Trattamento endovascolare dell'ictus ischemico cerebrale in fase acuta

RELAZIONE FARMACI e DEVICE Nelle COMPLICANZE EMORRAGICHE

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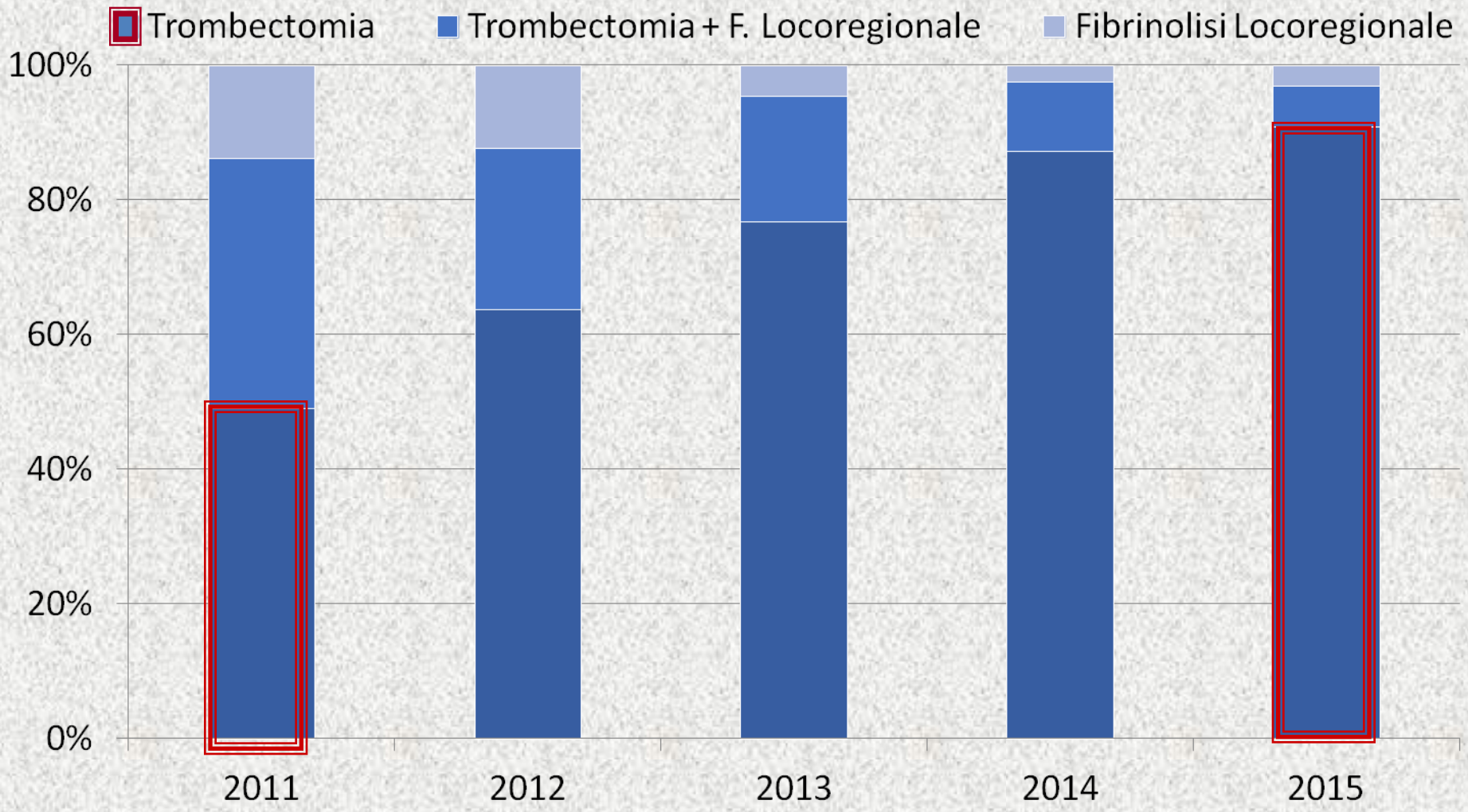
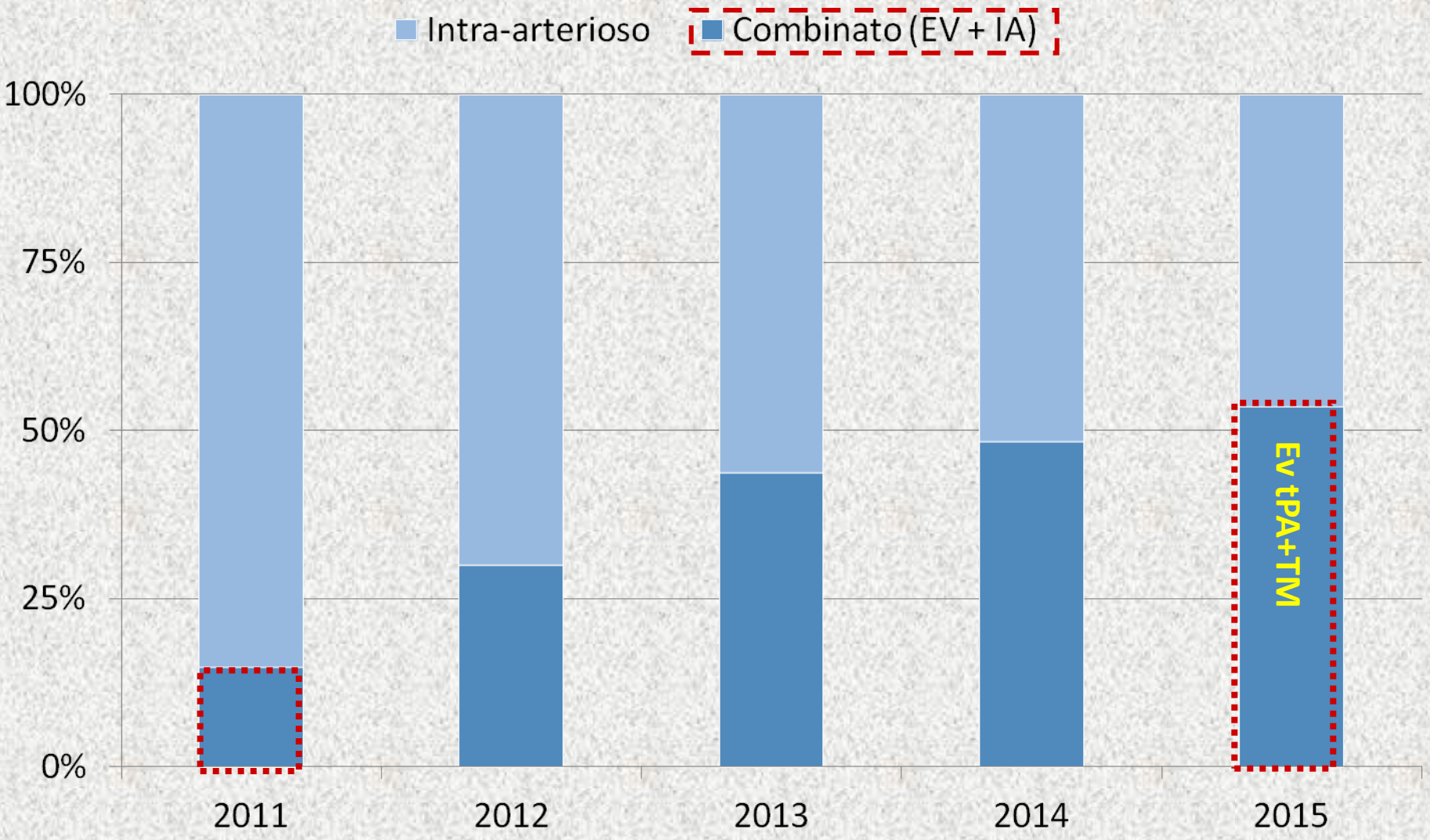
Treatment modality



Combined treatment



Does it make sense to speak about drugs when all endovascular treatments are based on «mechanical» procedures?

