DAWN™ Trial: Novel at its Inception and Timely Now

SVIN – November 7, 2014

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DAWN ™ Trial Co-PIs

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Steering Committee

- Blaise Baxter (Erlanger) – interventional neuroradiologist
- Anthony Furlan (Case Western) – stroke neurologist
- Rishi Gupta (Kennestone) – interventional neurologist
- Olav Jansen (University of Kiel) – interventional neurologist
- Tudor Jovin (UPMC) – interventional neurologist
- Raul Nogueira (Emory) – interventional neurologist
- Vitor Pereira (U of Geneva) – endovascular neurosurgery
- Marc Ribo (Vall d'Hebron) – interventional neurologist
- Jeff Saver (UCLA) – stroke neurologist

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Independent Core Labs and Committees:

Angio Core Lab	David Liebeskind, MD, UCLA
CT/MR Core Lab	iSchemaView (Greg Albers, MD)
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DMC	Wade Smith, MD, UCSF Steve Hetts, MD, UCSF Daryl Gress, MD, U of Virginia Roger Lewis, MD, PhD, DMC
RAPID software	iSchemaView (Greg Albers, MD)

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DAWN™ Trial Milestones

Protocol submitted to FDA as IIS (IDE)	Early 2012
DAWN IDE transferred to Stryker NV	Aug 17, 2012
Study Design finalized (Adaptive Design)	May 28, 2013
Stryker NV submitted Initial IDE	Sep 26, 2013
Stryker NV IDE approval received	Apr 24, 2014
Competent Authority/EC Submissions	Q2-Q3, 2014
First Site Initiation Visit / First Subject In	Q3, 2014
150 Subject Interim Analysis	Q4 2015

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Trial Design and Protocol Overview

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DAWN™ IDE Clinical Trial

DWI or CTP **A**ssessment with Clinical Mismatch in the Triage of **W**ake-Up and Late Presenting Strokes Undergoing **N**eurointervention

Objective

To demonstrate superior *clinical outcomes* at 90 days with Trevo plus medical management compared to medical management alone in *appropriately selected* patients *treated 6–24 hours* after last seen well

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DAWN™ Study Design

- Prospective, randomized (1:1), multi-center, Phase II/III (feasibility/pivotal), adaptive, population enrichment, blinded endpoint, controlled trial
- 50 sites (worldwide)
- 150 subjects (feasibility) up to 500 (pivotal) max
- Primary endpoint
  - Difference in *average weighted* mRS at 90 days between treatment and control in the *enriched* patient population

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The Importance of DAWN™ Clinical Trial

- Patient Benefit
- Establishing new options for an underserved patient population currently only eligible for medical management
- Thrombectomy between 6–24 hours
- Best in class study design
  - Adaptive design
  - Carefully selected and controlled patient population
  - Limiting confounding variables
- Data will reflect next generation Trevo® Retriever family of products
  - Trevo® XP ProVue Retriever
  - Trevo ® ProVue Retriever

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Clinical Evidence

Control Arm Estimates*			Treatment Arm Estimates		
Study	ICA/M1	mRS 0-2	Study	ICA/M1 +	mRS 0-2
Germans Trias Barcelona	6-24 hr	17.4%	SWIFT	0-8 hr (all comers)	37%
STOP Stroke	0-8 hr	18.4%	TREVO 2	0-8 hr (all comers)	39.9%
FIRST	0-8 hr	20.4%	Pre-DAWN	8-24 hr	40%
PROACT II	0-6 hr (+ M2)	25%			

*Late presenting patients presumed to have good collaterals and better outcomes

Expected Treatment Effect = 10-15%

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Preliminary Data for the DAWN™ Trial

IBET for Proximal Anterior Circulation Occlusions >8 Hours from LSW in 237 Stroke Patients

A total of 169 patients from the original cohort met the following criteria:

- Baseline NIHSS score ≥10
- ICA or MCA-M1 occlusion +/-cervical occlusion
- TLSWT between 8-24 hours
- MRI or CTP Selection (vs. CT in PROACT-II)

Jovin TG, Nogueira RG et al., *Stroke*, 2011

Age (years)	
Mean±SD	64±16
Median	68
Range	19-91
Baseline NIHSS Score	
Mean±SD	17±4
Median	17
Gender % (n)	
Male	46% (78)
Female	54% (91)
TLSWT	
Mean±SD	12.6±3.7
Median (IQR)	12 (9.5-14.4)
Site of Occlusion (%)	
MCA-M1	54% (91/169)
ICA-T	22% (38/169)
Tandem ICA/MCA	17% (26/169)
Tandem ICA/ICA-T	7% (12/169)
TIMI 2-3 Revascularization	74% (125/169)
Symptomatic ICH	10% (17)
90-day mRS ≤2	40% (57/142)
90-day mRS ≤3	58% (82/142)
90-day Mortality	25% (42/167)

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DAWN™ Clinical Trial
Unique Design Elements

stryker Neurovascular

Clinical Imaging Mismatch

- Standardizes clinical imaging to select patients
- Literature supports core infarct size being predictive of outcomes
- No gold standard to define salvageable brain tissue
- NIHSS assessment (clinical deficit) represents tissue at risk in real time, can be easily administered (and repeated) multiple times, and is validated in clinical practice

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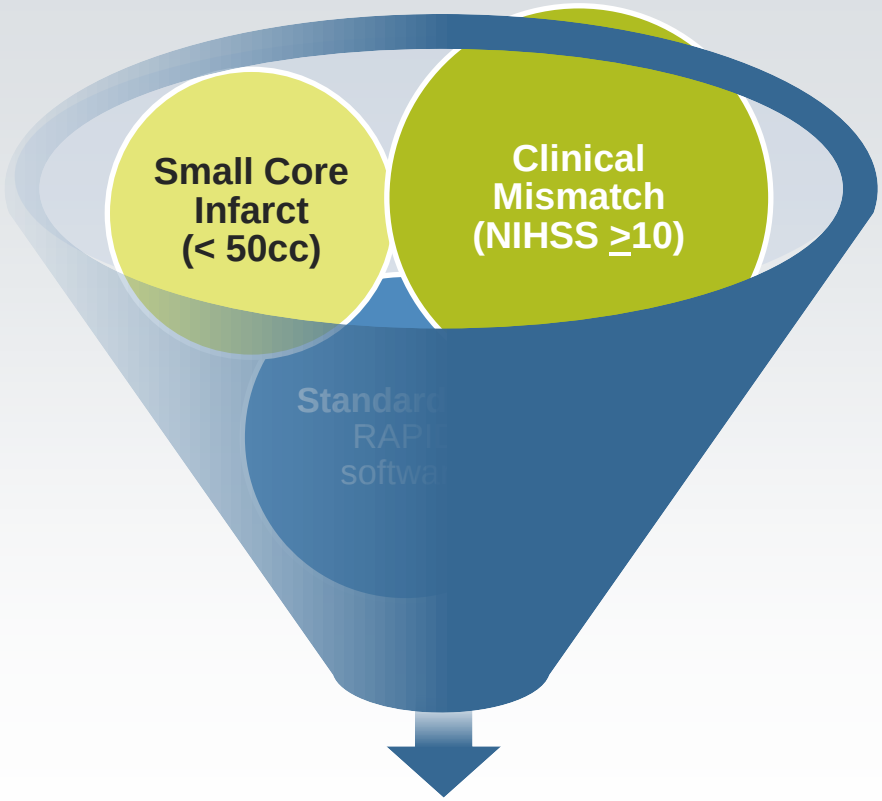
DAWN™ Clinical Trial
Clinical Imaging Mismatch

stryker Neurovascular

Goal: To identify the Target Mismatch Patient



Randomization
Balanced re: CIM subgroup, time and occlusion location

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DAWN™ Clinical Trial
Unique Design Elements

stryker Neurovascular

Adaptive Bayesian Design

- Adjusts predicted probability of success/failure at frequent interim analyses (every 50 patients)
- Unknown Natural History = Unknown treatment effect
- Interim analyses allow for “fine tuning” or “enriching” the patient population
- Eliminate patients not being helped/being harmed by treatment)
- Novel weighted mRS endpoint

