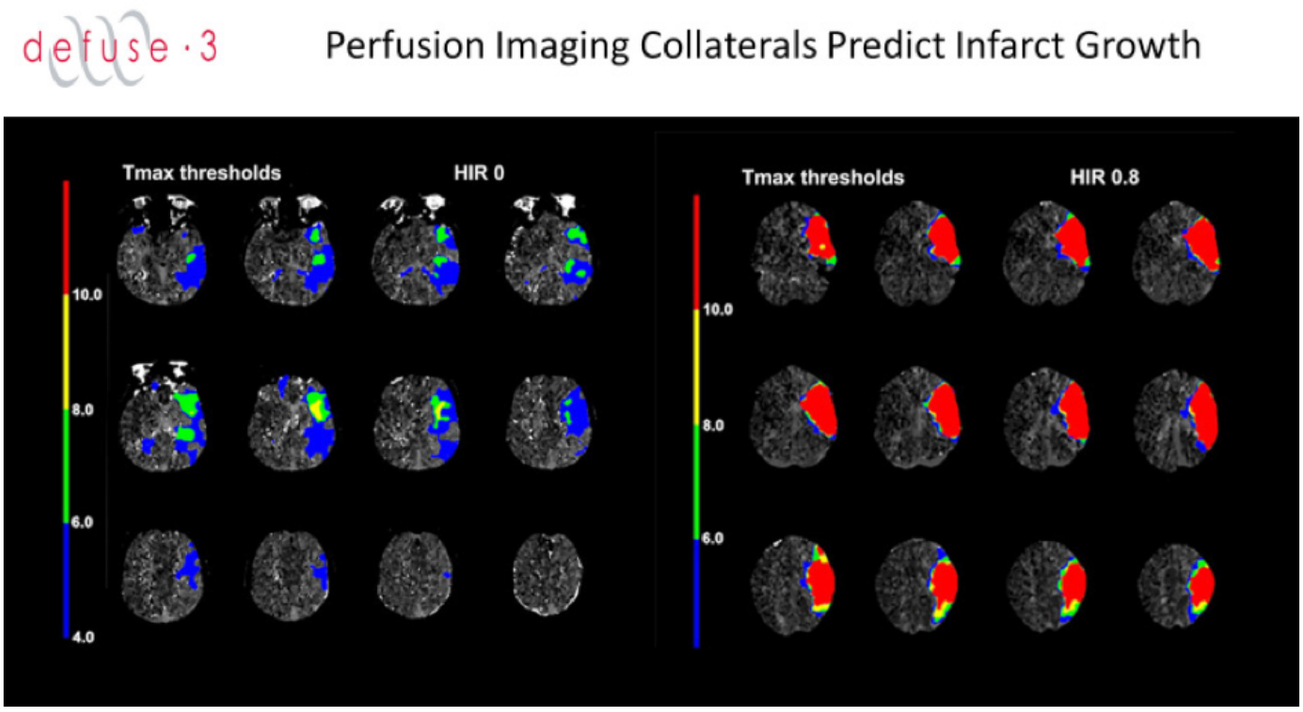
STANFORD SCHOOL OF MEDICINE
Stanford University Medical Center

MRI vs. CT Perfusion?

Study	N	90-day mRS 0-2	90-day mRS 0-2	Absolute Benefit (%)
		Control (%)	Thrombectomy (%)	
SWIFT PRIME*				
MRI	34	33	63	30
CTP	139	40	60	20
DEFUSE 3*				
MRI	49	19	61	42
CTP	133	16	39	23
DAWN				
MRI	83	Not Reported	35	NA
CTP	123	Not Reported	29	NA

*CTP and MRI groups had statistically significant benefits on the primary outcome

Professor Albers acknowledged that ultra-urgent MRI imaging was more widely practised in Europe than in the US, where CT Perfusion is more widely used in patient selection for thrombectomy decisions, in both clinical trial and "real world" settings. On the question of whether to repeat the imaging performed at primary centres, where, in the USA this is increasingly based on CT Perfusion, Professor Albers noted that a significant clinical change in the patient e.g. suspected recanalization, or signs of clinical deterioration would be reasonable grounds for re-imaging. At Stanford, a recent investigative focus has been on perfusion imaging of collateral vessels as a predictor of infarct growth during patient transfer. In the following images, the patient on the left with predominantly blue images has good collateral blood vessels and a good hypoperfusion intensity ratio (HIR) with no red in the collateral map. In contrast, the status of the patient on the right, with poor collaterals, red images, and a high HIR, is predictive of faster infarct growth.



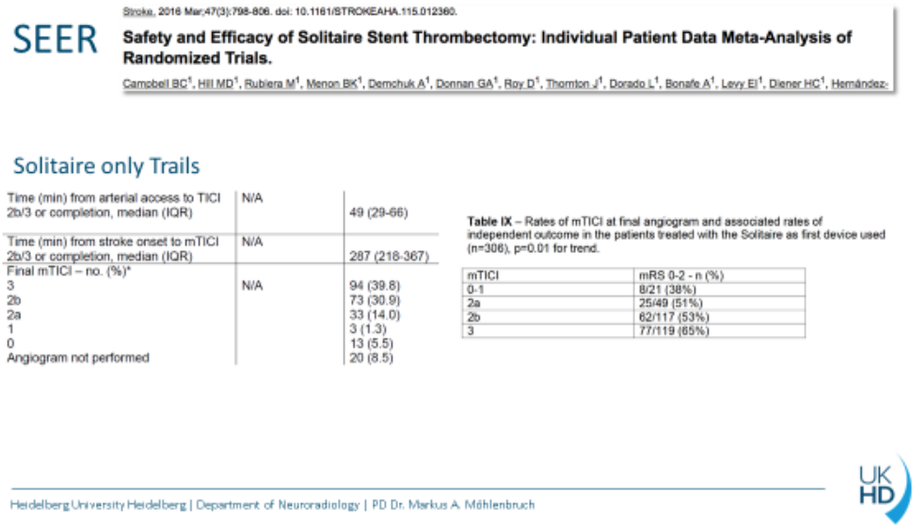
Professor Albers explained that that his team have recently carried out a preliminary investigation of the transfer of acute stroke patients with good collaterals, versus patients with poor collaterals, from a hospital three hours away from Stanford. Patients with good CT perfusion collaterals had minimal or no growth during transfer, whereas patients with poor collaterals typically had substantial growth. For patients arriving with poor collaterals, following a transfer of ≥2 hours, Professor Albers advised that these patients should be re-scanned to determine if they still had salvageable tissue.

In summary, Professor Albers stressed that advanced imaging is expected to help optimize patient selection for thrombectomy in both early and late-window stroke patients; however, he cautioned there is still a considerable effort required to optimize the clinical and imaging selection criteria to reach the optimum number needed to treat (NNT). This will ensure endovascular treatment can be provided to those patients who will benefit and is avoided in those who will not. With CT Perfusion in the early time window, a different relative cerebral blood flow (rCBF) threshold for identifying ischemic core should be considered, with <20% for "1st hour" patients now deemed more appropriate. The availability of automated computed tomography angiography (CTA) and ASPECTS programmes will help optimize identification of patients who should be transferred to thrombectomy centres. Furthermore, if an automated CT Perfusion assessment of collaterals, prior to transporting the patient can be validated as a predictor of infarct growth, this will prove invaluable in determining how the patient should be handled on arrival at the comprehensive stroke center. Finally, Professor Albers emphasized that recent late-window trials have completely changed neurologists' perspective of how strokes evolve, with a substantial number of patients having a very different infarct evolution from previous expectations. This knowledge is good news and paves the way for further treatment opportunities for late-presenting ischemic stroke patients.

Solitaire™ Platinum: 1st Year Experience. PD Dr Markus A Möhlenbruch

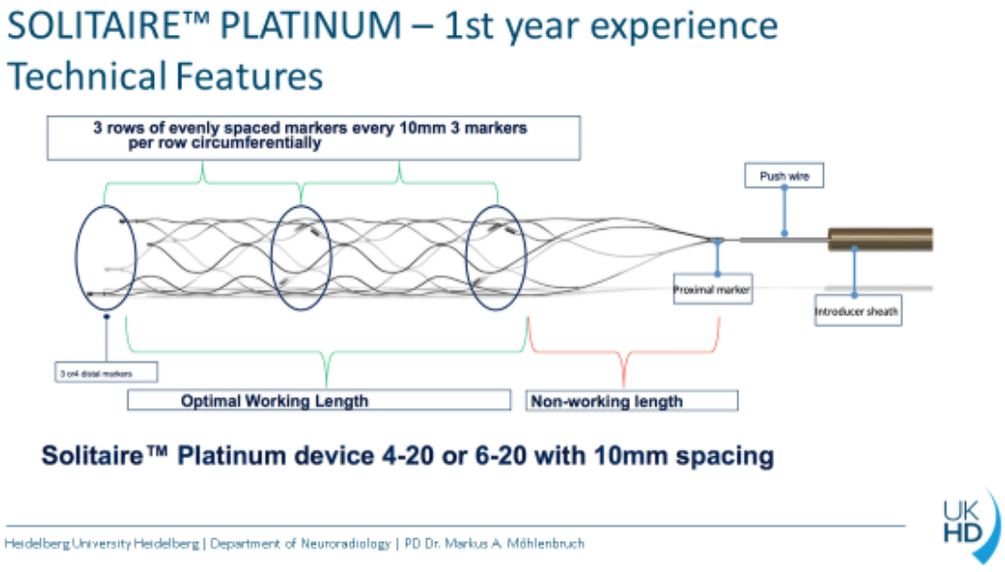
Dr Möhlenbruch reviewed the HERMES meta-analysis[3] of five randomized trials of endovascular thrombectomy. He noted that that this meta-analysis did not focus in detail on thrombolysis in cerebral infarction (TICI) assessments. The SEER meta-analysis[4] was based on four randomised trials (ESCAPE, EXTEND-IA, REVASCAT and SWIFT PRIME) that utilised the Solitaire™ stent-retriever device.

Dr Möhlenbruch highlighted the different recanalization rates evident in SEER; notably, the final modified TICI 3 (full recanalization) and mTICI 2b recanalization rates of 32.9% and 38.2%, respectively. In the SEER trials that only used the Solitaire™ device final mTICI 3 and mTICI 2b recanalization rates of 38.8% and 30.9% were recorded, respectively. The Solitaire™ only trial recanalization rates are summarised in the following table.



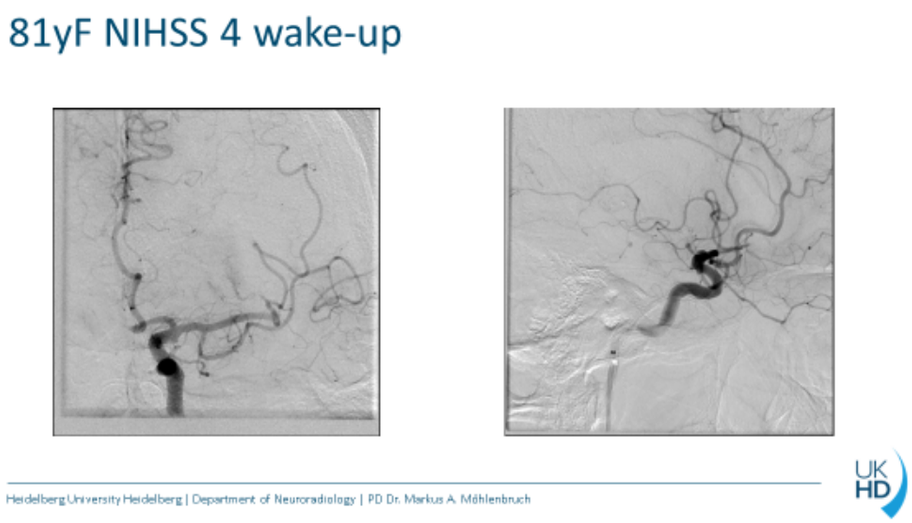
These recanalization rates set a standard for comparisons with any new stent-retriever devices or new endovascular interventions.