Yes ..for two reasons

- The **pharmacologic action** (anticoagulant, fibrionolityc or antiaggregant) will go on after the recanalization of the occluded artery and it will **extend differently during the phase of the cerebral reperfusion.**

- During the immediate recanaliztion , a **modifcation of the coagulative and platelet setting** may increase the natural risk of hemorrhagic conversion

To reduce the hemorragic conversion it is important

1) to know the pharmaco dynamic and effects of the drugs on board at the moment of the endovascilar interventison

2) to definy the hemoragic profile of each patients

To reduce the hemorragic conversion it is important

1) to know the pharmaco dynamic and pharmacological effects of the drugs on board at the moment of the endovascilar interventison

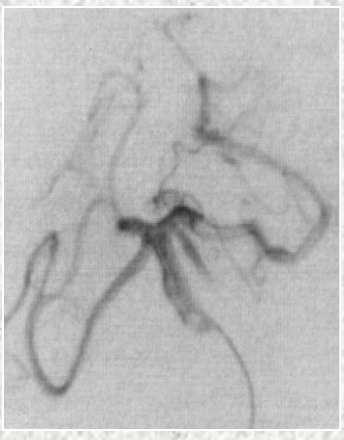
- Heparine
- Fibrinolytics
- Antiplatelet

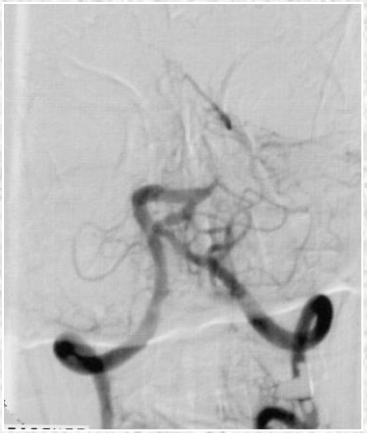
- Action on coagulation
- Action on microcirculation
- Action on BBE

- Fibrinolytics work slowly (UK, rTPA)
- Could be accompained by procoagulant activity (retro-thrombosis)
- Not very efficient on microcirculation: (local PAI-1 activation)
- May induce pro-inflammatory response if administrated too late

Resistance to fibrinolytics

During fibrinolysis (rtPA,UK) the clot releases
Fibrinogen Trombine -Fragments
Resistent to AT III (heparin)
that activate the coaugulation cascade and PTL (fbg-Fibrina), with reorganization of the thrombus

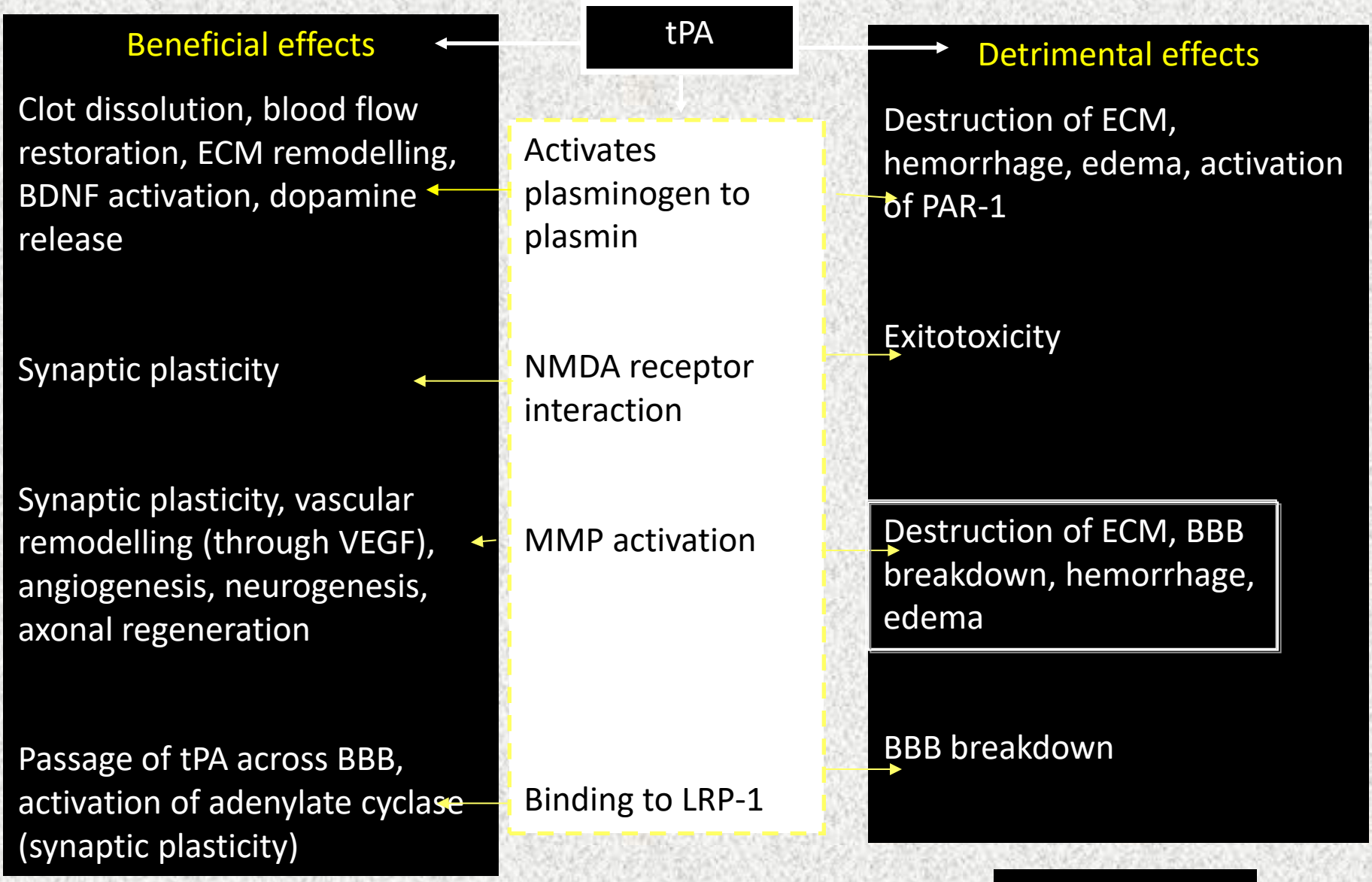




Retrothrombosis

- Platelet's activation
- New thrombin generation
- New production of PAI-1
- Thrombin binding to the thrombus increases the *reaction* of fibrinogen to fibrin!