Combined Feasibility/Pivotal

- Signal strength at interim analysis allows for study expansion

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DAWN™ Clinical Trial
Unique Design Elements

Primary Endpoint: Weighted mRS

- Captures health state transitions across the entire spectrum
- Endpoint that is a combination of both efficacy and safety
- Differentiates outcomes
- Patient-centered outcomes analysis

Measures effectiveness & safety in single endpoint

mRS	0	1	2	3	4	5	6
Weight	**10**	**9.1**	**7.6**	**6.5**	**3.3**	**0**	**0**

Enrichment

- Fine tune the patient population based on core infarct size
- Identify subgroups experiencing clinical benefit

0-50 cc → 0-45 cc → 0-40 cc → 0-35 cc → 0-30 cc

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Secondary Endpoints

- Good functional outcome at 90 days, defined as mRS 0-2
- “Early response” at Day 5-7/Discharge (whichever is earlier), defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1
- All cause mortality rates between the two groups.
- Median final infarct size at 24 (-6/+24) hours from randomization, by MRI T2/Flair or CT (if contraindicated for MR)
- Revascularization rates at 24 (-6/+24) hours from randomization, by CT-MR core lab assessment of vessel patency on CTA/MRA
- Treatment Arm Only: Vessel reperfusion rates (percentages) post device and post procedure, by angiography core lab measurement of modified TICI ≥ 2b

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Stroke: Our Only Focus Our Ongoing Promise.

Safety Outcomes (Both Arms)

Primary:

- Incidence of stroke-related death

Secondary:

- Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero)
- Incidence of neurological deterioration from baseline NIHSS score through Day 5-7/discharge (whichever is earlier) post randomization (time zero). Neurological deterioration is defined as ≥ 4 point increase in the NIHSS score from the baseline score

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Secondary Safety Outcomes (Treatment arm)

Incidence of procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post randomization (time zero) as adjudicated by the clinical events committee, and defined as:

- *vascular perforation*
- *intramural arterial dissection*
- *embolization to a new territory*
- *access site complication requiring surgical repair or blood transfusion*
- *intra-procedural mortality*
- *device failure (in vivo breakage)*
- *any other complications adjudicated by the CEC to be related to the procedure*

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General Inclusion Criteria

1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, and subject belongs to one of the following subgroups:
    a. Subject has failed IV t-PA therapy (defined as a confirmed persistent occlusion 60 min after administration)
    b. Subject is contraindicated for IV t-PA administration
2. Age ≥18
3. Baseline NIHSS ≥10 (assessed within one hour prior to measuring core infarct volume)
4. **Subject can be randomized between 6 to 24 hours after time last known well**
5. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1)
6. Anticipated life expectancy of at least 6 months
7. Subject willing/able to return for protocol required follow up visits
8. Subject or subject's Legally Authorized Representative (LAR) has signed the study Informed Consent form

* If approved by local regulations allowed to enroll a patient if, representative or person of trust is available. However, as soon as possible, the patient is informed and his/her consent is requested for the possible continuation of this research. (Not applicable to U.S. Sites).

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General Exclusion Criteria

1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history
2. Rapid improvement in neurological status to an NIHSS <10 or evidence of vessel recanalization prior to randomization
3. Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g. **dementia** with prescribed anti-cholinesterase inhibitor (i.e. Aricept)
4. **Seizures** at stroke onset if it makes the diagnosis of stroke doubtful and precludes obtaining an accurate baseline NIHSS assessment
5. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol)
6. Renal failure as defined by a serum creatinine >3.0 mg/dL (264 µmol/L)

   NOTE: subjects on renal dialysis may be treated regardless of serum creatinine levels

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General Exclusion Criteria cont.

7. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR > 3.0 or PTT > 3 times normal; If factor **Xa inhibitor** (e.g. apixaban) < 24 hrs ago must have normal ecarin clotting time and if 24-48 hrs ago must have normal PTT.
8. Any active or recent hemorrhage within the past 30 days
9. Baseline platelet count < 50,000/uL
10. History of severe allergy (more than rash) to contrast medium
11. Severe, sustained hypertension (Systolic Blood Pressure >185 mmHg or Diastolic Blood Pressure >110 mmHg)

    NOTE: If the blood pressure can be successfully reduced and maintained at the acceptable level using medication the subject can be enrolled
12. Female who is pregnant or lactating at time of admission
13. Current participation in another investigational drug or device study or registry
14. Presumed septic embolus, or suspicion of bacterial endocarditis
15. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization

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Imaging Exclusion Criteria

1. Evidence of intracranial hemorrhage on CT/MRI
2. Evidence of internal carotid artery flow limiting dissection on CTA/MRA
3. Severe proximal extra-cranial carotid artery stenosis, or occlusion of any etiology, where concurrent vessel angioplasty or stenting is expected to be necessary and the procedure cannot be delayed until after the 24 (-6/+24) hour assessments have been completed
4. Excessive tortuosity of cervical vessels on CTA/MRA that would likely preclude device delivery/deployment
5. Suspected cerebral vasculitis based on medical history and CTA/MRA

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Imaging Exclusion Criteria

6. Suspected aortic dissection based on medical history and CTA/MRA
7. Intracranial stent implanted in the same vascular territory that would preclude the safe deployment/removal of the Trevo device
8. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation) as confirmed on CTA/MRA , or clinical evidence of bilateral strokes or strokes in multiple territories
9. Significant mass effect with midline shift as confirmed on CT/MRI
10. Evidence of intracranial tumor (except small meningioma) as confirmed on CT/MRI

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Imaging Inclusion Criteria

1. < 1/3 MCA territory involved, as evidenced by CT or MRI
2. Occlusion of the intracranial **ICA and/or MCA-M1** as evidenced by MRA or CTA
3. Clinical Imaging Mismatch (CIM) defined as one of the following on RAPID MR-DWI or CTP-rCBF maps:

   a. 0-20 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old)

   b. 0-30 cc core infarct and NIHSS ≥ 10 (and age < 80 years old)

   c. 31 cc to ≤ 50 cc core infarct and NIHSS ≥ 20 (and age < 80 years old)

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Enrollment and Randomization

Oracle IRT – IVRS system

Enrollment in this study is automated, and done over the phone or web in “real time”.

After randomization, no crossover is permitted.

Enrollment in this study is defined as the moment when the randomization process is completed and the subject is assigned to a study arm.