Dr Möhlenbruch explained that a disadvantage of the first-generation Solitaire ™ device was its limited visibility in fluoroscopic images. The latest generation Solitaire™ Platinum device has markedly improved visibility with more markers. The technical features of the Solitaire™ Platinum 4-20 and 6-20 device are illustrated in the following diagram.

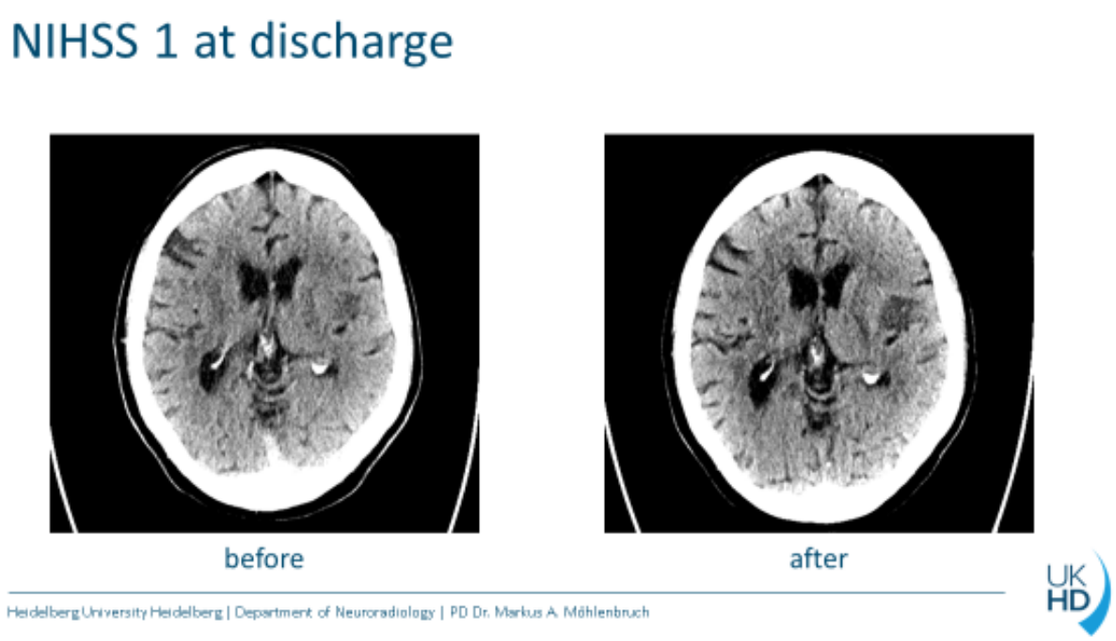


Other versions of this latest-generation device have 5 rows of markers with either 5, 6 or 10 mm spacing.

To illustrate how the Solitaire ™ device is typically deployed, Dr Möhlenbruch presented a case study of an 81-year old woman with a wake-up stroke and an NHSS score of 4.



At Heidelberg University Hospital, the Solitaire ™ device is deployed using the Solumbra technique in conjunction with a balloon guide catheter (BGC). A TICI 2b outcome was achieved in this case study patient who was discharged with an NIHSS score of 1. The before and after imaging is shown in the following scans.



Dr Möhlenbruch presented a summary of a recent study that investigated whether the radiopaque markers integral to the Solitaire™ Platinum stent-retriever influences the efficacy or safety of the enhanced stent-retriever.[5] This was a retrospective analysis based on data from two university hospitals and a maximum care facility with 24h/7d neurological and neuroradiological attendance. Consecutive patients with acute ischemic stroke due to large vessel occlusion in the anterior circulation, and with NIHSS >2 and ASPECTS >5 hospitalized between October 2016 and March 2017 were enrolled. Favourable early neurological recovery was graded utilizing SWIFT trial6 criteria (i.e. at hospital discharge: mRS = 0-2 or improvement of NIHSS ≥ 10). Patients initially admitted with a stroke severity of NIHSS 3–9 were rated as having a favourable early neurological recovery if NIHSS at discharge was 0.

Comparative technical (i.e. delivery and deployment) and clinical performance data of the Solitaire™ Platinum stent-retriever, compared with Solitaire™ 2 device experience, were obtained by questionnaire survey using 5-point scales. The baseline characteristics of the 75 patients in the study are summarized in the following table.

SOLITAIRE™ PLATINUM – 1st year experience
Baseline clinical and therapeutic characteristics

Patient characteristics		$n=75$
Baseline clinical characteristics		
Age (years), mean (SD)		75 (12)
Male, (%)		27 (36)
Hypertension, (%)		56 (74.7)
Diabetes mellitus, (%)		21 (28)
Atrial fibrillation, (%)		39 (52)
Coronary artery disease, (%)		11 (14.6)
Previous stroke, (%)		17 (22.7)
Initial NIHSS, median (IQR)		17 (11–21)
Intravenous rtPA, (%)		41 (54.7)
Unknown time of symptom onset, (%)		9 (12)
Radiological findings before mechanical thrombectomy		
ASPECTS, median (IQR)		8 (7–9)
CT angiographic collateral score[a], median (IQR)		2 (1–3)
Occlusion site[b]	Intracranial ICA (excluding carotid T), (%)	1 (1.3)
	Tandem occlusion (cervical ICA and carotid T, M1 or M2)[c], (%)	5 (6.7)
	Carotid T, (%)	11 (14.7)
	M1, (%)	42 (56)
	M2, (%)	16 (21.3)
	Occlusion site right, (%)	33 (44)

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The procedure results, notably: TICI 0-1 (8%), TICI 2b (40%), TICI 3 (52%) and symptomatic intracranial haemorrhage rate (4%) are summarized in the following table

SOLITAIRE™ PLATINUM – 1st year experience
Procedural aspects, complications and early outcome

Procedural aspects		$n=75$
Treatment in general anesthesia, (%)		37 (49.3)
Onset to groin puncture time[a], min, median (IQR)		238 (177–356)
Groin puncture to first intracranial flow restoration, min, median (IQR)		35 (24–47)
Groin puncture to final angiographic result (final TICI) time, min, median (IQR)		56 (41–79)
Duration of interventional procedure[b], min, median (IQR)		64 (51–85)
No. of device passes, median (IQR; min–max; mean)		2 (1–2; 1–5; 1.9)
Total no. of device passes (no. of patients treated) by size of Solitaire™ Platinum stent-retriever used	4×20 mm	99 (55)
	4×40 mm	17 (9)
	6×20 mm	8 (5)
	6×40 mm	18 (12)
Angiographic results	TICI 0–1, (%)	6 (8)
	TICI 2b, (%)	30 (40)
	TICI 3, (%)	39 (52)
Interventional complications		
Vasospasm, (%)		7 (9.3)
Emboli into a new territory, (%)		4 (5.3)
Dissection, (%)		0
Vessel perforation, (%)		0
Device related complication, (%)		1 (1.3)
Early outcome parameters		
Favorable early neurological recovery[c], (%)		47 (62.7)
In-house mortality, (%)		10 (10.7)
Incidence and anatomic distribution of intracranial hemorrhages on follow-up NCCT[d]	1a, (%)	2 (2.7)
	1b, (%)	2 (2.7)
	1c, (%)	1 (1.3)
	2, (%)	2 (2.7)
	3a, (%)	0
	3b, (%)	0
	3c, (%)	6 (8)
	3d, (%)	0
Symptomatic intracranial hemorrhage[d], (%)		3 (4)

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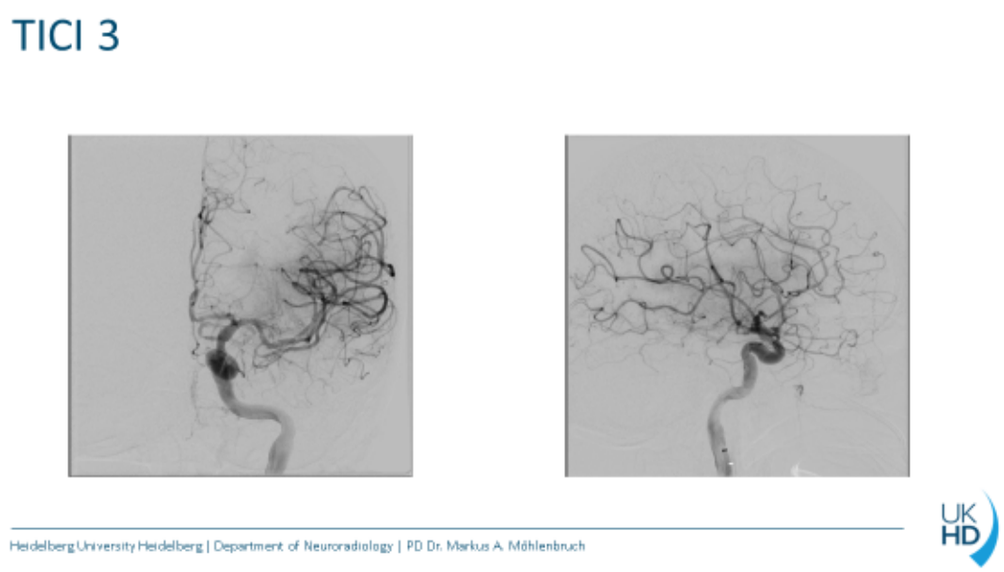
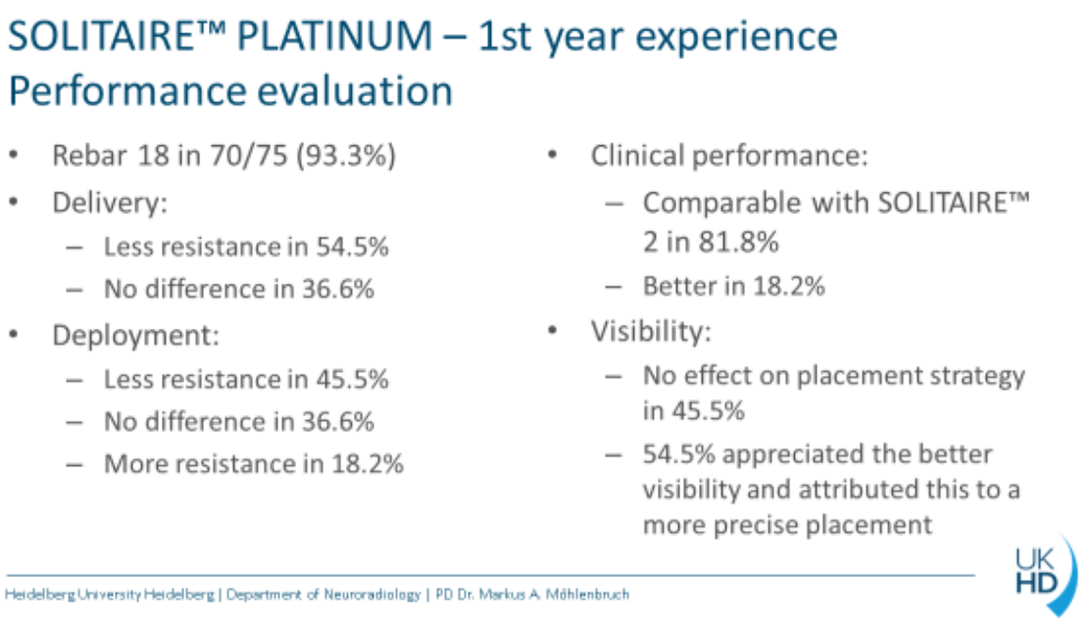
Dr Möhlenbruch presented case details of 91-year old female patient from the study; she was hospitalised with a NIHSS score of 15, 6.5 hours after symptom onset. A Solitaire™ Platinum 6 x 40 was deployed, and following one retrieval, a TICI 3 outcome was subsequently achieved. This is illustrated in the following images. This patient was subsequently discharged with an NIHSS score of 0.