Pleiotropic actions of tPA



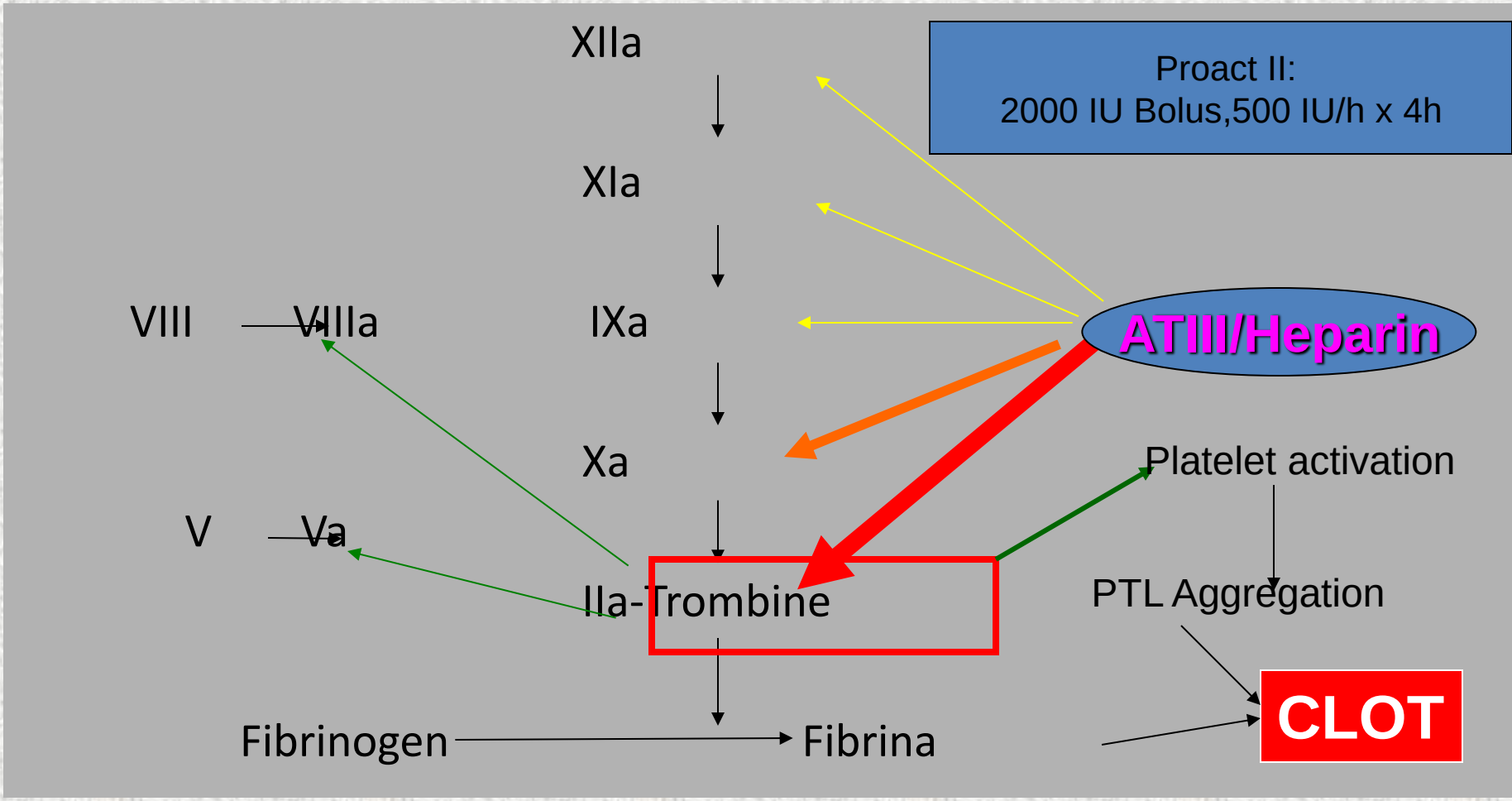
Adibathia, 2008

Heparine

- Heparine reduces the production of thrombine and the platelets activation
- Stops generation of a new fresh clot
- It is useful to avoid the progression of thrombosis and re-occlusion of a partially re-opened artery (retrothrombosis)

Increases the recanalization rate after IA fibrinolisys

Administration of Heparin at high dosage * and fibrinolytics increases bleeding risk (SIH)



* High dose:100 IU/kg bolus,1000IU /h x 4h

Hemorrage vs heparine

Heparine		N	Hemorr 24h	symptom	Hemorr 90 days	Hemorr symptom
High	proUK	11	72%	27%	72%	27.3%
	Placeb	5	20%	20%	40%	20%
Low	Pro-uk	15	20%	6.7%	33%	6.7%
	placeb	9	0%	0	33%	11.1%
Total	prouk	26	42,3%	15.4%	50%	15.4 %
	placeb	14	7%	7.1%	35.7%	14.3%

G.J del Zoppo "Proact :a phase II randomized Trial of Recombinant Pro-Urokinase by Direct Arterial Delivery in acute Middle Cerebral Artery Stroke **(Stroke,1998;29:4-11)**

- No Heparine infusion for 24 h after IAT (except patients with on-going AF and atrial thrombus)

Take home message

- The i.v. administration of heparine during the procedures of thrombectomy should be minimised

  (either Guiding Catheter Flushed with 5000 UI in 1 L or bolus of 2000 UI at the beginning of the procedure

GPIIbIIIa inhibitors

GP IIbIIIa Inhibitors

CLOT

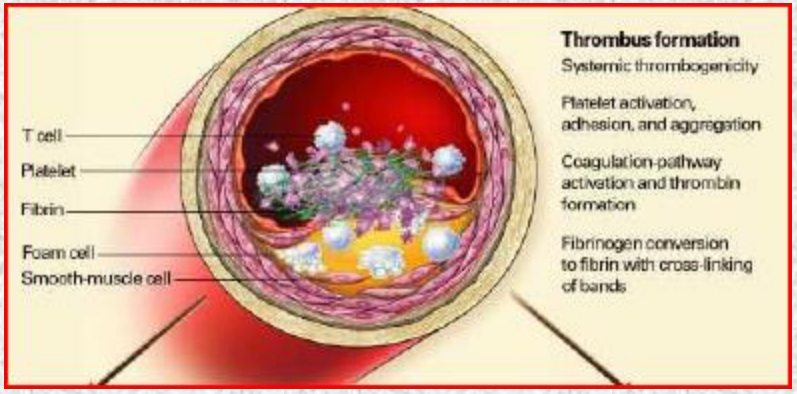
PTL

FIBRINE

THROMBINE

UK rtPA

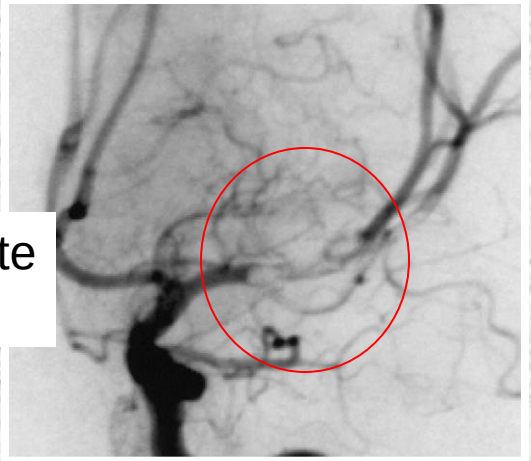
Platelet activation



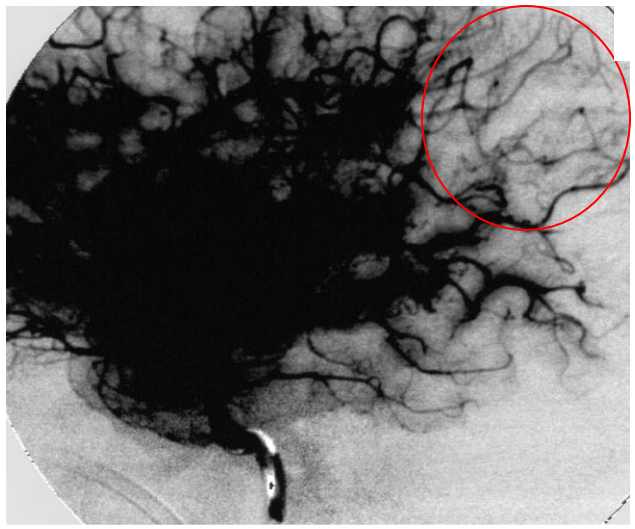
GP IIb/IIIA receptor inhibitors

Reduce new clot generation blocking the PTL-FBN aggregation
Increase the efficacy of IA thrombolysis (de-thrombosis):
Reduce local production of PAI-1
Reduce changing in PTL Phosfolipid membrane :cofactor for thrombine production

- Platelet disaggregation
- Enhancement of clot lysis



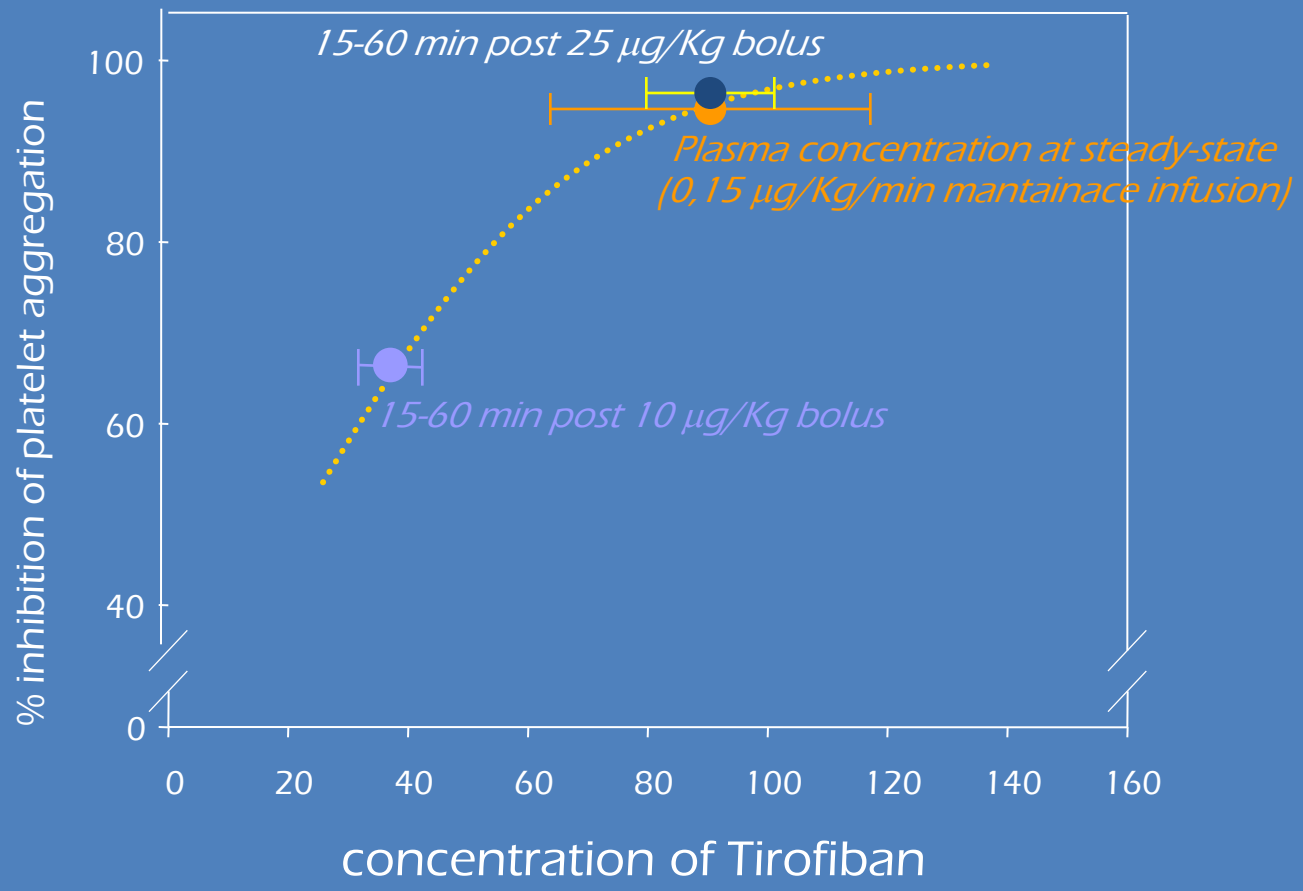
Increased recanalization rate
reduced distal embolization