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Treatment Arm Considerations

Arterial Access:

1. Initiate between 6 and 24 hours from time of symptom onset or Time Last Seen Well
2. Obtained within 60 minutes of randomization

End of Interventional procedure:

1. Neurological deterioration or alteration in function is detected leading to the suspicion of an intracranial hemorrhage
2. The time from groin puncture reaches 2 hour
3. Modified TICI grade 2b or 3flow is established
4. The occlusion is refractory to six retrieval attempts in a single vessel

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Schedule of Events

Event	Scrn/ B/L	Proc (Treat arm only)	24 Hr (-6/+24) post random	Day 5-7 / DC (earlier)	DC	Day 30 ± 14	Day 90 ± 14
Inclusion/Exclusion criteria	✔						
Demographics/Medical History/ Baseline Medications	✔						
Baseline Characteristics	✔						
Baseline Labs	✔						
Informed Consent	✔						
Randomization (t=0)	✔						
Angiography Procedure Details (Treatment arm only)		✔					

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Schedule of Events

Event	Scrn/ B/L	Proc (Treat arm only)	24 Hr (-6/+24) post random	Day 5-7 / DC (earlier)	DC	Day 30 ± 14	Day 90 ± 14
mRS	✔ (pre stroke)			✔		✔	✔
NIHSS	✔		✔	✔		✔	✔
Neuro imaging (hemorrhage, occlusion location, vessel patency, and infarct volume)	✔		✔	✔			
AEs / SAEs (from time of randomization)		✔	✔	✔	✔	✔	✔
Concomitant Medications		✔	✔	✔		✔	✔
In Hospital Med Management					✔		
Intubation details					✔		

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Thank you!

We are finally at the DAWN of a New Era

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DAWN™ Clinical Trial
RAPID Software

Standardized measurement of core infarct size

- Supports objectivity in a randomized clinical trial
- Especially important for 6+ hour patient population with unknown treatment effect
- Randomization stratified based on core infarct size and NIHSS mismatch
- 510(k) cleared
- Previous use in clinical trials

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RAPID software web-based training

– Dr Greg Albers, iSchemaView

Stroke: *Our Only Focus Our Ongoing Promise.*

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Case Review – Dr. Tudor Jovin

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Case #1 – Wake up stroke

- 87 year old man who woke up with acute onset right sided weakness, aphasia, gaze deviation
- Last seen normal 12 hours prior to presentation
- B/L NIHSS = 20

- B/L ASPECTS = 9
- CTA = Left M1 MCA occlusion

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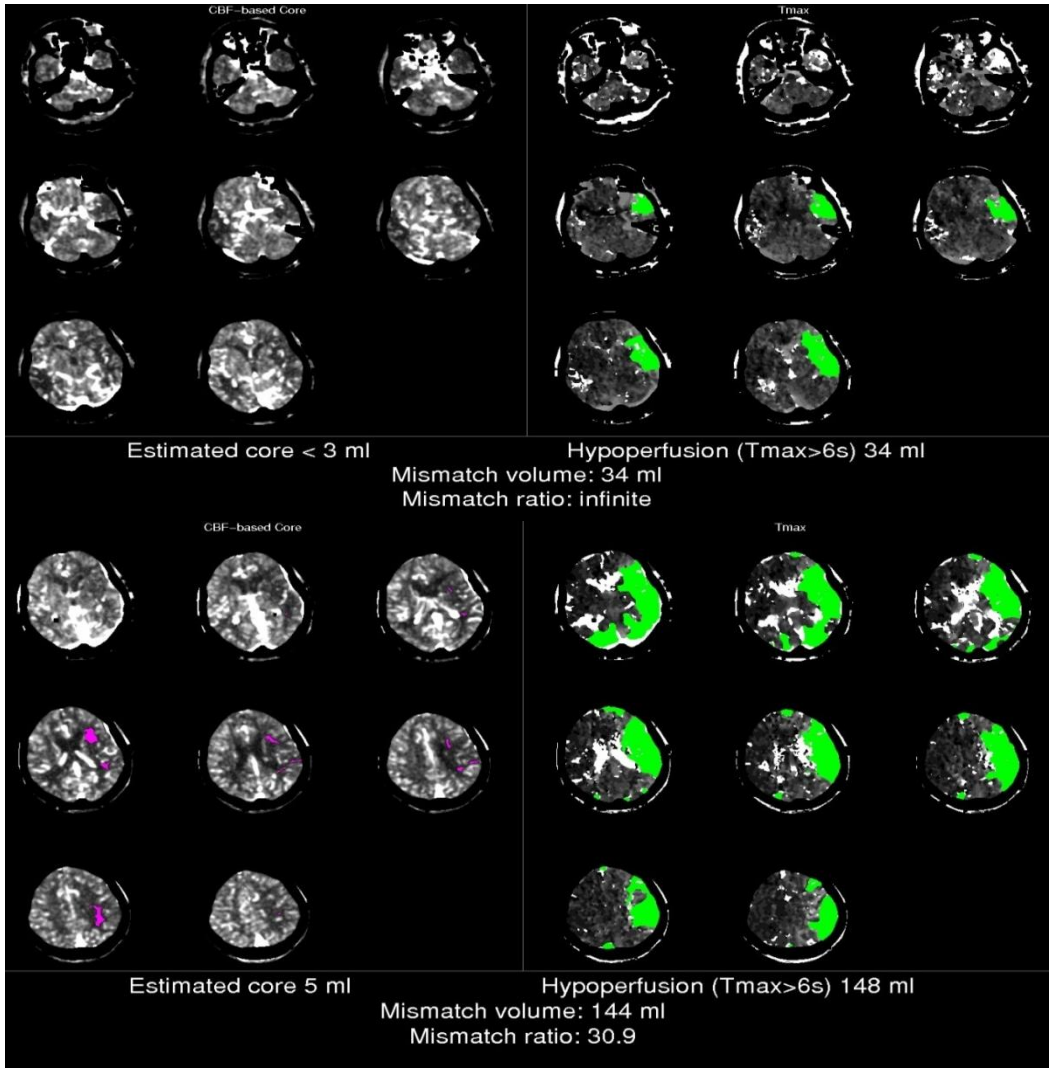
CTP RAPID Output - Core Volume 5 cc's



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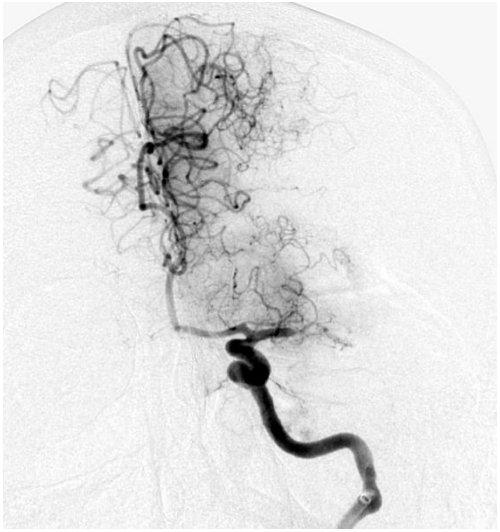
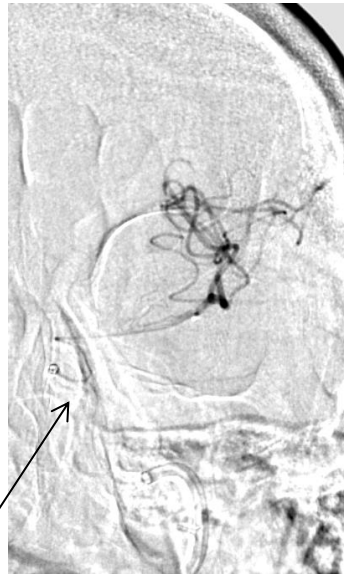
Case Details