Overall, early neurological recovery, as assessed by a modified Rankin Scale (mRS) of 0-2 or an improvement in NIHSS score of ≥ 10, at discharge, was evident in 47/75 of patients (62.7%). In-house mortality occurred in 10/75 patients (10.7%). A Rebar 18 microcatheter was used in 70/75 patients (93.3%). Compared with the questionnaire respondents' experience of the Solitaire™ 2 device, the Solitaire™ Platinum device was judged to have improved, or similar, deployment and clinical performance characteristics, as shown in the following summary. Notably, 54.5% of respondents reported better visibility with the Solitaire™ Platinum device.



The procedure time for Solitaire™ Platinum, TICI 2b and TICI 3 outcomes achieved, and the number of device passes with Solitaire™ Platinum were similar to those reported in other endovascular randomized controlled trials (RCTs). These comparisons are illustrated in the following table.

SOLITAIRE™ PLATINUM – 1st year experience
Discussion – procedure details

	EXTEND-IA n = 35	REVASCAT n = 103	SWIFT PRIME n = 98	SOLITAIRE™ PLATINUM N = 75
Groin puncture to final angiographic result median (IQR)	43 (24, 53)	59 (36, 95)	29	56 (41, 79)
TICI 2b (%)	38	35.9	19.3	40
TICI 3 (%)	48	43.7	57	52
No. of device passes median (IQR)	1.6	2 (1, 4)	-	2 (1, 2)

Heidelberg University Heidelberg | Department of Neuroradiology | PD Dr. Markus A. Möhlenbruch

The Heidelberg Bleeding Classification (HBC)[7] was used to categorize the bleeding rates in the study. Intracranial haemorrhages with the Solitaire™ Platinum device, in terms of location and incidence, were similar to those recorded in the Heidelberg patient cohort. The comparative bleeding rates for both studies are presented in the following table.[8]

SOLITAIRE™ PLATINUM – 1st year experience
Discussion – Intracranial hemorrhages

Stroke. 2017 Jul;48(7):1983-1985. doi: 10.1161/STROKEAHA.117.016735. Epub 2017 Apr 28.

Classification of Bleeding Events: Comparison of ECASS III (European Cooperative Acute Stroke Study) and the New Heidelberg Bleeding Classification.

Neuberger U[1], Möhlenbruch MA[1], Herweh C[1], Ulfert C[1], Bendszus M[1], Pfaff J[2].

Description	Class	SOLITAIRE™ PLATINUM n = 75	Heidelberg n = 768
Hemorrhagic transformation of infarcted tissue – small petechia	1a	2.7%	<1%
Hemorrhagic transformation of infarcted tissue – confluent petechia	1b	2.7%	2.1%
Hematoma within infarcted tissue, occupying <30%, no substansive mass effect	1c	1.3%	3.3%
Hematoma occupying >30% or more of the infarcted tissue, with obvious mass effect	2	2.7%	7
Parenchymal hematoma remote from infarcted brain tissue	3a	0	<1%
Intraventricular hemorrhage	3b	0	1.6%
Subarachnoid hemorrhage	3c	8%	6.6%
Subdural hemorrhage	3d	0	<1%

Heidelberg University Heidelberg | Department of Neuroradiology | PD Dr. Markus A. Möhlenbruch

The key clinical outcome with Solitaire™ Platinum, early neurological recovery, was achieved in 62.7% of patients; this compares with 58% reported in the SWIFT trial.[6] The mortality rate with endovascular thrombectomy with Solitaire™ Platinum was 10.7%, and this compares with 9.7% recorded in the REVASCAT trial.[9]

Dr Möhlenbruch noted there are different variants of the thrombolysis in cerebral infarction (TICI) scale. The modifications to this scale and the clinical studies that have utilised specific variants of the TICI scale are shown in the following table. A recent development with the TICI scale is the inclusion of a new 2C categorization (near complete perfusion).

Memo: What is meant by "TICI"?

Table 1. Comparison of the Existing TICI Grading Scale Criteria

TICI Grade	Original TICI	Modified TICI	Modified TICI With 2c
0/1	No/minimal reperfusion	No/minimal reperfusion	No/minimal reperfusion
2a	Partial filling <2/3 territory	Partial filling <50% territory	Partial filling <50% territory
2b	Partial filling ≥2/3 territory	Partial filling ≥50% territory	Partial filling ≥50% territory
2c	…	…	Near complete perfusion except slow flow or few distal cortical emboli
3	Complete perfusion	Complete perfusion	Complete perfusion

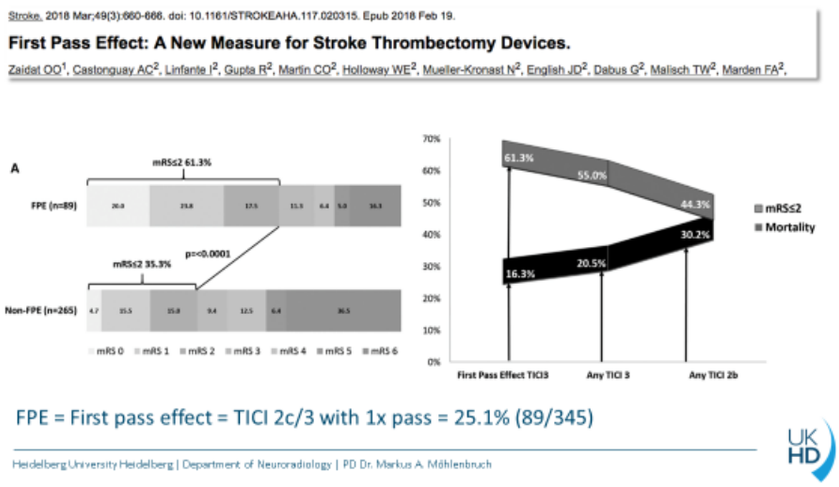
TICI indicates thrombolysis in cerebral infarction.

ESCAPE
REVASCAT
MR CLEAN
EXTEND IA
SWIFT PRIME
ASTER
COMPASS

Heidelberg University Heidelberg | Department of Neuroradiology | PD Dr. Markus A. Möhlenbruch

Dr Möhlenbruch explained that available clinical literature that has focused on the distinctions between TICI 2b, TICI 2c, and TICI 3, indicate a better mRS functional outcome at 90 days with modified TICI 3 graded patients compared with TICI 2b patients. Additionally, mTICI 2c patients also showed better functional outcome than TICI 2b patients. Notably, mTICI 2c/3 reperfusion had a better predictive value than TICI 2b/3 for favorable 90-day outcome. In the light of this latter finding, Dr Möhlenbruch felt that interventional neurologists should adopt a new aim: to achieve mTICI 2c/3 reperfusion. Furthermore, mTICI 2c/3 rates should be included as a safety measure in studies evaluating mechanical thrombectomy devices and endovascular techniques.

The first-pass effect (FPE) is a new performance measure for stroke thrombectomy devices.[9] FPE is defined as achieving a complete recanalization with a single thrombectomy device pass. In a post-hoc analysis based on the North American Solitaire Acute Stroke Registry database, from a total of 354 acute ischemic stroke patients who underwent thrombectomy, FPE was achieved in 89 out of 354 (25.1%).[9] The achievement of complete revascularization from a single Solitaire thrombectomy device pass (FPE) is associated with significantly higher rates of good clinical outcome and lower mortality. This is illustrated in the following figure.

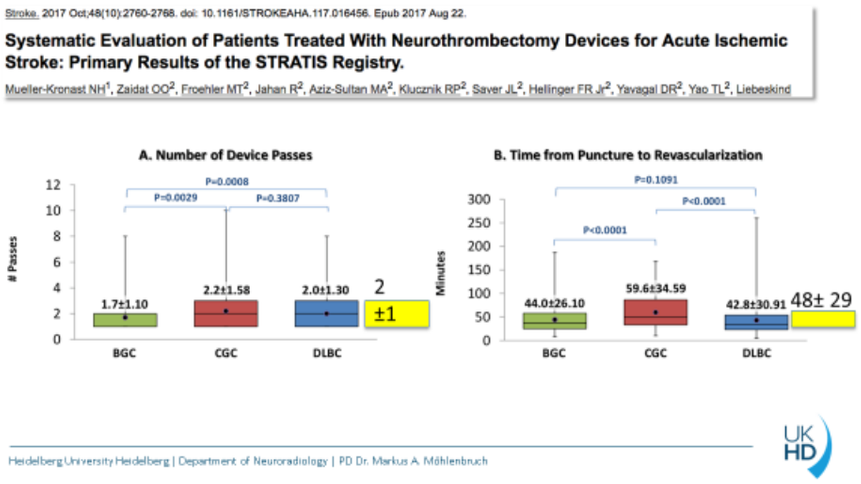


FPE = First pass effect = TICI 2c/3 with 1x pass = 25.1% (89/345)

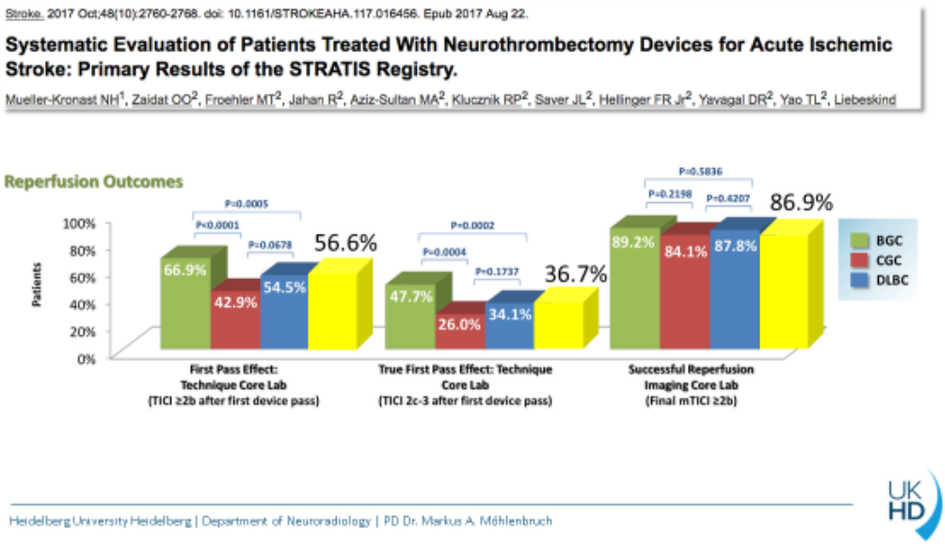
Heidelberg University Heidelberg | Department of Neuroradiology | PD Dr. Markus A. Möhlenbruch

During the period from April 2017 up to December 2017, 287 patients underwent mechanical thrombectomy at Heidelberg; of these, 116 were treated with Solitaire™ Platinum as the first -line device. Around 40% of these patients had pre-morbid mRS scores of 2-4. Dr Möhlenbruch explained that the Heidelberg Solitaire™ Platinum patient cohort (n = 116) has been compared with data from the STRATIS registry[10], a US source of real-world SolitaireTM safety and efficacy data. It should be noted that the STRATIS patients (n = 906) were included in the registry with pre-mRS scores of 0-1 and are categorized by the type of thrombectomy technique used i.e. balloon guide catheter (BGC), conventional guide catheter (CGC) or CGC with Distal Large Bore Catheter (DLBC).