- Viscosity reduction
- Decrease of endothelial PAI-1 release
- Inhibition of PTL/PMN interactions

Effect on patency of microcirculation of the Infarcted zone

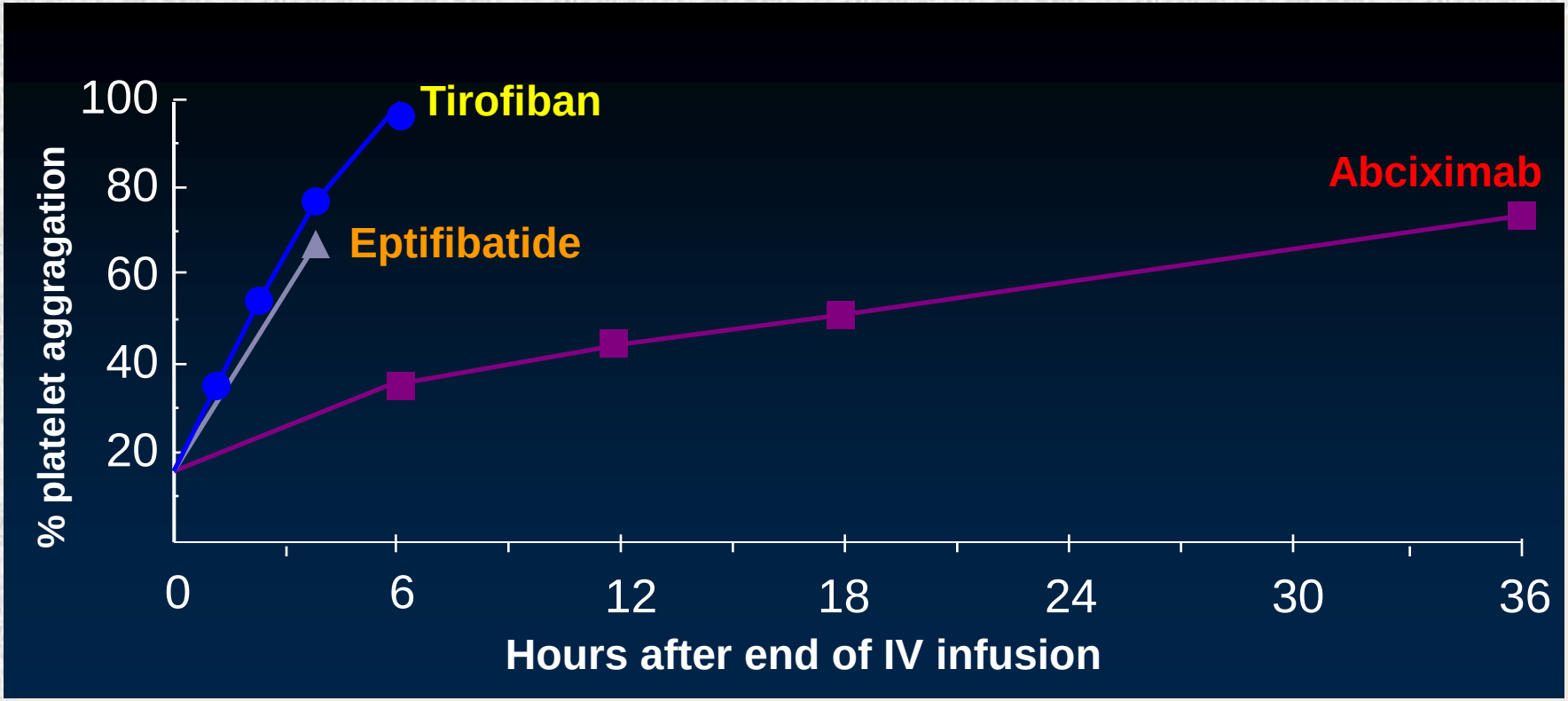
Early platelet inhibition - Pharmacokinetics of Tirofiban -



Schneider, Am J Card 2003

Antagonists of the Gp IIb/IIIa

farmacokinetics



Mousa et al. Drugs Future 1996;21: 1141-54

Gp IIb-IIIa Inhibitors

Cardiologic Protocol

- **ABICIXIMAB (Reopro)** :
- 025,mg/Kg rapid bolus (1min.) followed by IV continous infusion (0,125 microgr./Kg/min for 12 h post-Procedure.
- **EPTIFIBATIDE (Integrilin):**
- double IV bolus of 180-microg/Kg after 10 min + IV infusion of 2-microg/Kg/min.for 18-24 h.
- **TIROFIBAN (Aggrastat):**
- IV bolus di 10 microg/Kg in 3 min.+ infusion 0,15 microg/Kg/min. per 18-24 h.

Normalization of bleeding time: 3-4 hours after end of IV infusion of INTEGRILIN and AGROSTAT,12h end of REOPRO infusion

Neuro-interventional protocol
IV Bolus of Tirofiban (2/3 total dose) in 3 min
IV infusion (1/2 dose depending on weight no longer than 6 hours)
Use only in case of stent deplyment

To reduce the hemorragic conversion it is important

2) to definy the hemoragic profile of each patients

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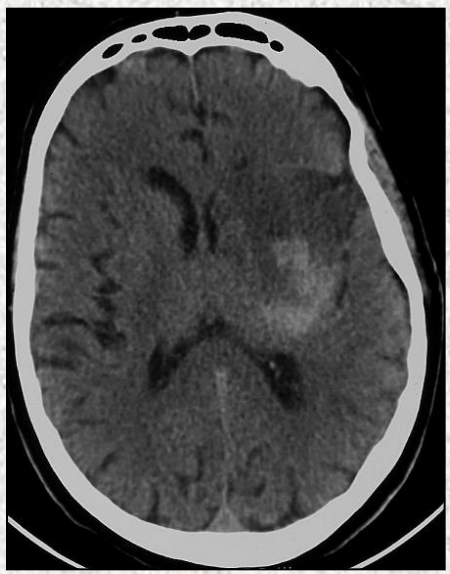
- **Indivdual factors** (microcirculation leuocoaraiosis, anticogulants INR)
- Age, Hypertension

- **Perfusional profile**

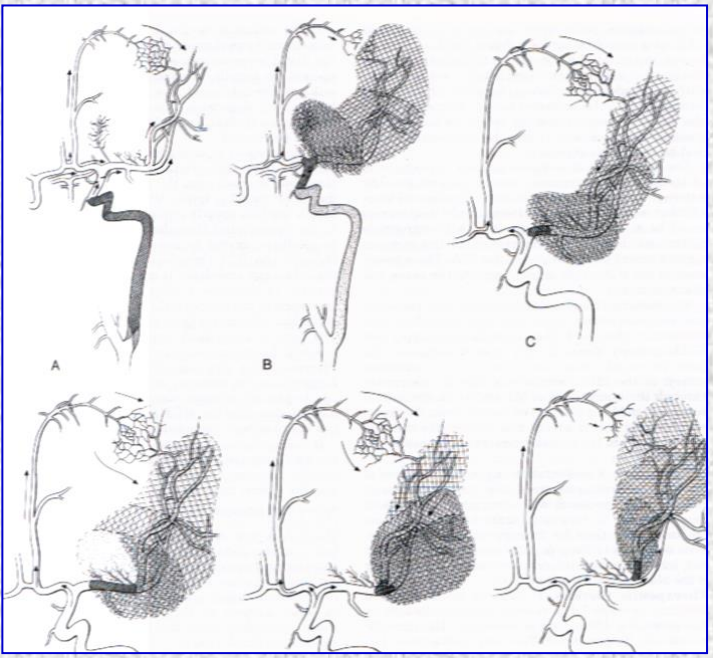
The grade of cerebral hypoperfusion and the status of the microcirculation at the moment of the recanalization