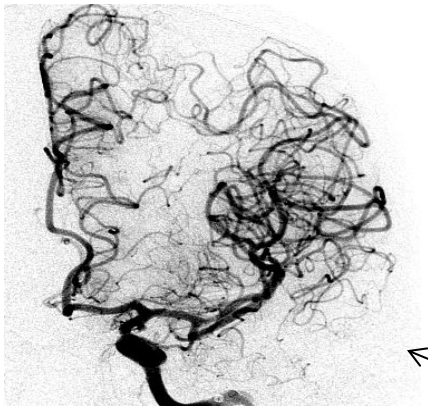


Groin puncture 11.05 am

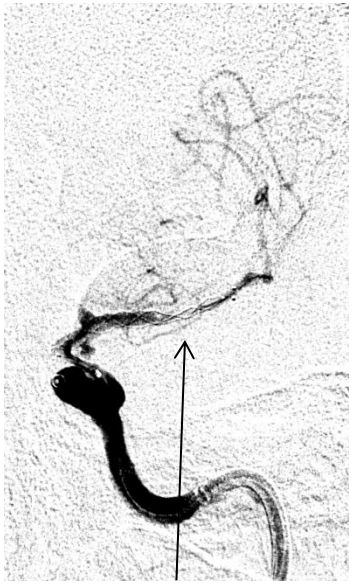
NeuronMax catheter in L ICA 11.15 am

.72 Navien + 18L in terminal ICA –MCA 11.20 am





Groin puncture to Reperfusion – 20 min



Trevo XP ProVue across clot 11.23 am

Stentriever and Manual Aspiration Thrombectomy (SMAT) with 0.72 Navien in MCA 11.24 am

TICI 3 11.25 am

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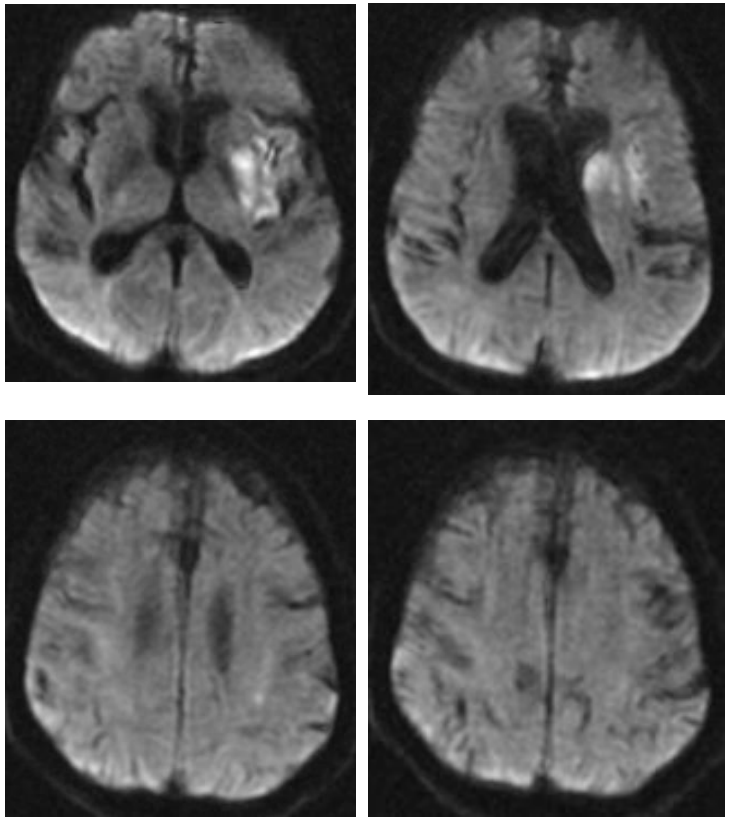
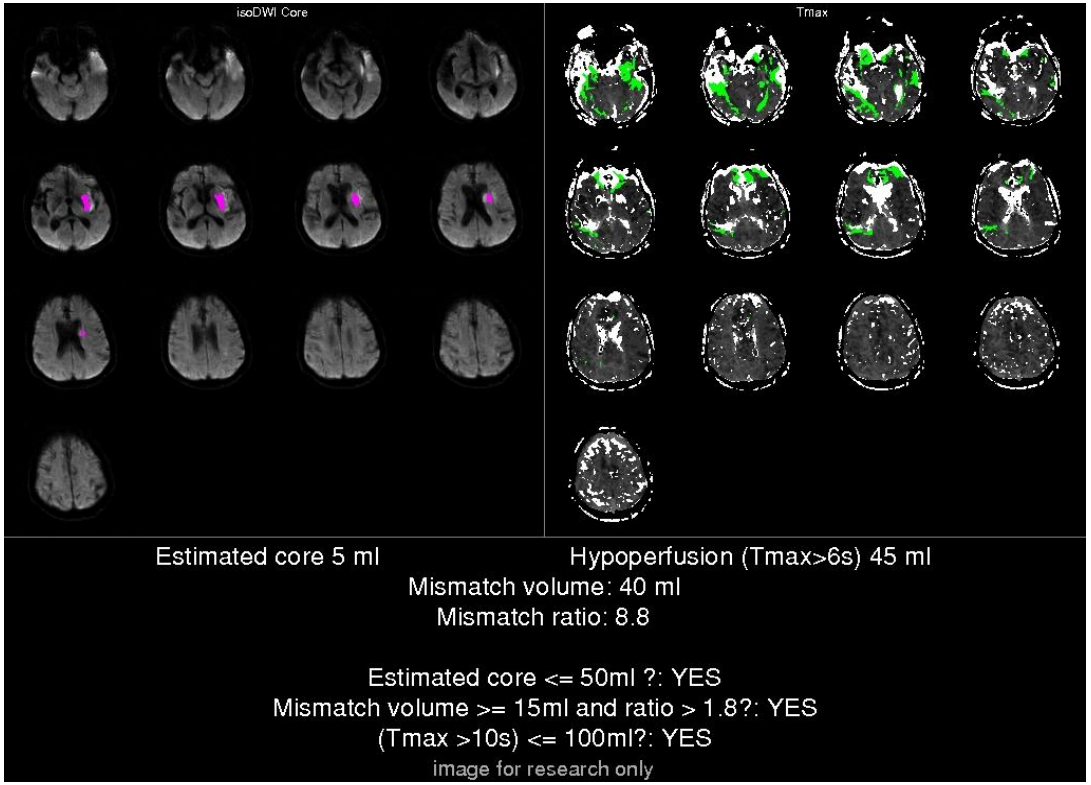
Acute Outcomes





- Final infarct volume: 11 cc
- 24 hour NIHSS = 6

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Case # 2 – Late Presenting Stroke

- 63 year old man
- History of HTN, H. Chol and CAD
- Baseline NIHSS =12
- Left ICA terminus occlusion
- 9.5 hours from onset to groin puncture
- Conscious sedation