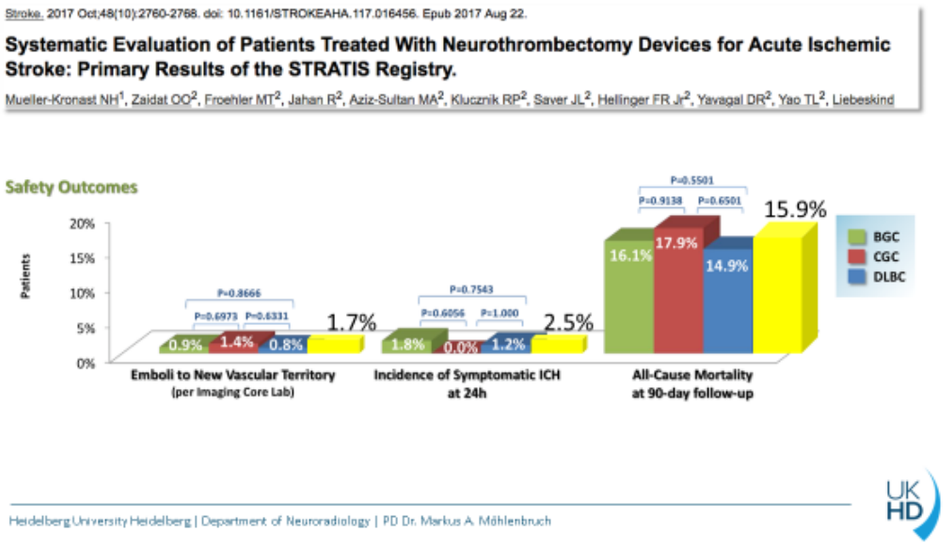
In the following summary graphs, the Heidelberg SolitaireTM Platinum patients are represented by the yellow bars. Both the number of device passes and the time from puncture to revascularization in the Heidelberg patients were similar to the STRATIS patients. This is shown in the next graph.



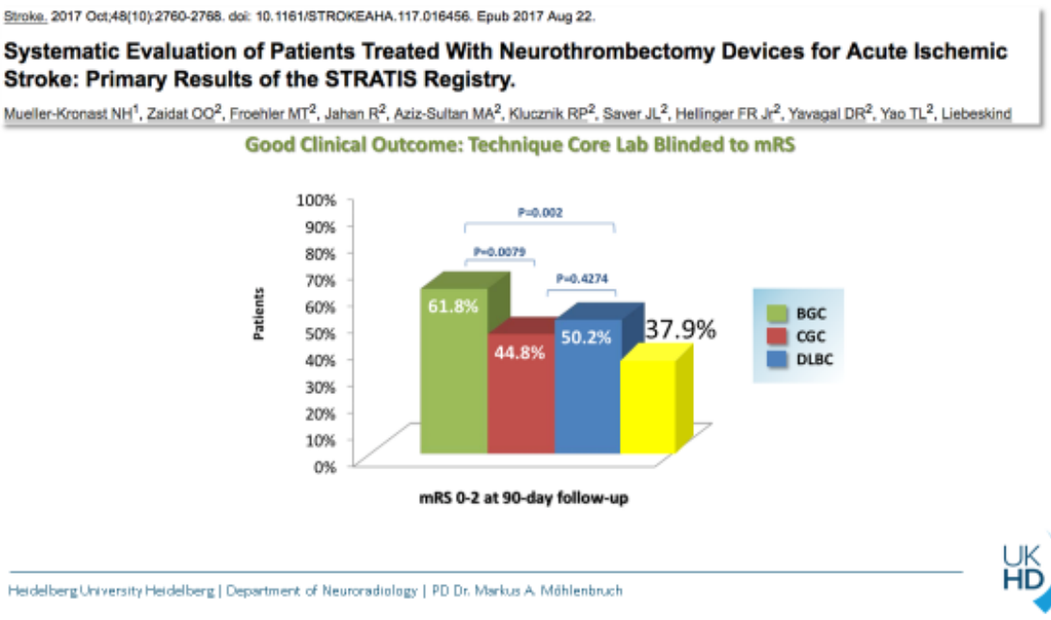
Reperfusion outcomes, first pass effect, true first pass effect, and successful reperfusion as defined by final mTICI ≥2b, in the Heidelberg patients, were similar to those recorded for STRATIS patients. These comparisons are shown in the next graph.



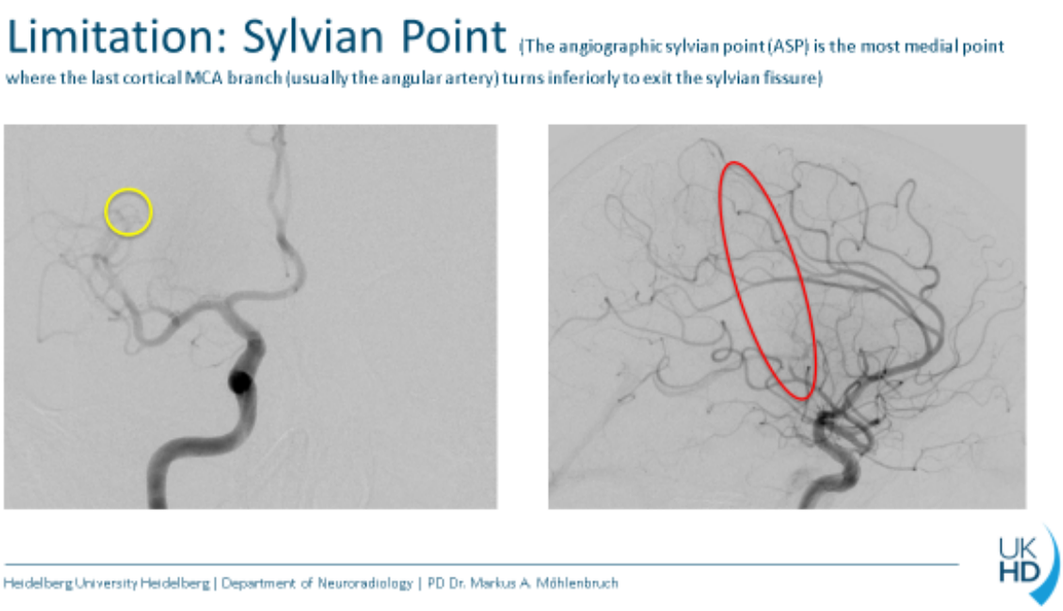
The safety data collated for the Heidelberg Solitaire™ Platinum patient cohort, notably: the patient percentage values for the emergence of emboli in new vascular territory, for incidence of symptomatic intra-cranial haemorrhage (ICH) at 24 hours, and all-cause mortality at 90-day follow-up were comparable to those recorded for STRATIS patients. These comparisons are shown in the following graph.



The percentage of Heidelberg Solitaire™ Platinum patients with a good clinical outcome, as assessed by mRS 0-2 at 90 days, was lower than that recorded for the STRATIS patients, reflecting the inclusion of 40% of patients with pre-mRS scores of 2-4 in the Heidelberg cohort. These comparisons are illustrated in the following graph.



Dr Möhlenbruch acknowledged that one of the limitations of mechanical thrombectomy is deployment of the stent-retriever at the angiographic sylvian point (ASP) or at a position distal to it. There is a risk that the stent-retriever will straighten the curvature on the artery and sever the transcortical branches potentially leading to a subarachnoid haemorrhage (SAH).



In conclusion, Dr Möhlenbruch confirmed that analysis of recent Heidelberg Solitaire™ Platinum stent-retriever usage, for mechanical thrombectomy in acute ischemic stroke patients, has shown this device to be highly effective, and its deployment was not accompanied by an increaser peri-procedural complication rate. User feedback from neurological interventionalists confirms the newly added radiopaque platinum markers provides increased visibility of the Solitaire™ Platinum stent-retriever device, and this was deemed to be helpful for alignment of the device with the target clot.

ATRIAL FIBRILLATION IN STROKE PATIENTS: ARE YOU LOOKING LONG ENOUGH? PROFESSOR DR MED MARTIN KÖHRMANN

Atrial fibrillation – a treatable risk factor for acute ischemic stroke

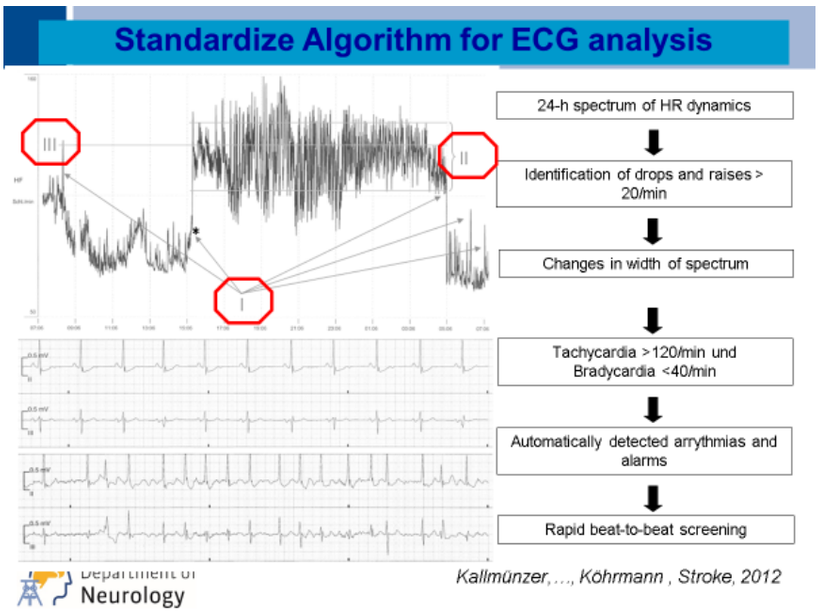
After the immediate management of the stroke patient in the acute phase, secondary prevention becomes the next imperative for preventing the occurrence of further strokes. Professor Köhrmann noted that the association between atrial fibrillation (AF) and stroke was recognised early in the history of medicine. Notably, Johann Jakob Wepfer, in 1658, famously linked apoplexia with individuals "whose pulse was constantly unequal". Atrial fibrillation is now a well-established independent risk factor for ischemic stroke with 30% of these strokes associated with AF, and the condition is associated with a 5-17-fold increased risk for a stroke; it is responsible for a high recurrence of strokes, more severe strokes, and a doubling of the mortality risk. Professor Köhrmann emphasized that effective anticoagulant therapies are available for patients with AF that can reduce the risk of stroke by 70%. Accordingly, vigilance in the diagnosis and subsequent treatment of AF is a major secondary preventative measure particularly in ageing populations where AF is a growing problem.