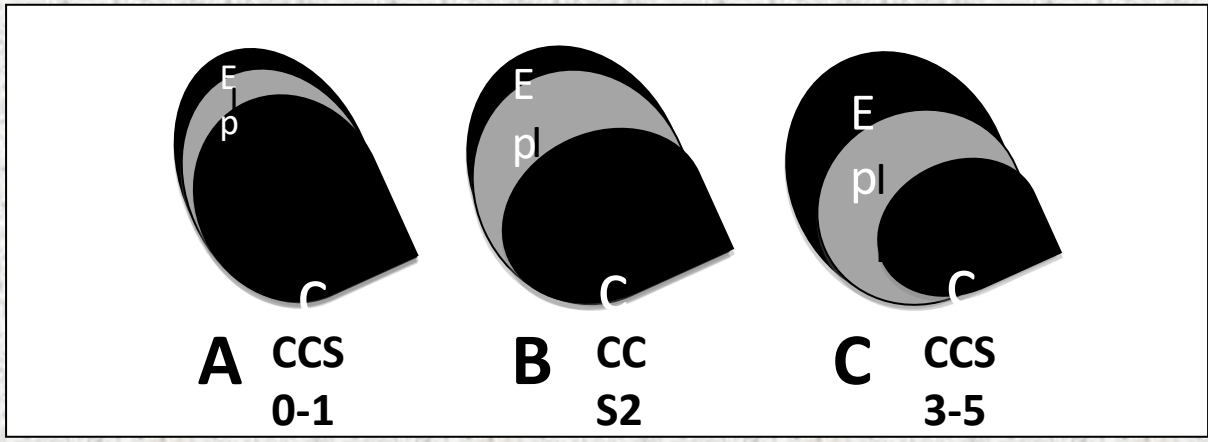
Cerebral hypoperfusion and hemorrhagic risk

- Patients with severe cerebral hypoperfusion may more easily associated with hemorrhagic conversion (symptomatic hemorrhage) following recanalization
- The hemorrhagic areas are localised within or at the periphery of the ischemic lesion and are realted to the development of the ischemia
- The hemorrhagic areas show an intense enhancement or contrast pooling after endovascular procedure, secondary to the rupture of the BEE



The **perfusional profile** of a patient is linked to the efficacy of the retrograde reperfusion through the microcirculation supported by pial anastomoses or the polygone of Willis





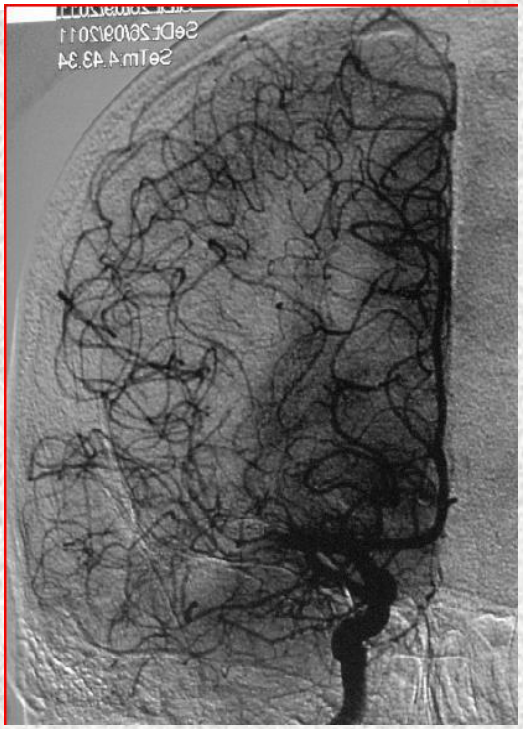
Site of occlusion

Correlation with core extension

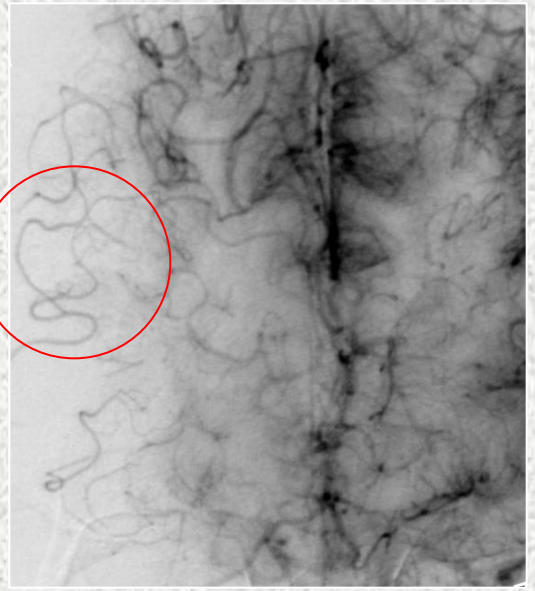
Effectiveness of the collateral circulation