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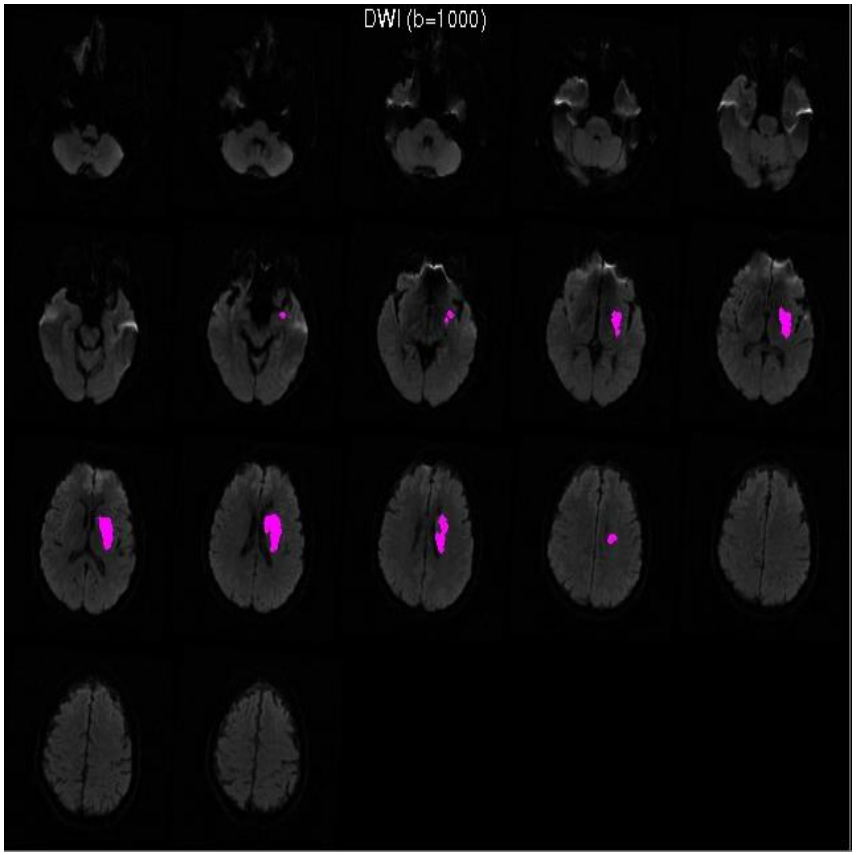
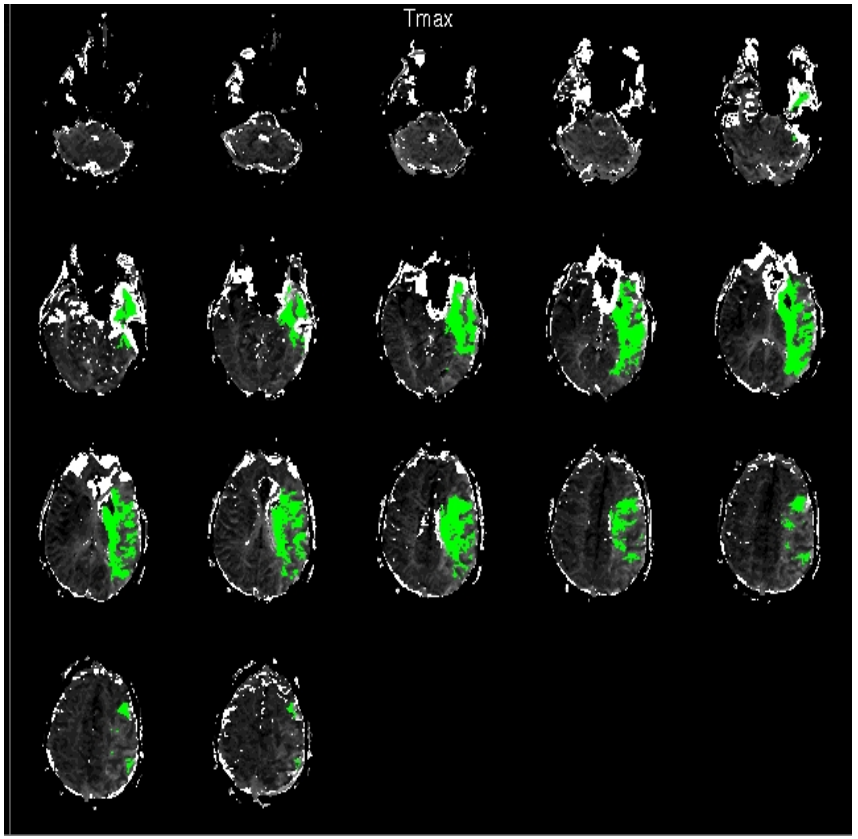
Baseline MRI – DEFUSE protocol





DWI lesion: 13 ccm PWI (Tmax>6s) lesion: 89 ccm
Mismatch ratio: 6.9

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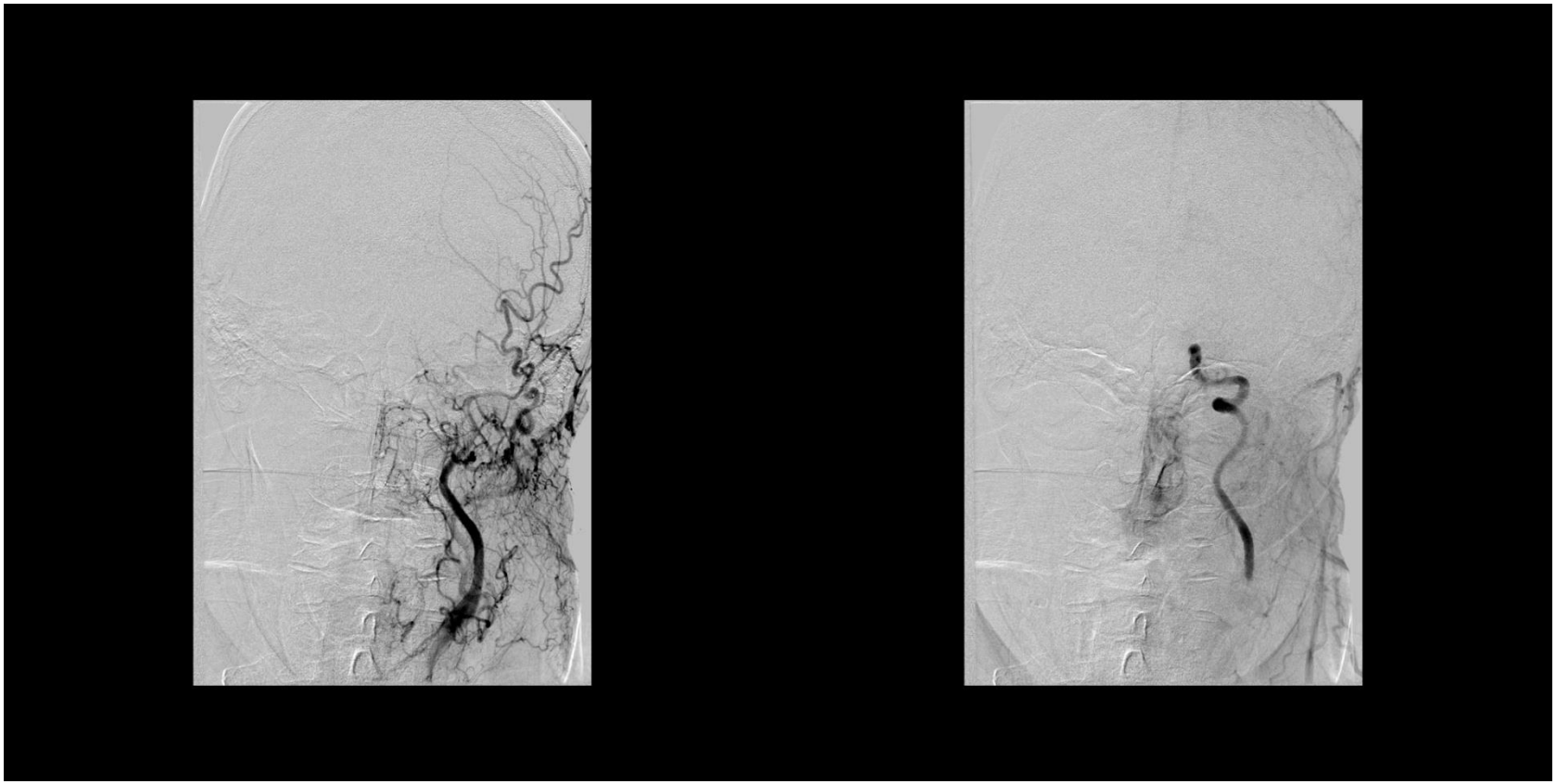
Baseline Angiograms