Diagnosis of AF

Professor Köhrmann emphasised that physicians should not forget the basics in their detection of AF. A detailed and comprehensive medical history can provide valuable diagnostic information and medical examination should always include careful pulse measurements. It also pays to instruct patients how to take their own pulse properly as this can provide important contributory information to the diagnosis. Most studies on ECG monitoring on stroke units have been based on 24-hour Holter ECG monitoring, where patients may be undergoing telemetric monitoring at the same time. Sending Holter-ECGs to cardiologists introduces delay, with interpretative results usually returned after the patient has left the stroke unit. Professor Köhrmann noted available evidence supports

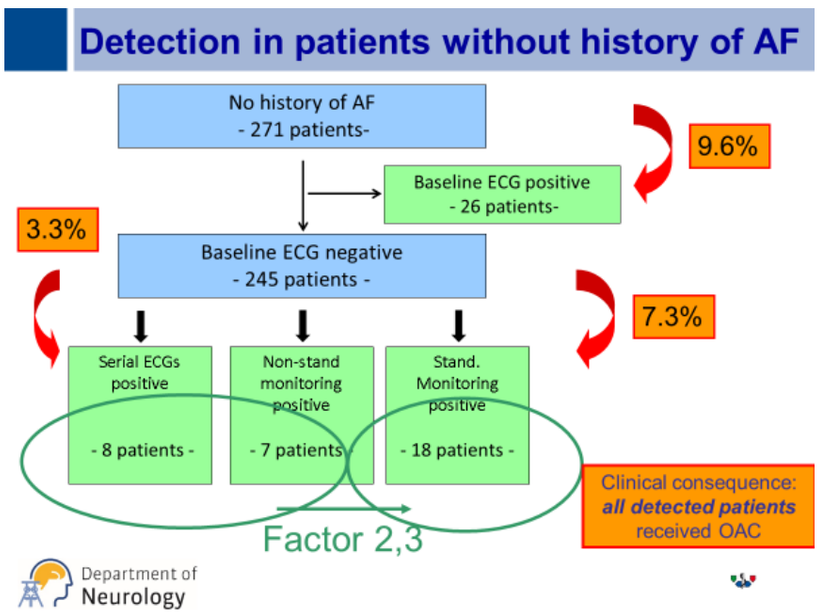
extending 24-hour monitoring with continuous 72-hour monitoring; in addition, he felt the current ECG-monitoring used on many stroke units was designed to detect life threatening arrythmias and not AF. The available data from published monitoring studies is inconsistent because the methodology is not standardised with some studies identifying few or no patients with AF.

Professor Köhrmann stressed that, increasingly, the onus is now on neurologists to learn how to use continuous ECG-monitoring data by adopting strategies already in place in e.g. those in place on cardiology wards and chest pain units. At Essen, Professor Köhrmann and colleagues have setup a structured standardized reading algorithm, which is similar to Holter-ECGs, to analyse telemetric monitoring. Monitoring is based on 24-hour pulse recordings; this allows identification of patients with AF usually based on a single assessment. Generally, patients with early AF are not receiving rate control medication, so episodes of tachycardia are quickly evident. A typical case is illustrated in the following figure.

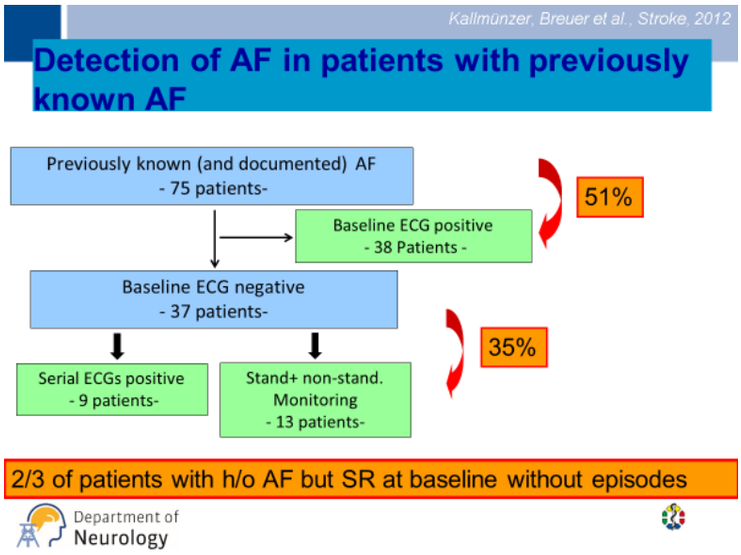


Professor Köhrmann presented an overview of a trial conducted by his team that identified shortcomings in his department's previous approaches to patient monitoring. The assessments that led to detection of AF in patients with no prior history is shown in the following figure.

By systematically adopting and reviewing these procedures identification of AF can be increased by a factor of 2 or 3 on the stroke unit and oral anticoagulant (OAC) treatment initiated.

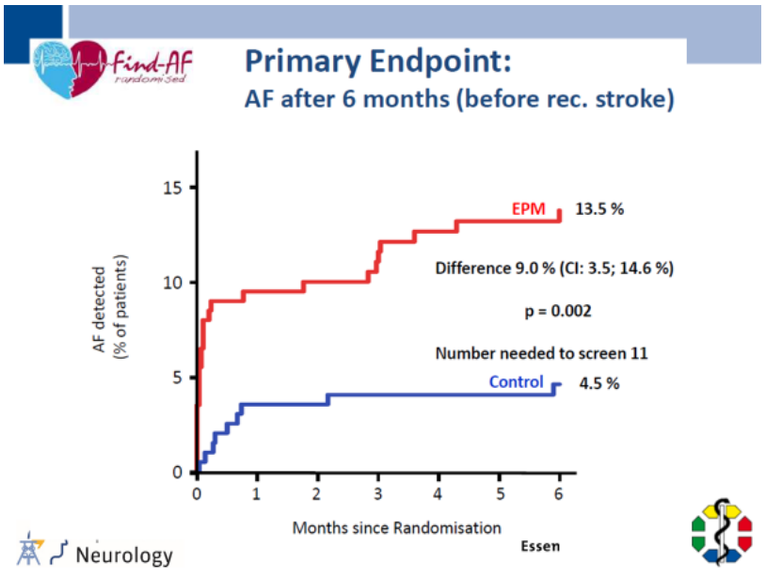


Within the trial patients with a previously documented history of AF (n=75) were monitored. Half of these patients were hospitalised with a baseline ECG-positive for AF. Half of the patients (n =37) had sinus rhythm on initial presentation. Around 2/3rds of patients with a history of AF had baseline sinus rhythm and no episodes of AF during their hospital stay. Prolonged monitoring would be required to identify AF in these patients who did not have episodes during their hospital stay. Because AF is a major risk factor for recurrent ischemic stroke, but often remains undiagnosed in patients who have had an acute ischaemic stroke, follow-up ECGs should be performed on these patients. These observations are summarized in the following slide.

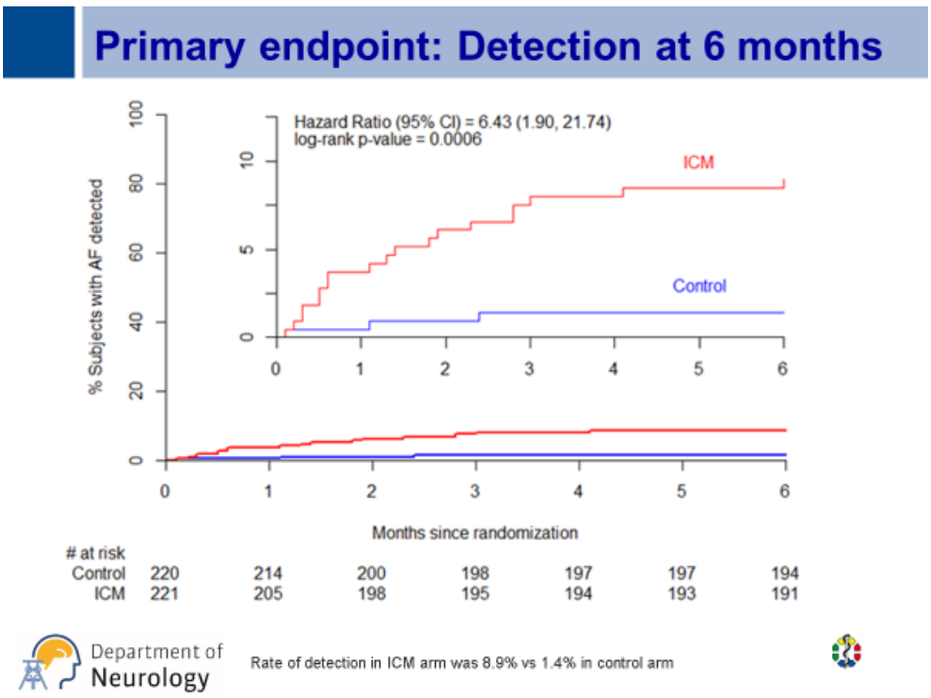


Long-term monitoring

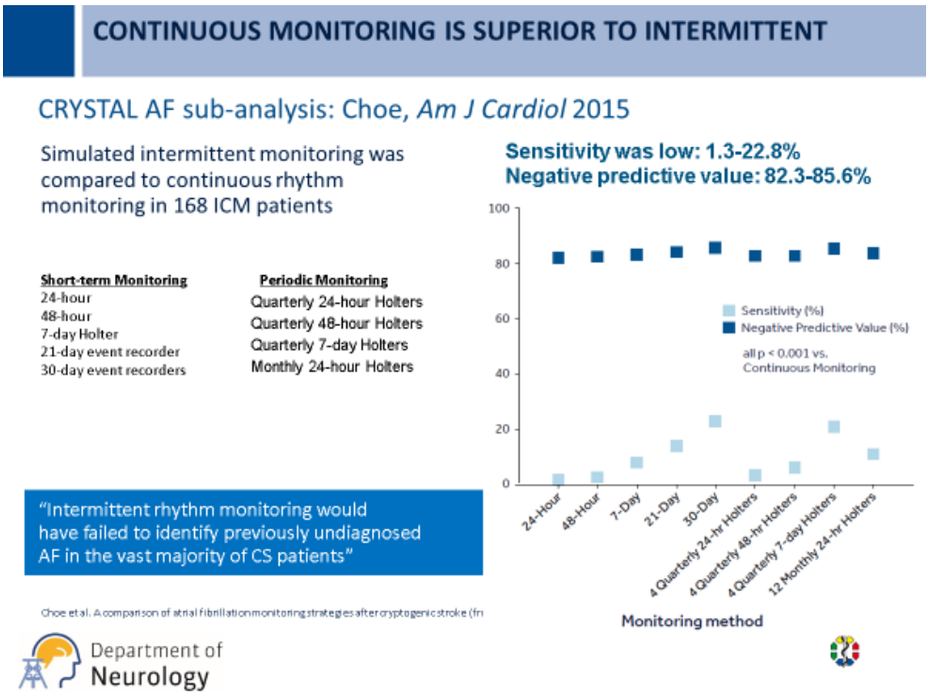
Professor Köhrmann stressed the importance of follow-up ECG diagnostics for those stroke patients who do not have AF episodes during initial hospital observation. AF is a progressive disease and approximately 70% of patients will progress to persistent AF within 5-6 years of the first episode. The randomized Finding Atrial Fibrillation in Stroke study[11] evaluated enhanced and prolonged Holter-ECGs involving three 10-day monitoring periods (0, 3 and 6 months) versus standard-of-care work-up (including at least 24 hours of ECG monitoring). The primary endpoint for this study was the detection of AF after six months. AF was detected in 13.5% of 200 patients in the enhanced and prolonged monitoring group, versus 4.5% in the control group (absolute difference 9.0%; 95% CI 3.5-14.6, p=0.002; number needed to screen 11). These findings, summarized in the following graph, support prolonged monitoring particularly if the detection of AF can result in a change in medical management e.g. initiation of anticoagulation therapy.



The CRYSTAL AF trial[12] investigated whether long-term monitoring with an insertable cardiac monitor (ICM) is more effective than conventional follow-up (control) for detecting atrial fibrillation in patients with cryptogenic stroke. Professor Köhrmann explained the control group investigations and observations in this study reflect current clinical reality. Of the 220 patients in the control group, only 88 received follow-up ECGs, only 20 patients received 24-hour Holter ECGs, and only one patient received an ICM. Crystal AF demonstrated a highly significant advantage associated with ICMs; by 6 months, AF had been detected in 8.9% of patients versus 1.4% of patients in the conventional follow-up control group. The improved AF detection associated with ICM use, at six months, in this population with cryptogenic stroke is illustrated in the following figure.