Three different types of perfusional profiles

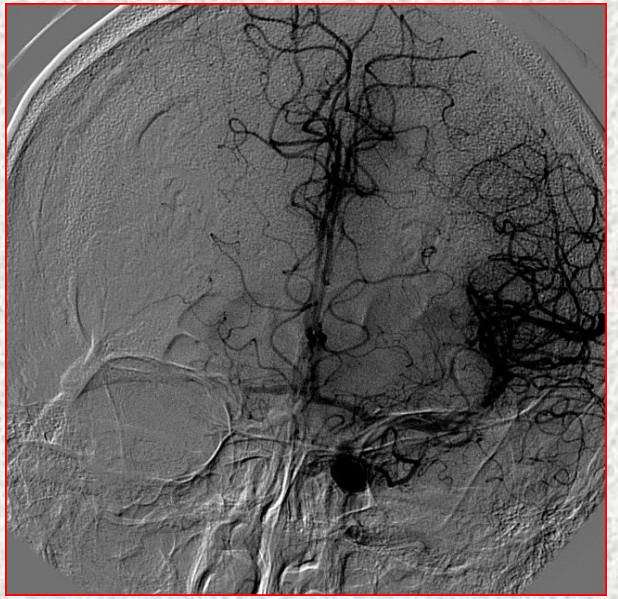
Type A: good collaterals



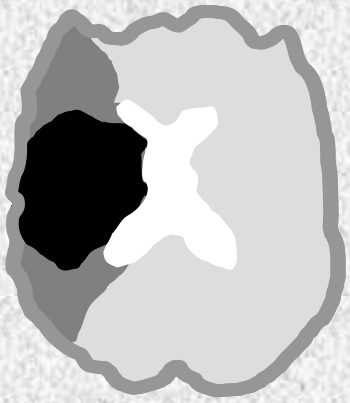
Type B: Poor collaterals

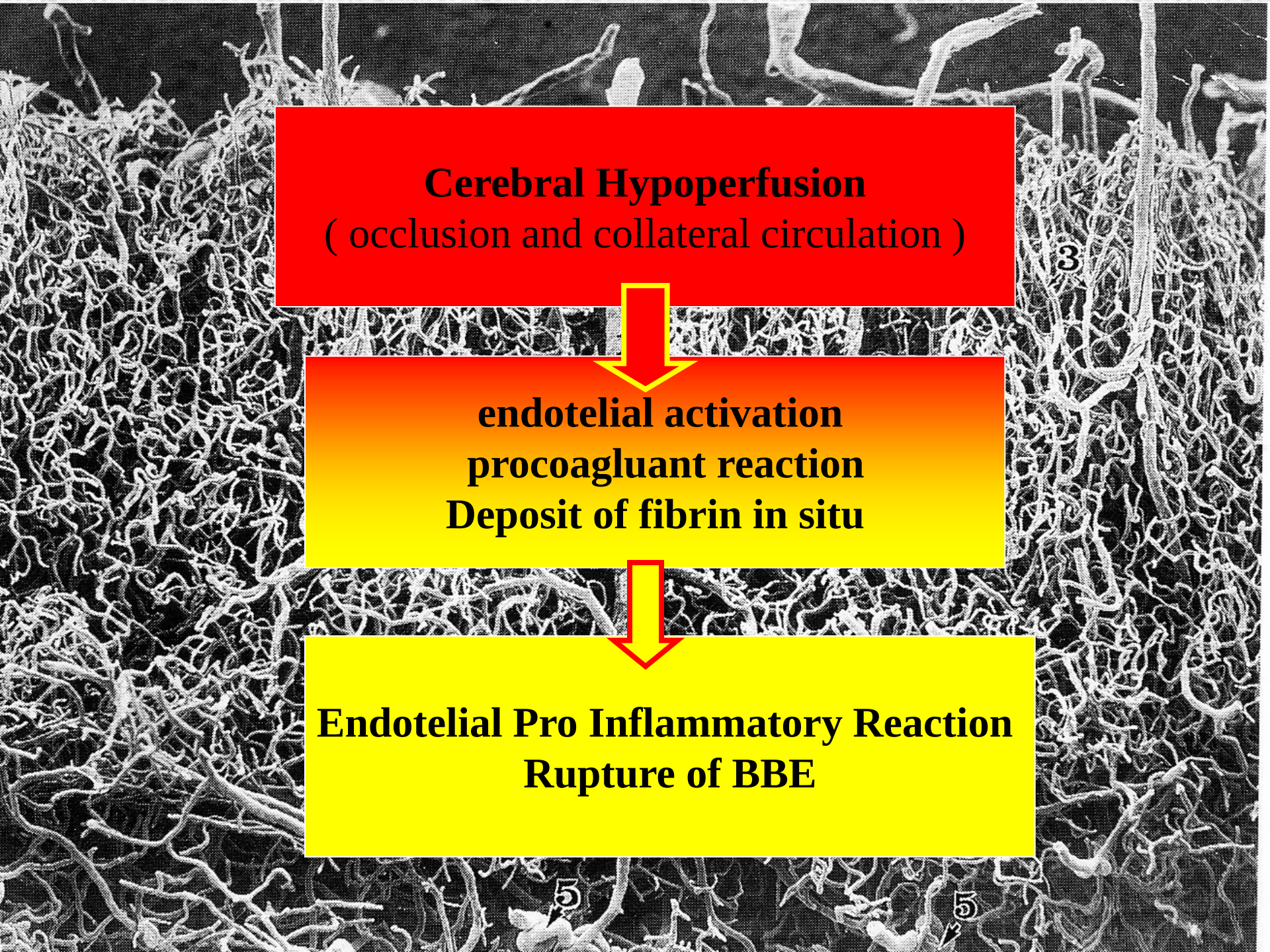


Type c: absent collaterals



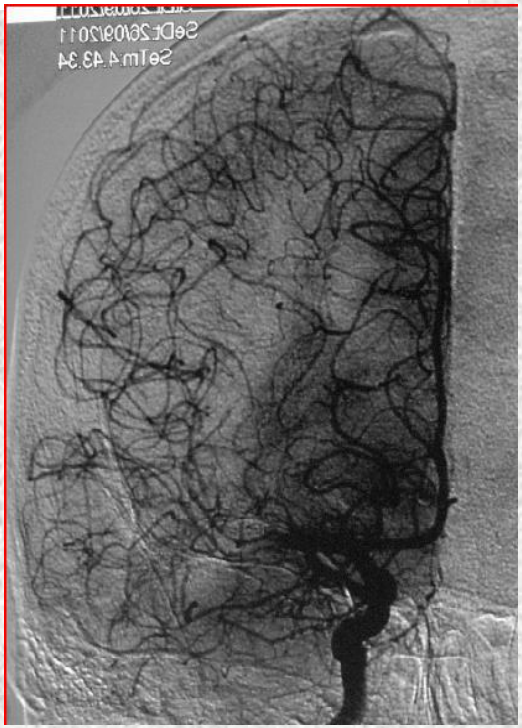
acute




Cerebral Hypoperfusion
(occlusion and collateral circulation)
endotelial activation
procoagluant reaction
Deposit of fibrin in situ
Endotelial Pro Inflammatory Reaction
Rupture of BBE

Three different types of perfusional profiles

Type A: good collaterals



acute

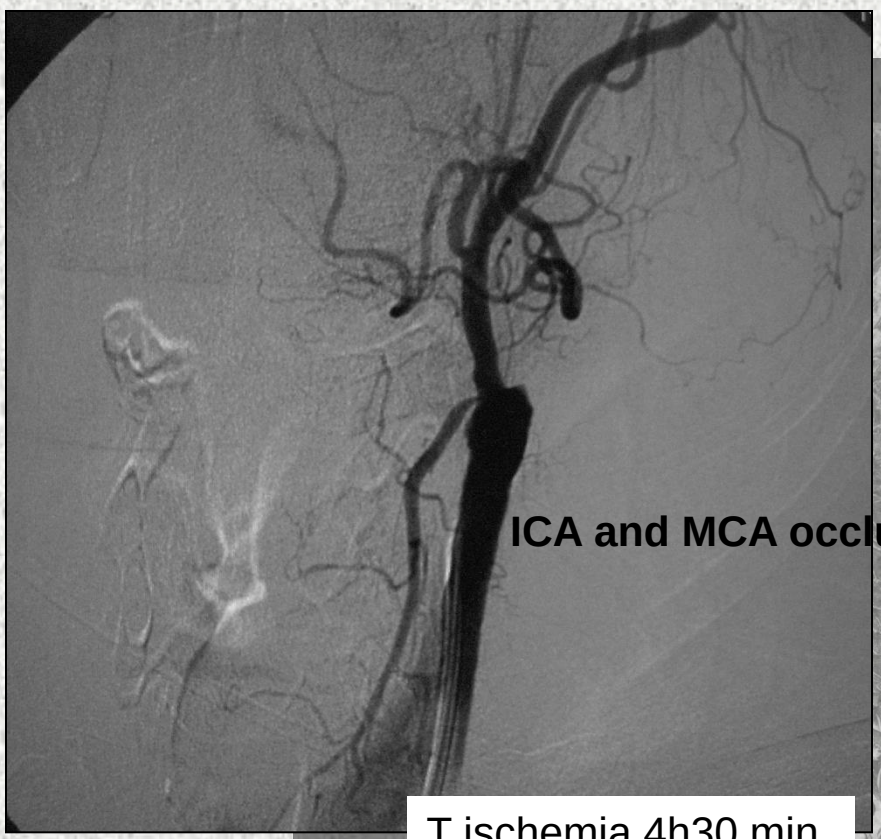
The retrograde perfusion by the microcirculation is effective to contrast the progression of the ischemic core and to preserve the stability of the BBB

The expansion of the ischemic core is probably slow (almost time-independent), possible treatment even beyond 6 hours

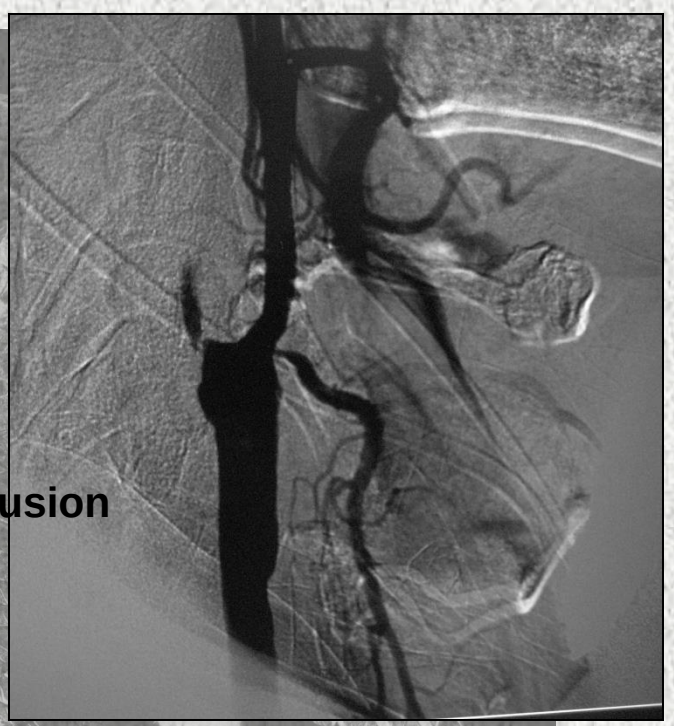
The alterations of the BBB are minimal

The risk of hemorrhagic conversion after efficient reperfusion is minimal

A good collateral perfusion (CCS 5-4) is a Predictor of good clinical outcome and low Risk of hemorrhagic conversion