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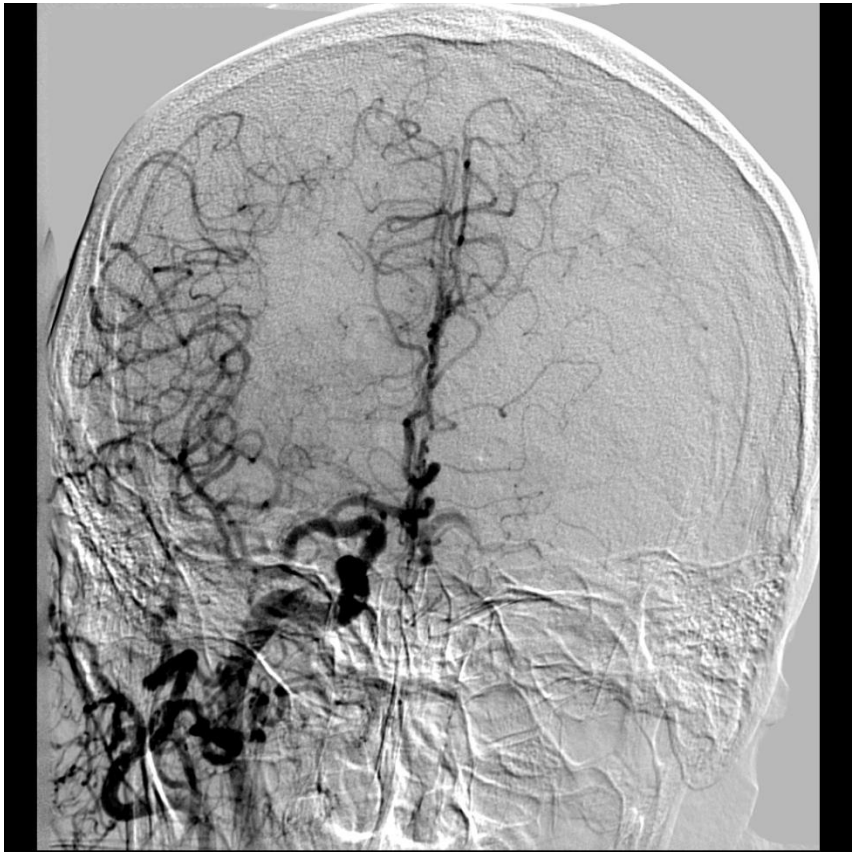
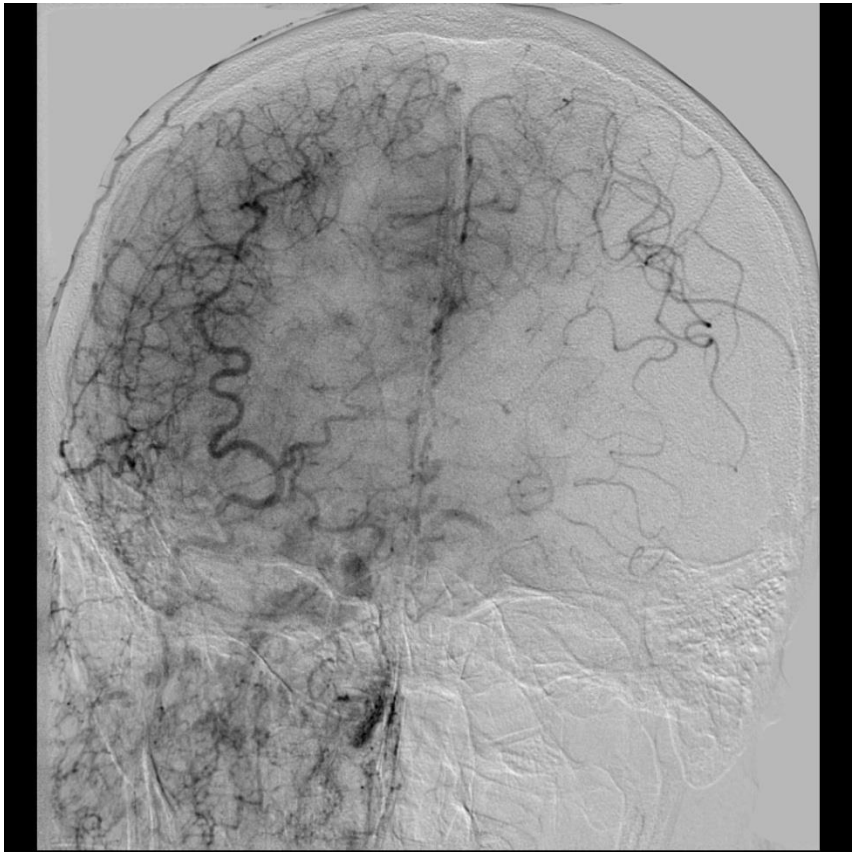
Collaterals





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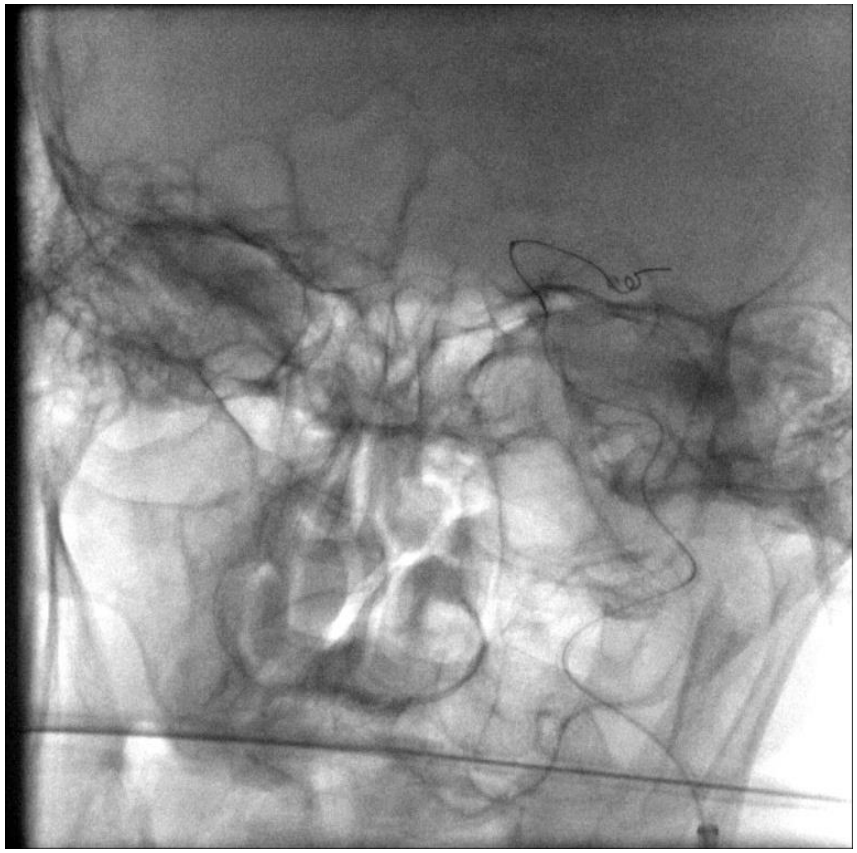
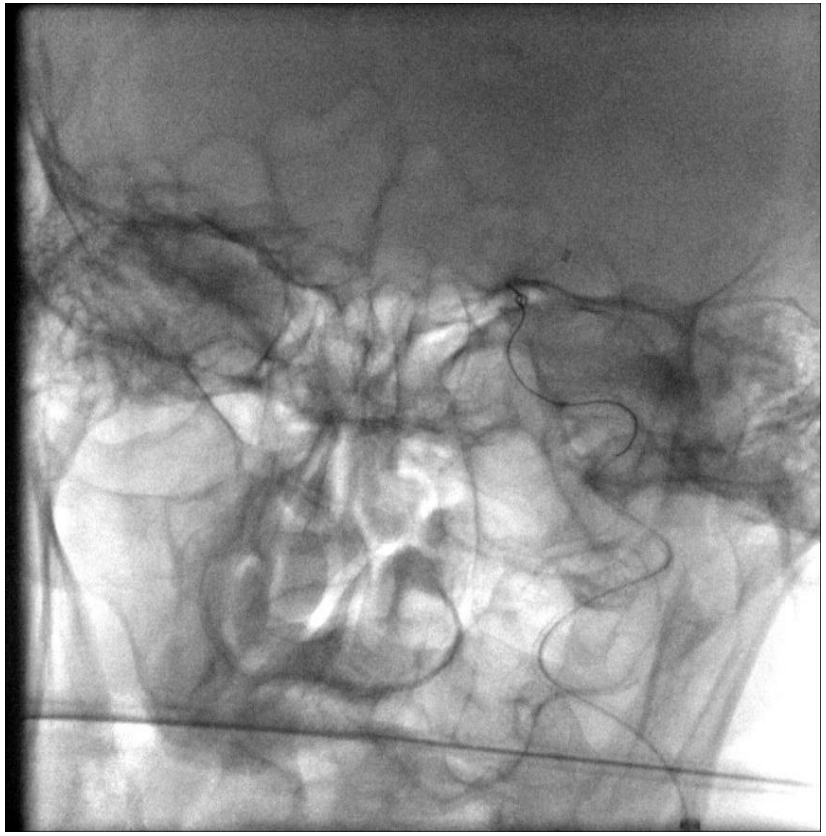
Manual Aspiration + Merci