Professor Köhrmann presented summary results from a CRYSTAL AF sub-analysis.[13] This evaluated the sensitivity and negative predictive value (NPV) of various external monitoring techniques within a cryptogenic stroke cohort. Simulated intermittent monitoring strategies were compared with continuous rhythm monitoring in 168 ICM patients from the CRYSTAL AF trial. Short-term monitoring included a single 24-hour, 48-hour, and 7-day Holter and 21-day and 30-day event recorders. Periodic monitoring consisted of quarterly monitoring through 24-hour, 48-hour, and 7-day Holters and monthly 24-hour Holters. For a single monitoring period, the sensitivity for AF diagnosis was lowest with a 24-hour Holter (1.3%) and highest with a 30-day event recorder (22.8%). The NPV ranged from 82.3% to 85.6% for all single external monitoring strategies. Quarterly monitoring with 24-hour Holters had a sensitivity of 3.1%, whereas quarterly 7-day monitors increased the sensitivity to 20.8%. The NPVs for repetitive periodic monitoring strategies were similar at 82.6% to 85.3%. Long-term continuous monitoring was superior in detecting AF compared to all intermittent monitoring strategies evaluated ($p < 0.001$). This sub-analysis confirms long-term continuous electrocardiographic monitoring with ICMs is significantly more effective than any of the simulated intermittent monitoring strategies for identifying AF in patients with previous cryptogenic stroke. The summary findings from this sub-analysis are summarized in the following figure.



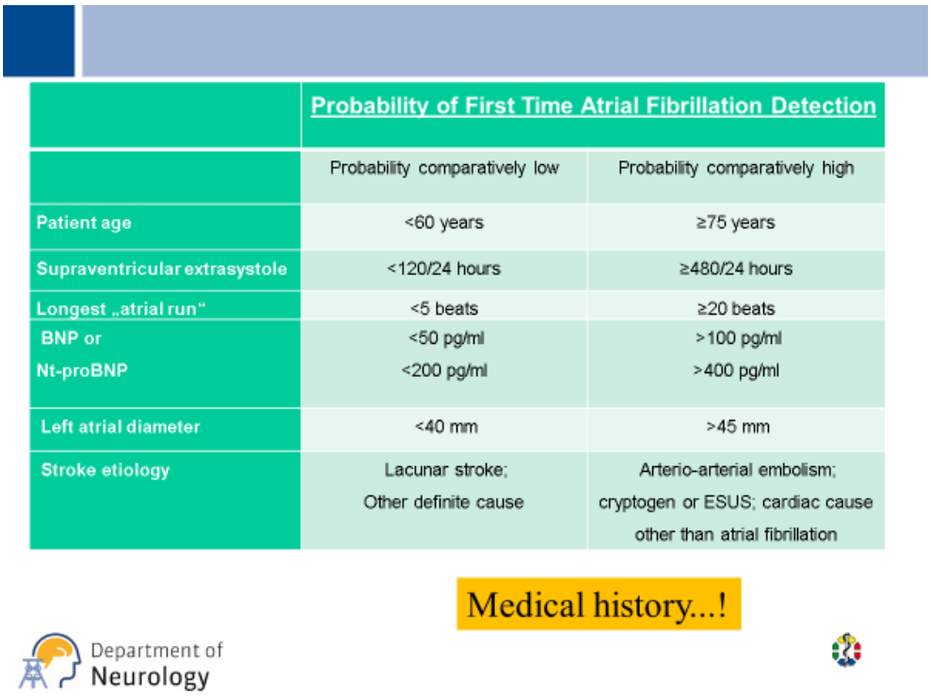
Professor Köhrmann stressed that insertion of ICMs is a straightforward, quick, and easy procedure; he hoped more neurologists will perform ICM insertion routinely given the well-established superior AF detection provided by continuous monitoring. With increased use of the Reveal LINQ™ ICM in Professor Köhrmann's department the ECG data generated has expanded significantly. Cardiac data are transmitted from ICMs to Medtronic's FOCUSON service for data monitoring and triaging. This provides a doctor-to-doctor communication service with high quality ECG readings and interpretative evaluation with triage based on urgency.

Cryptogenic stroke i.e. cerebral ischemia of obscure or unknown origin was identified in the TOAST 1993 publication[14] as stroke with no defined cause despite a diagnostic work-up; however, Professor Köhrmann noted the TOAST criteria also included patients who have not received any kind of diagnostic work-up, and therefore the TOAST criteria could not be used for present day clinical trials. Embolic stroke of undetermined source (ESUS) is a defined classification based on a defined work-up which provides criteria for clinical studies. Hart el al (2104)[15] propose that embolic strokes of undetermined source are a therapeutically relevant entity, which are defined as a non-lacunar brain infarct without proximal arterial stenosis, high risk cardiac disease, or cardioembolic sources. Professor Köhrmann cautioned that the ESUS diagnosis, based on only one 12-lead ECG and one period of 24-hour Holter monitoring, is unlikely to be sufficient if AF is suspected as the cause of the stroke. If AF is not actively looked for and identified, anticoagulant therapy may result in increased haemorrhages.

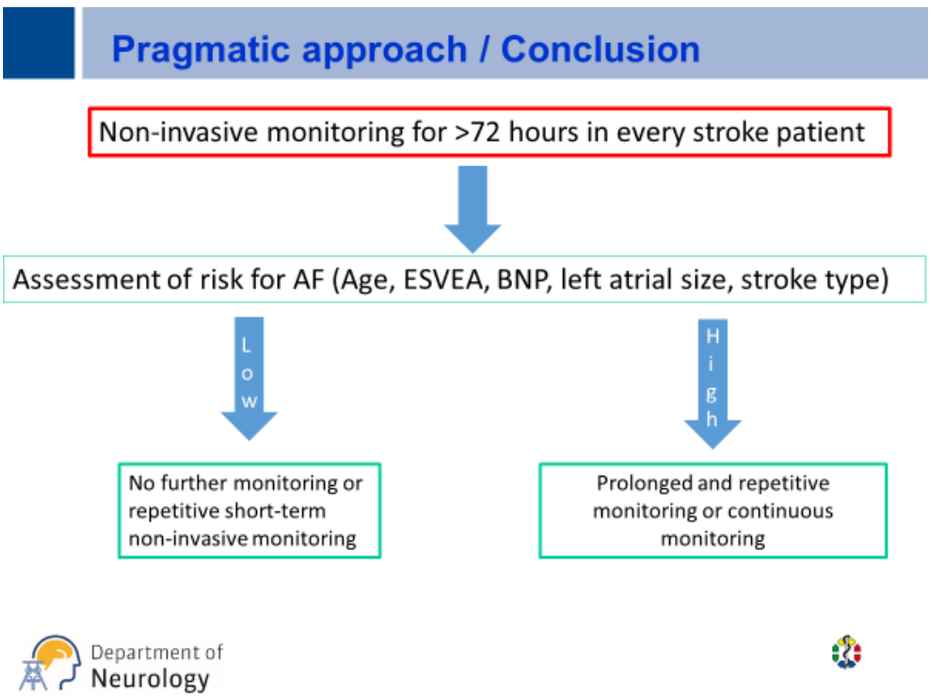
Professor Köhrmann cited the NAVIGATE ESUS study[16] where no further ECG diagnostics were progressed and no implantable loop recorders (ILRs) were used. Only 3% of patients in NAVIGATE were reported with an AF diagnosis during the trial. This compares with up to 25% in observational ILR studies. Professor Köhrmann noted the increased risk of bleeding reported with rivaroxaban in NAVIGATE and suggested more diagnostics may have been helpful in this study. He raised the question of whether neurologists should implant only after ESUS or cryptogenic strokes? However, in the Find-AF trial[11] no difference in AF detection rate was evident between cryptogenic and non-cryptogenic stroke patients.

Professor Köhrmann felt there is now a shift in the paradigm used by neurologists to think about stroke; he noted that the aetiology of a second stroke is often very different from the initial stroke. However, looking for AF that may lead to a second stroke is always important in all patients with a history of acute ischemic stroke. Stroke should be considered more as an index event in patients with a high risk of AF and secondary strokes. Stroke patients have a high risk of underlying AF irrespective of stroke etiology and should be anticoagulated if AF is detected.

A recent position paper on AF detection after ischemic stroke has been issued jointly by the German Stroke Society and the German Cardiac Society. This has identified risk factors in stroke patients who may have AF. The factors and patient characteristics associated with low and high probability of detecting first time AF are summarized in the following table.



In conclusion, Professor Köhrmann recommended a pragmatic approach to monitoring and AF detection for all stroke patients, with high risk patients selected for prolonged and repetitive monitoring or continuous monitoring with implantable devices. This is approach summarised in the following flow diagram.



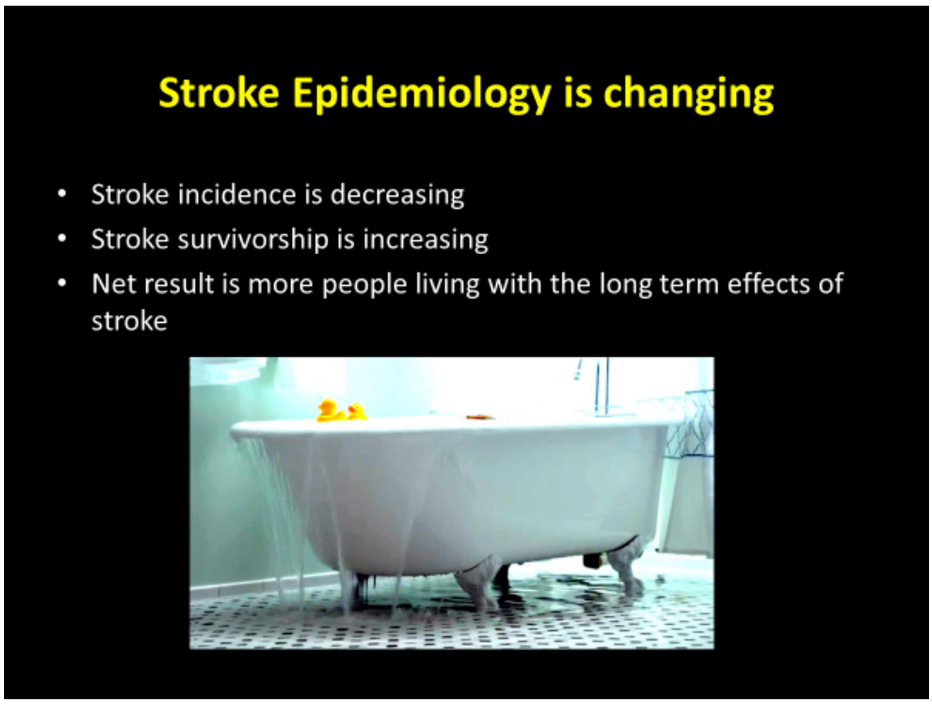
This pragmatic approach is to be investigated in the forthcoming Find-AF 2 trial where initial non-invasive monitoring will be followed by implantation of ICMs in high AF risk patients.

INTRA THECAL BACLOFEN (ITB) THERAPY FOR POST STROKE SPASTICITY – NEW EVIDENCE FOR AN UNMET NEED. PROFESSOR GEOFFREY CLOUD.

Background, changing epidemiology and disease burden

Professor Cloud acknowledged that more people are surviving stroke but, as a consequence, more people are being left with long-term disabilities, despite the advances in reperfusion interventions and secondary prevention strategies. In particular, one of the most wretched sequelae of stroke is severe spasticity.

In developed countries the incidence of stroke is decreasing and the incidence of in-hospital mortality due to stroke e.g. in the UK, has halved; however, the net result of increased survival is that more people are having to live with the incapacitating long-term effects of their stroke.