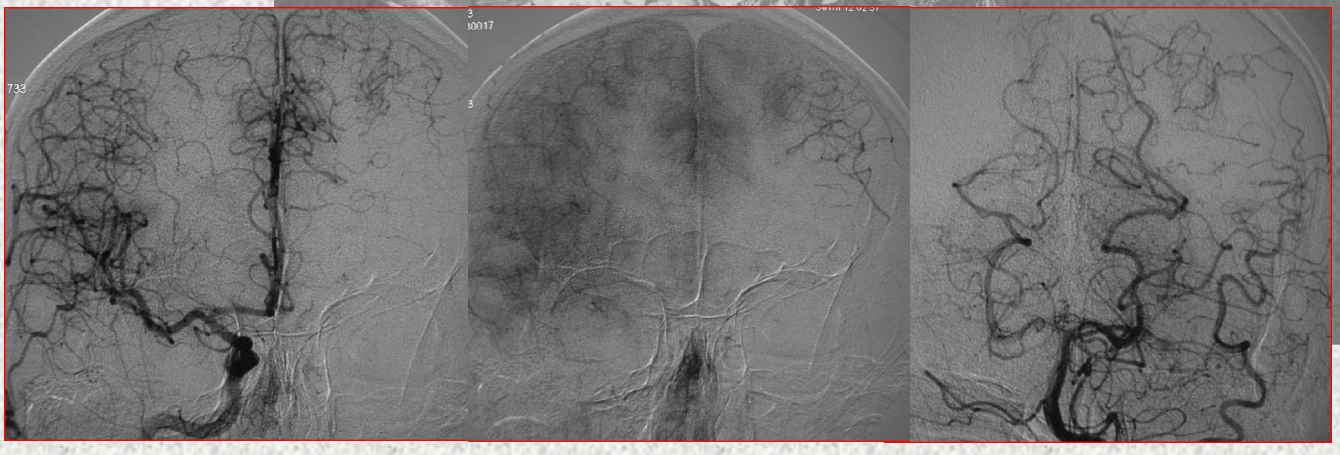


ICA and MCA occlusion

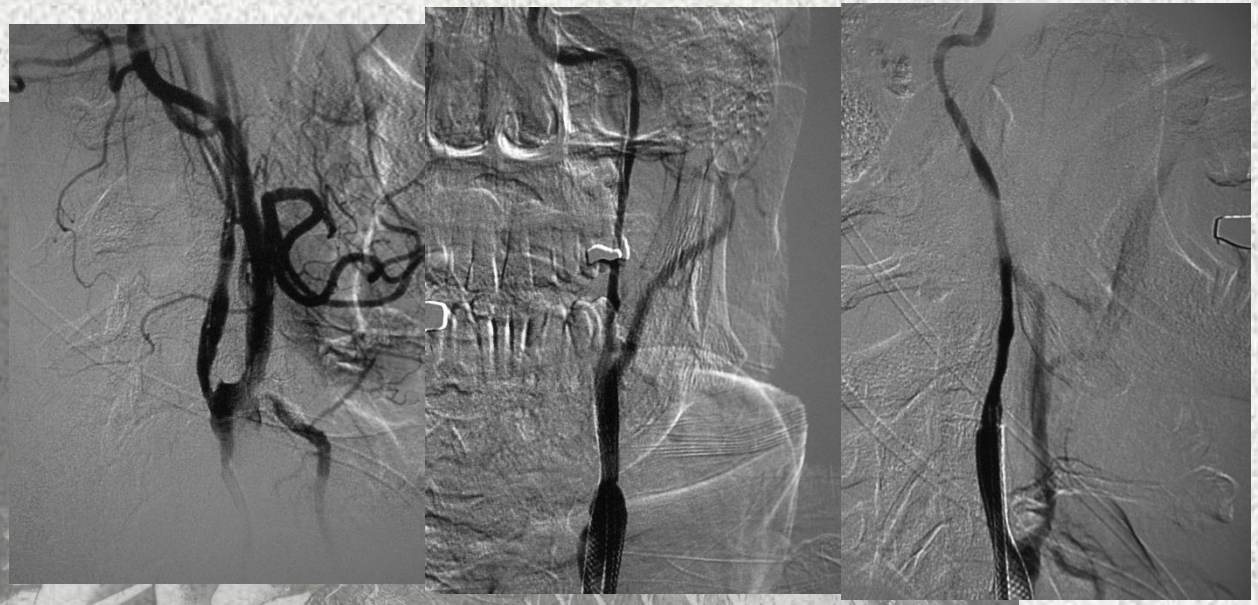


RESCUE

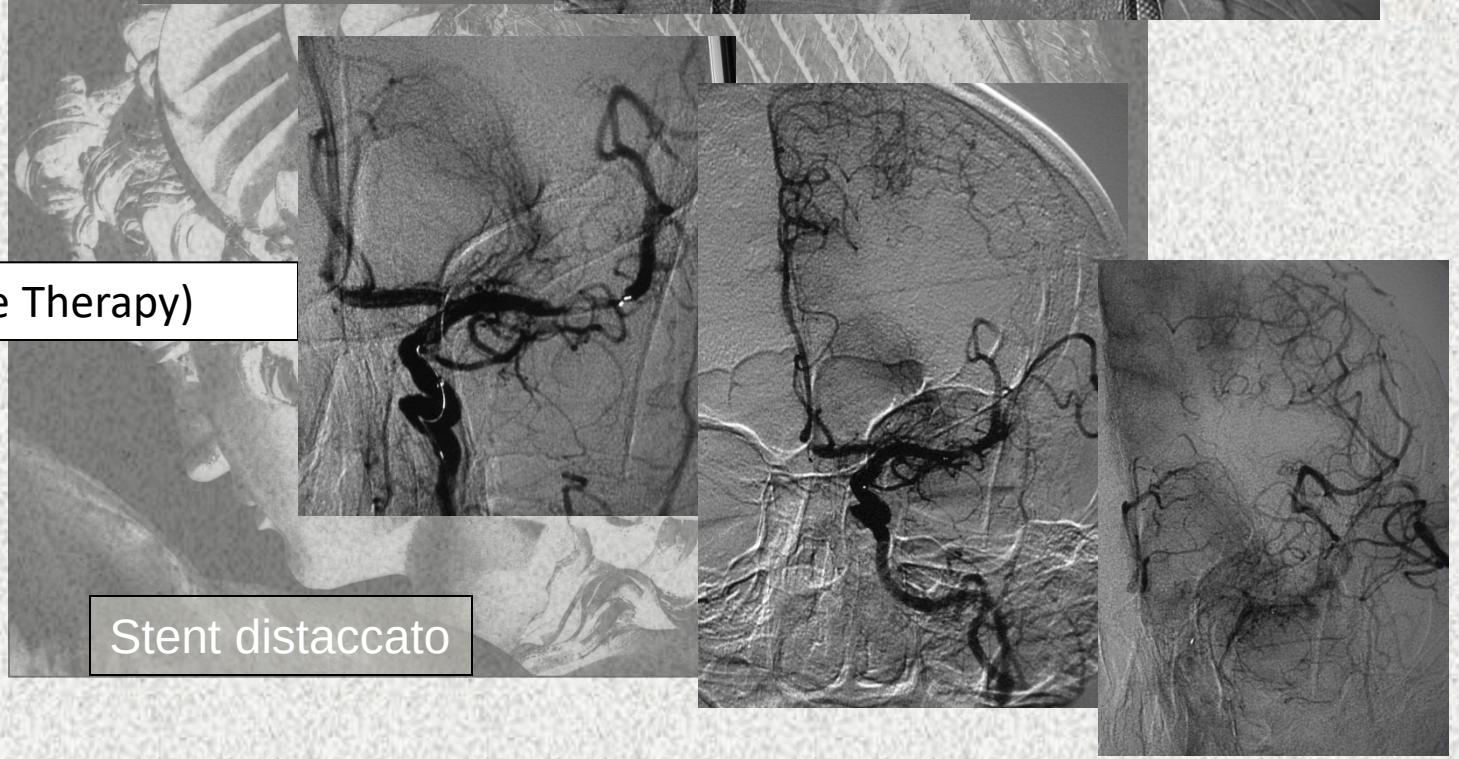
T ischemia 4h30 min



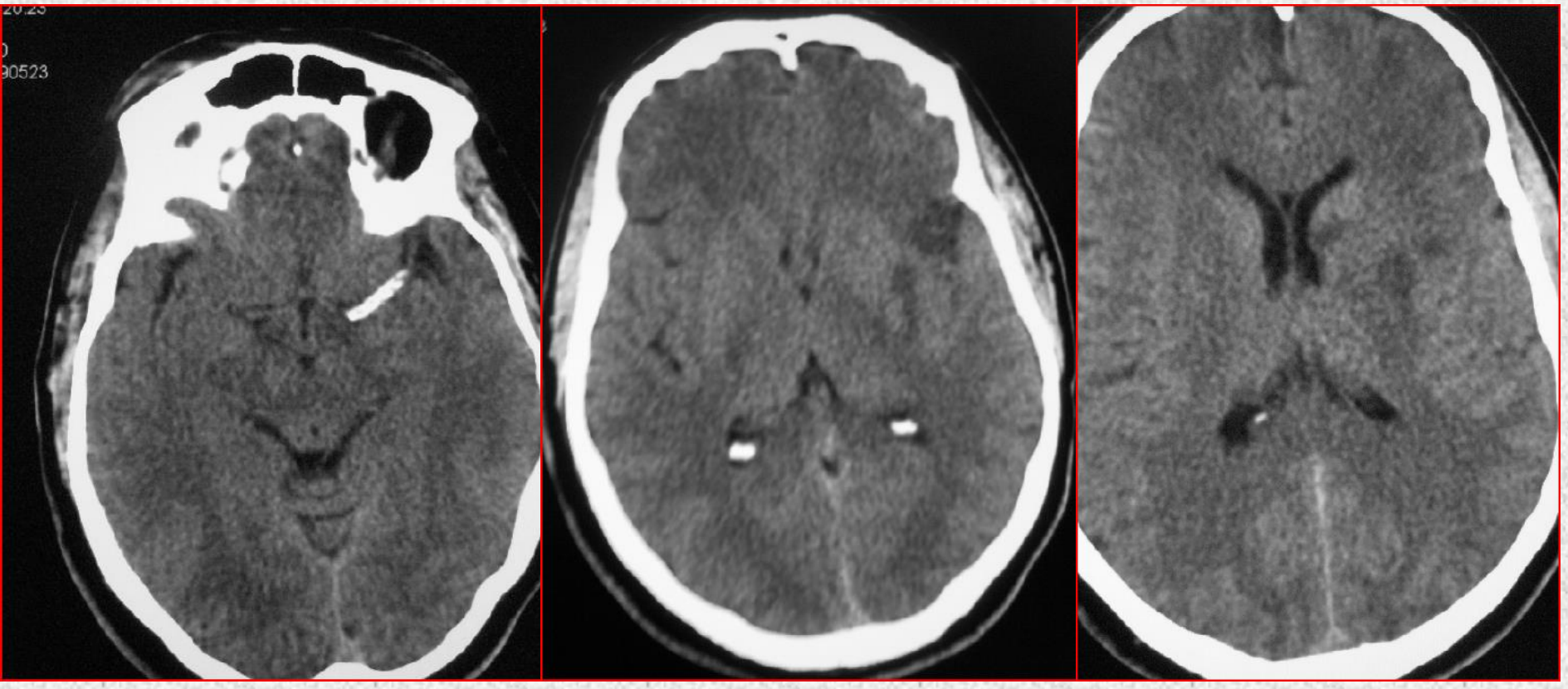
Carotid Wall Stent