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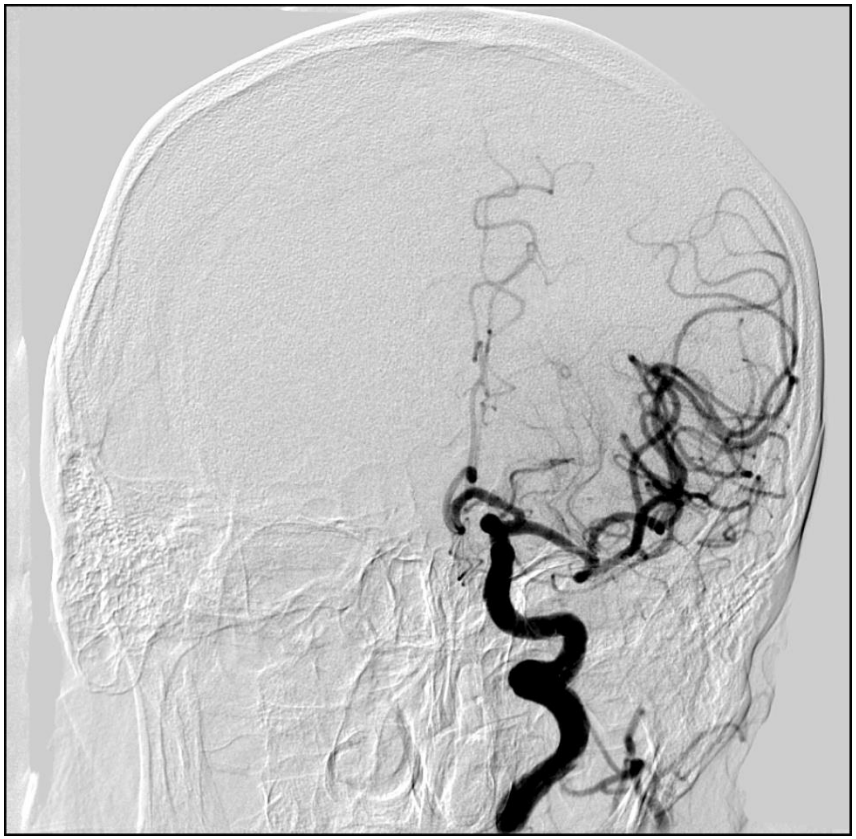
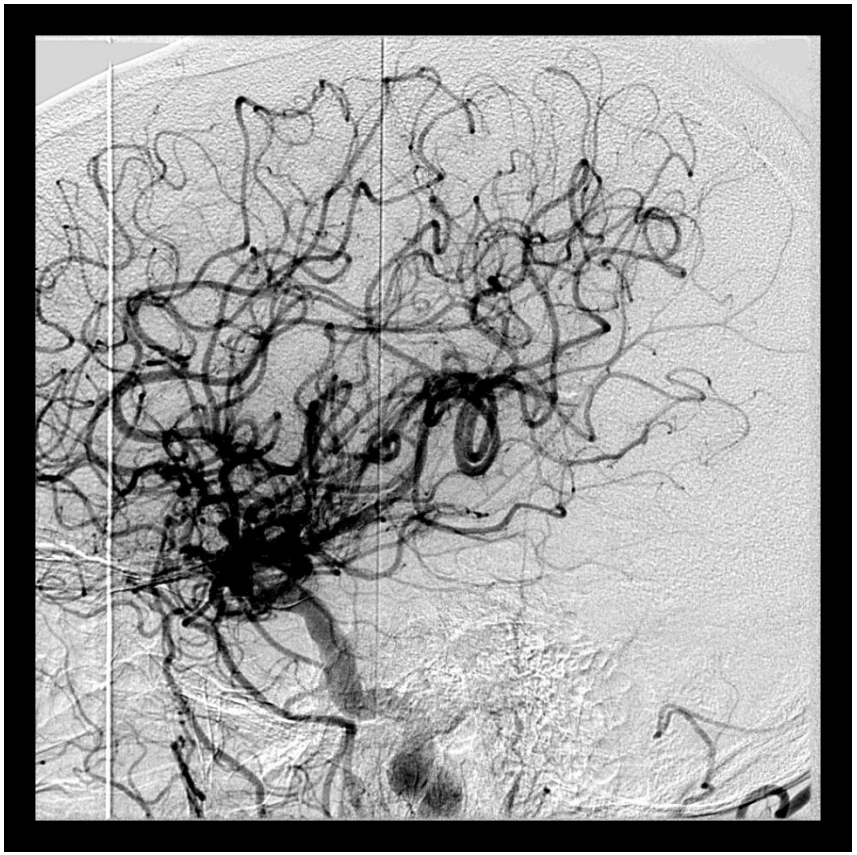
Final Angiogram