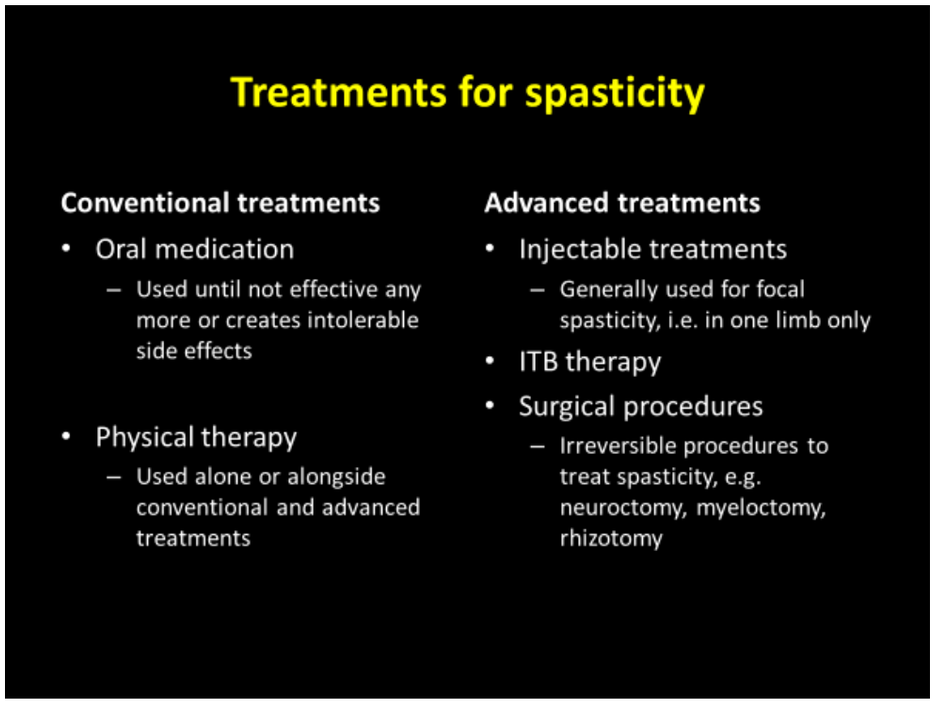


Professor Cloud explained that spasticity is a common after effect of stroke. Estimates vary, but between 17-43% of patients will develop post-stroke spasticity. In addition, 4-13% of stroke survivors will develop severe, disabling spasticity. This represents a very significant unmet need; in the USA it is estimated that over 440,000 patients are living with untreated severe spasticity.[17] Spasticity is probably best described as disordered sensorimotor control resulting from an upper motor neuron lesion, presenting an intermittent or sustained involuntary activation of muscles. Spasticity can be considered as severe when it is problematic for the patient or their caregiver(s). It is defined by functional or comfort limitation rather than solely by a numerical rating. The signs of spasticity are usually obvious: patient's muscles are tight and stiff; this makes movement difficult or uncomfortable, often with a characteristic gait pattern. Patients also experience painful muscle spasms that interfere with activities of daily living.

Professor Cloud reviewed the burden imposed by post-stroke spasticity. The impact on quality of life is considerable: compared with matched stroke survivors without spasticity, spasticity reduces quality of life by around 20%. Spasticity reduces functional ability by 35-40%; it increases anxiety and depression in carers, and is associated with a significant health economic burden. The long-term consequences are therefore significant; however, these effects have not been well studied in controlled clinical trials of post-stroke patients.

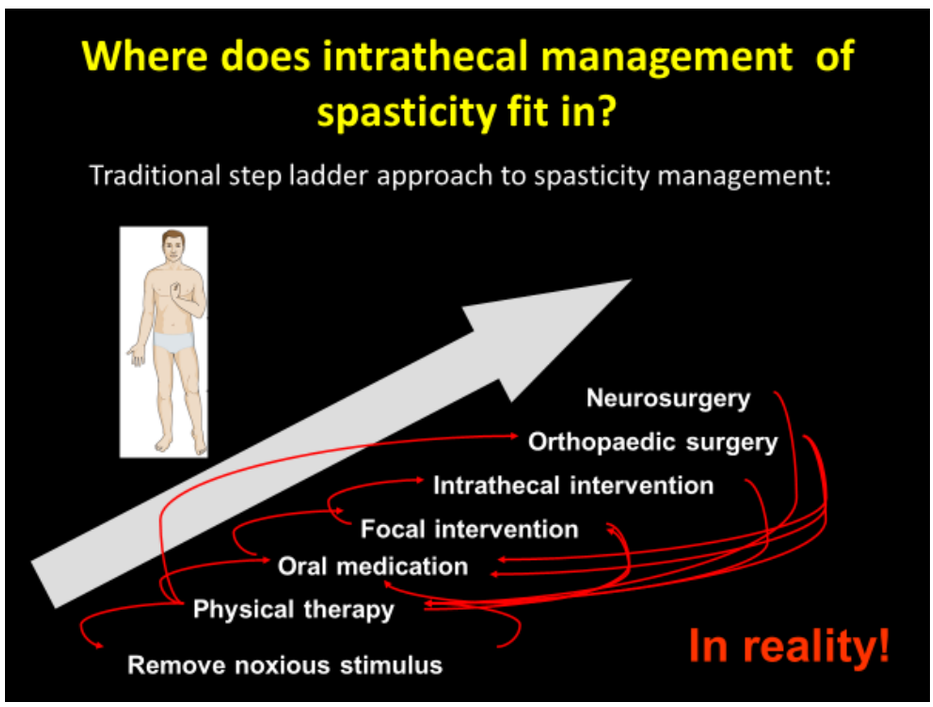
Patient management and treatments

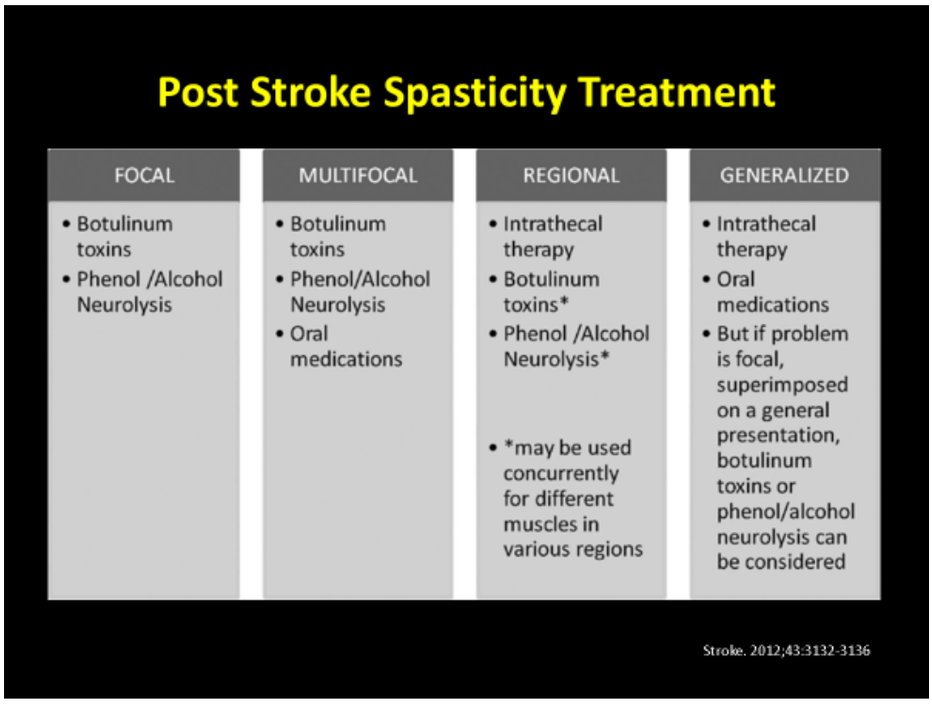
Treatment options for spasticity include conventional treatment based on oral medication (with baclofen the cornerstone of oral treatment) and physical therapy. Advanced treatments include injectable treatment, notably, botulinum neurotoxins, intrathecal baclofen (ITB) therapy, and as a last resort, surgical procedures.



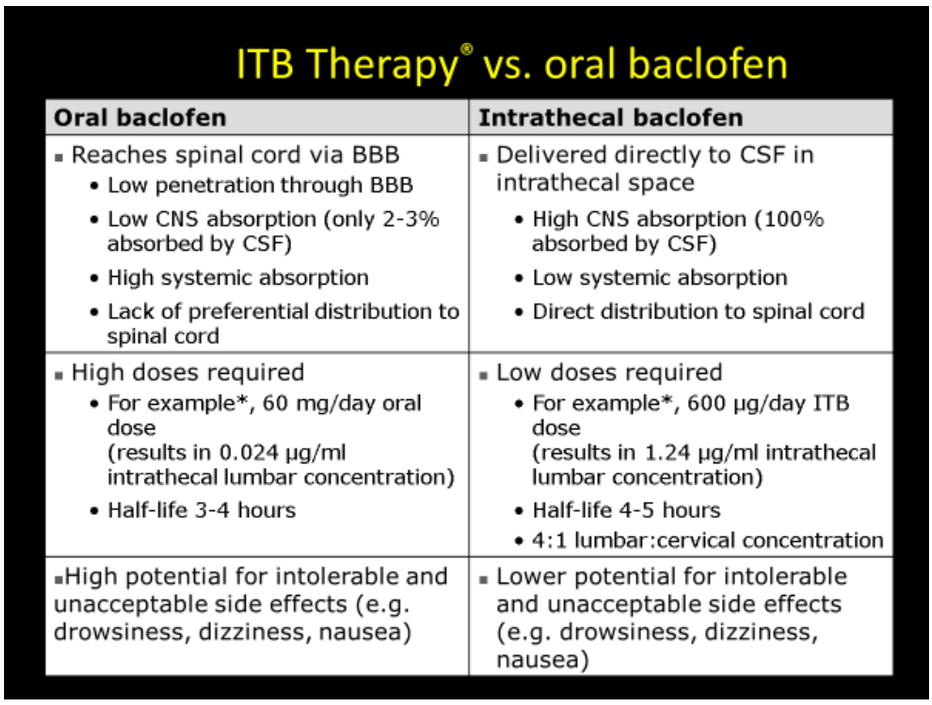
A management plan for spasticity should be initiated when it interferes with patients' functioning, positioning, comfort and care, and when spasticity is not considered useful, bearing in mind some patients need spasticity in order to stand. Treatment decisions should be driven by an honest expectation that the treatment will provide meaningful improvement. Specific, realistic, individualized goals should be set that are reflective of the impact of spasticity on daily function, comfort, caregiving, medical conditions and psychosocial issues. Goals should be set in a collaborative and holistic way, and fully documented; they should involve the patient, family, other caregivers, and the wider multidisciplinary healthcare team.

A traditional "stepped care" approach to the management of spasticity is often advocated, but Professor Cloud explained that, in reality, the picture is more convoluted and less well structured.