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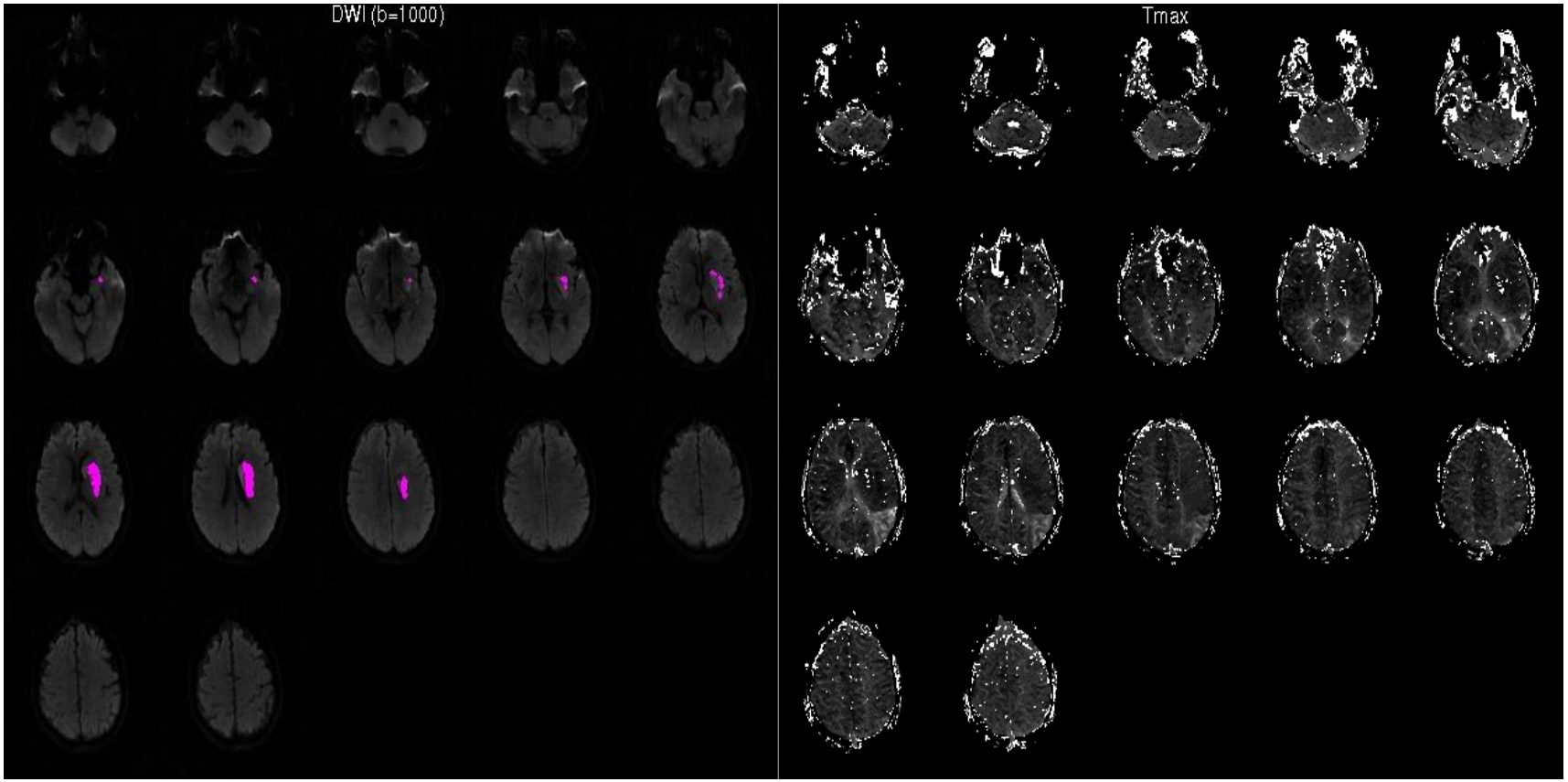
Acute Outcomes



DWI lesion: 8 ccm PWI (Tmax>6s) lesion: <3 ccm
Mismatch ratio: 0.0

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Clinical Outcome & Summary

- Small BG Infarct
- Discharged to home on day 2
- NIHSS 2 at the time of discharge

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Is there a difference in outcomes or safety in wake-up stroke versus witnessed onset stroke treated beyond 8 hours of TLSW?

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Beyond 8 hours of TLSW – Anterior Circulation Occlusions

- Total 130
  - WUS (39%, n=51)
  - Non WUS (61%, n=79)
    - Patients with witnessed onset beyond 8hrs from TLSW (55%, n=72)
    - Patients without witnessed onset but TLSW>8hrs (5%, n=7)

Aghaebrahim et al., ISC 2012

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Baseline Characteristics

Variable	Median (IQR)
Age	64 (19-89)
NIHSS	14 (4-25)
Time to procedure (hrs)	11 (8-97)

Variable	N (%)
N	130
Wake up stroke	51 (39)
Witnessed beyond 8hrs	72 (55)
Unknown time*	7 (5)
Male	72 (55)
Hypertension	88 (67)
CAD	28 (22)
DM	22 (16)
Atrial Fibrillation	29 (22)
Smoking	43 (36)
Hyperlipidemia	38 (30)

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Procedural Data

Variable	N (%)
Occlusion Location	
M1	73 (56)
M2	15 (19)
ICAT	32 (42)
IV tPA	16 (12)
IA lytic (t-PA, urokinase, retevase)	51 (39)
Merci	99 (76)
Penumbra	30 (23)

Aghaebrahim et al., ISC 2012

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Outcomes

Variable	N (%)
Successful Recanalization (TIMI 2or 3)	109 (84)
Favorable outcome in 3 month (mRS ≤ 2)	68/128 (53)
Symptomatic Hemorrhage (PH-1 or 2)	15 (11.5)
3 month mortality	22/128 (17)

Aghaebrahim et al., ISC 2012

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Outcomes

Variable	Median
Pre infarct volume, mL	20
Final infarct volume, mL	74
Infarct growth, mL	54

Aghaebrahim et al., ISC 2012

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WUS versus Non WUS Results

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Aghaebrahim et al., ISC 2012

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Clinical Outcome

Variable	WUS	Non WUS TLSW >8hrs
Successful Recanalization	83%	85%
Favorable Outcome at 3 months (mRS $\leq$ 2)	46% (n= 23)	57.7% (n= 45)
sICH (any PH)	13.7 % (n=7)	10.1% (n=8)
3 month mortality	18.8% (n=9)	17.1% (n=13)

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Imaging Characteristics

Variable	WUS	Non WUS TLSW > 8 hrs
Pre Infarct volume, ml (mean)	20	19
Final infarct volume, mL (mean)	82	68
Change in infarct volume, ml (mean)	62	49

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Results

- Predictors of good outcome (Multivariate logistic regression model)
  - Successful recanalization (OR 13.7, p 0.006, CI 2.15-87.7)
  - Final infarct volume (OR 0.9, p 0.003, CI 0.97-0.99)
  - Mode of presentation (WUS vs witnessed onset) not a significant predictor in univariate or multivariate analysis

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Results

- No difference in favorable outcome rates amongst WUS vs non WUS groups
- No difference between groups regarding symptomatic hemorrhage or mortality at 3 months

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Conclusion

Clinical outcomes following endovascular treatment in patients with anterior circulation occlusion presenting beyond 8 hours of TLSW do not seem to differ according to mode of presentation relative to TLSW (WUS vs non WUS)

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Discussion and Q & A

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Discussion Points

- Screening:
  - % WUS vs late presenting?
  - % < 12 hrs vs > 12 hrs?
  - current patient/referral base and/or planned outreach?
- Randomizing:
  - RAPID software installation/ use?
  - Patient flow and anticipated Screen Fail rates/reasons?
  - IVRS/IWRS system & EDC (InForm) – experience?
- Follow up:
  - Obtaining 24 hr imaging for vessel patency / hemorrhage and core infarct in ALL subjects?
  - mRS at Day 7-10 or D/C, 30 and 90 days done by a blinded, evaluator for ALL cases?

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Gracias

Danke

Merci

¡

Thank you!

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