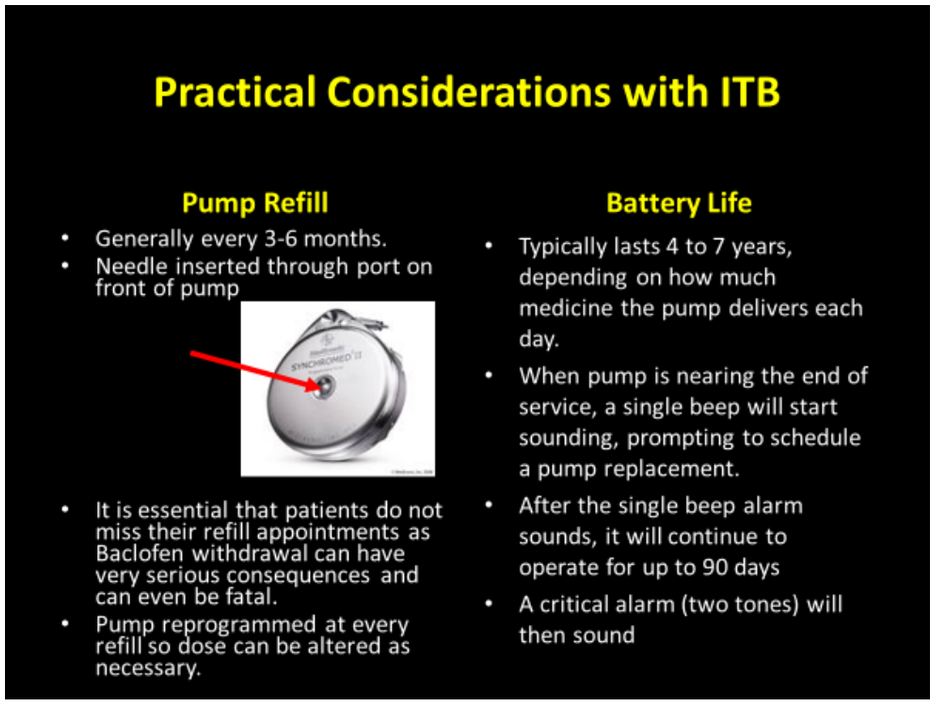




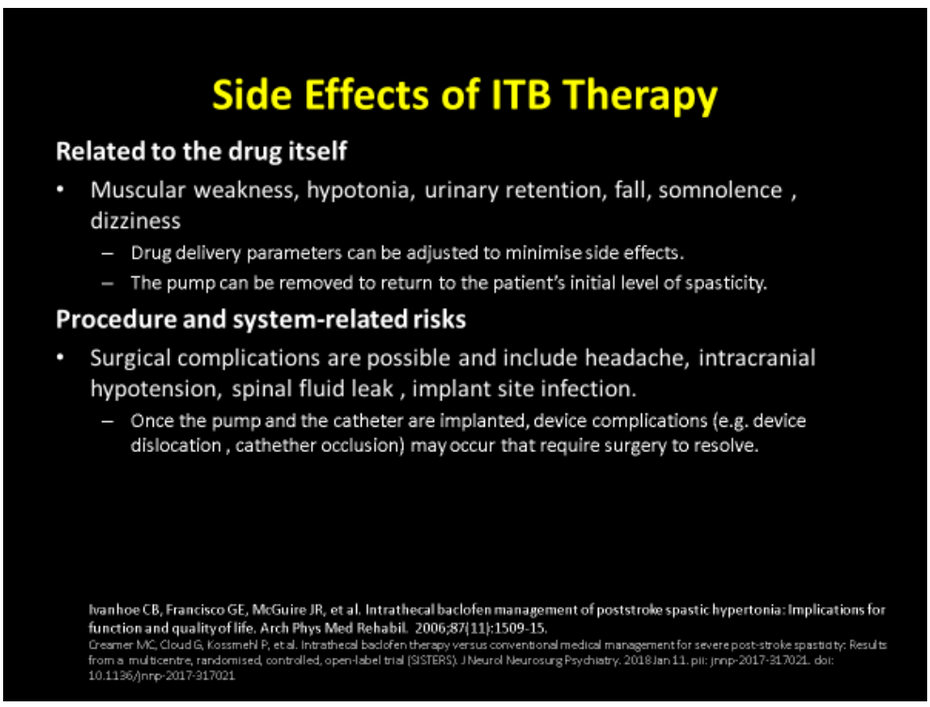
Intrathecal baclofen (ITB) therapy delivers the drug directly to the cerebrospinal fluid (CSF), in the intrathecal space, via a catheter and an implanted programmable pump. ITB allows the use of 100 to 1000 times smaller directly targeted doses, with a longer half-life compared with oral baclofen. Consequently, ITB is expected to produce fewer intolerable side effects compared with oral baclofen with its low CNS absorption and its propensity for systemic side effects. The key differentiating characteristics between oral and intrathecal baclofen are summarized in the following table.



There are a number of practical considerations associated with the use and maintenance of the pump during ITB therapy, particularly pump re-fill requirements and battery life expectation. It is extremely important that the patient does not run out of intrathecal baclofen; withdrawal can have very serious and potentially fatal consequences for the patient. These considerations are summarized in the following bullet points.

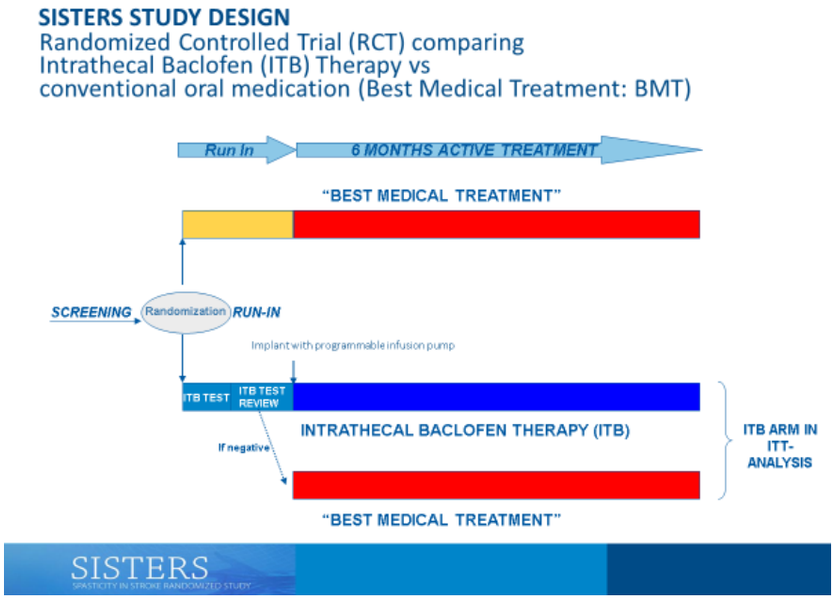


Professor Cloud illustrated the potential benefits of ITB therapy with video footage of a patient with obvious clonus and when ambulatory had a characteristic hemiparetic gait. Following ITB treatment, the clonus was much less evident, and the gait pattern had improved considerably. There are side effects with ITB; these can arise from the drug itself, or from the procedure and these are summarized in the following table.

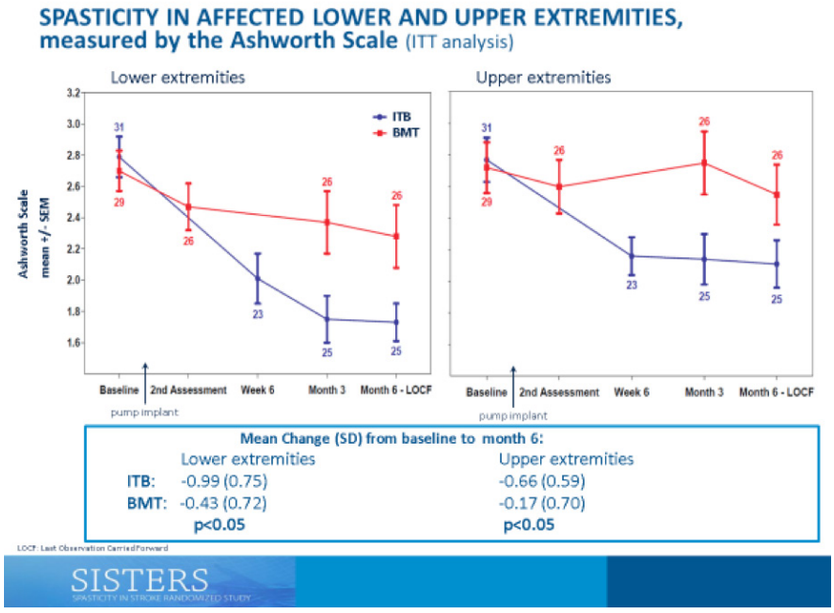


The SISTERS study

Professor Cloud presented summary results from the first prospective, randomized controlled trial of intrathecal baclofen versus best medical treatment (BMT) in the management of severe post-stroke spasticity (the SISTERS trial).[19] Patients with chronic stroke with spasticity assessed by the Ashworth Scale (AS) score ≥3 in at least two affected muscle groups in the lower extremities (LE) were randomised (1:1) to ITB or BMT. Both treatment arms received physiotherapy throughout. Patients in the BMT group continued with their oral medications for their spasticity, whilst patients were weaned off oral medication in the ITB group. The SISTERS study design is illustrated in the following chart.



This was a multinational multicentre study involving 11 EU sites and seven US sites. Patients were relatively young, in their 50s, and were refractory to prior treatments after 4 or 5 years since their stroke. Of 60 patients randomised to ITB (n = 31) or BMT (n = 29), 48 patients (24 per arm) completed the study. The primary outcome was the change in the average AS score in the LE of the affected body side from baseline to month 6. Analyses were performed for all patients as randomised (primary analysis) and all randomised patients as treated (safety analysis). A positive outcome in favour of ITB has emerged from this study. Clear separation between treatments for both spasticity in the leg and arm were obtained, as illustrated in the following graphs.



For the Functional Independence Measure (FIM) total score, a positive trend for improvement with ITB therapy versus CMM was observed, despite the relatively short follow-up period. Most patients (73%) were satisfied with the reduction in their spasticity with ITB and would recommend this therapy to a friend.

Professor Cloud identified who is most likely to benefit from ITB. This therapy is appropriate for patients with severe, non-focal spasticity who cannot be manged effectively with orally administered drugs and physical interventions. Patient selection is important: they need to have realistic, achievable goals and expectations, and both patients and their carers must be committed to long-term reliance on, and correct maintenance of, the implanted pump. Professor Cloud concluded by stressing that post-stroke spasticity is common, and ITB definitely has a role in managing severe post-stroke spasticity in adults.

CONCLUSIONS

This symposium reviewed current advances and progress made in all stages of the care continuum and management of the stroke patient. In the acute phase, positive late-window studies such as DAWN and have DEFUSE 3 have changed neurologists' perception of how ischaemic strokes evolve; these studies have challenged previously held dictums regarding the cut-off point beyond which endovascular intervention was unlikely to be considered. Advanced perfusion imaging techniques are helping to identify late presenting patients with salvageable tissue and most likely to benefit from endovascular intervention. Consequently, late-window therapy is expected to have a major impact on reducing stroke morbidity in carefully selected patients.

Stent-retriever device technology continues with improved design and refinements to aid visualization, deployment, and reperfusion performance. Recent one-year clinical experience with Medtronic's latest generation Solitaire™ Platinum stent-retriever, at Essen in Germany, confirms the effective reperfusion performance of this device. The addition of newly added radiopaque platinum markers provides increased visibility, and user experience confirms less resistance in deployment compared with earlier versions of this device.

Atrial fibrillation (AF) is a well-established independent risk factor for stroke. Diagnosis of AF and initiation of anticoagulation therapy is an important aid to secondary prevention; however, Holter monitoring for AF in post-stroke patients in many units is not consistent, and monitoring periods are too short to identify AF risk effectively. Detection of AF risk increases markedly with continuous electrocardiographic monitoring using insertable cardiac monitors (ICMs) such as Medtronic's Reveal LINQ™. The insertion procedure for an ICM is quick and straightforward and increasing use by neurologists would result in increased detection of AF. Equally important, identification of patient who do not have AF avoids unnecessary anticoagulation treatment and the associated increased risk of intracranial haemorrhage (ICH).

More patients are surviving stroke, but an increasing number are left with long-term disability. Severe post-stroke spasticity is common in stroke patients, but effective treatment options are currently limited. The recent SISTERS trial has demonstrated the superiority of intrathecal baclofen (ITB) compared with current standard medical treatment for the treatment and relief of severe post-stroke spasticity. The SISTERS results confirm that ITB therapy is likely to find increased long-term use to meet a current significant and growing unmet clinical need.

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