Solitaire 4x20 (Rescue Therapy)

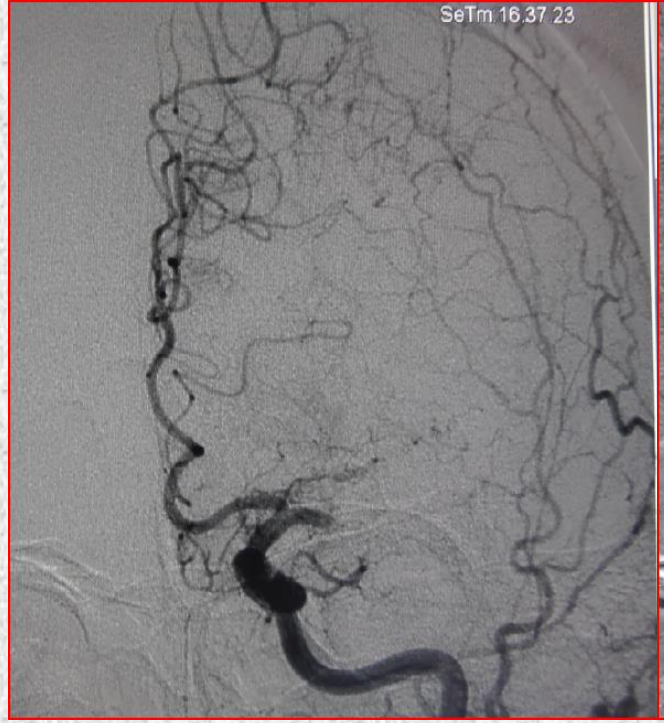


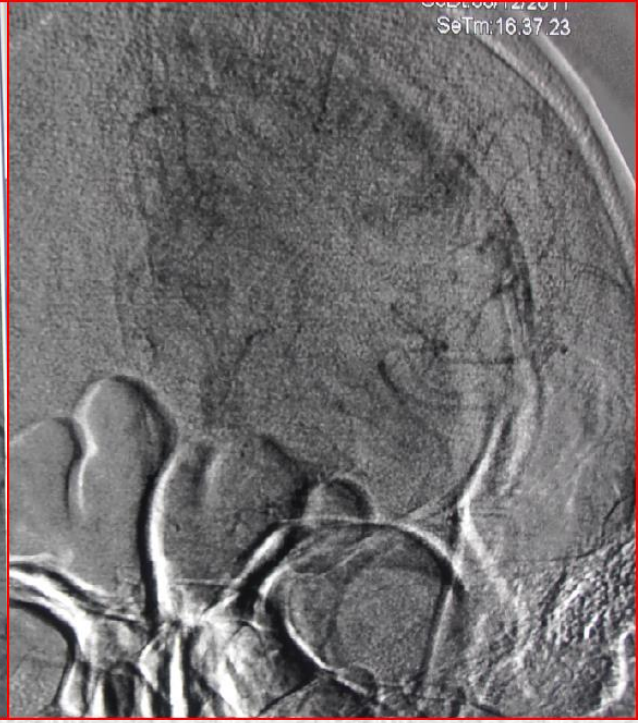
Stent distaccato

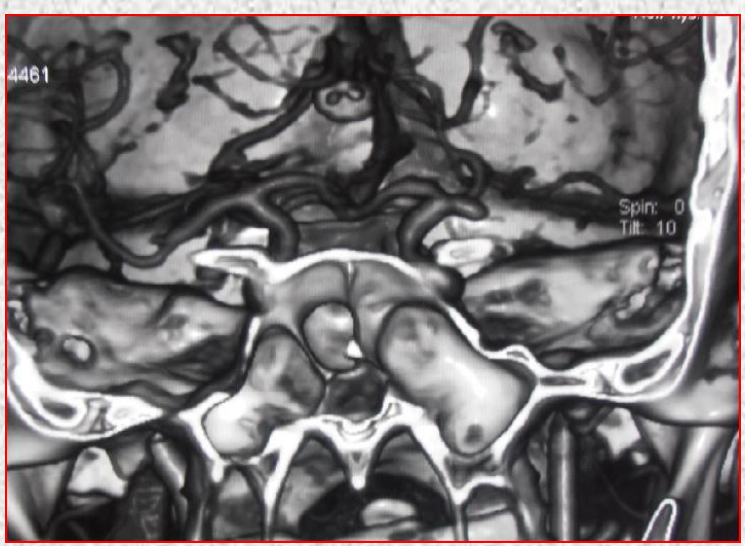


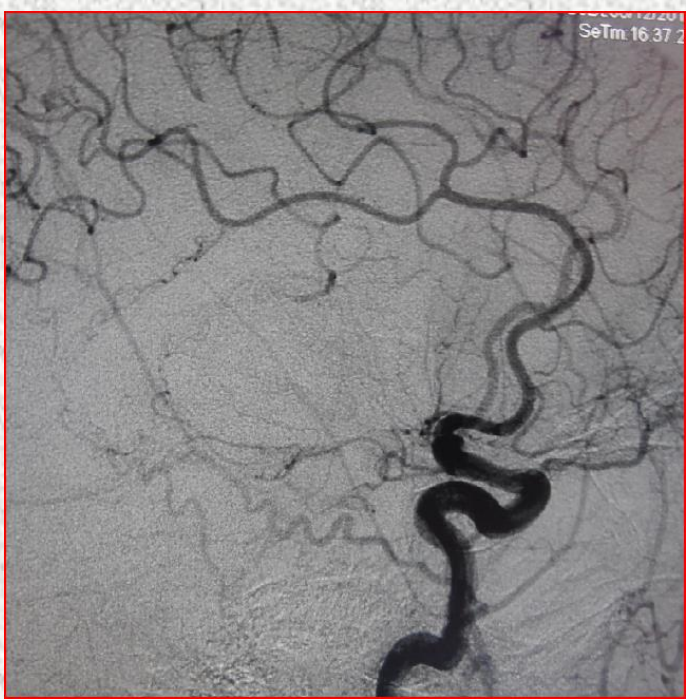
mRS 0
3 months FU

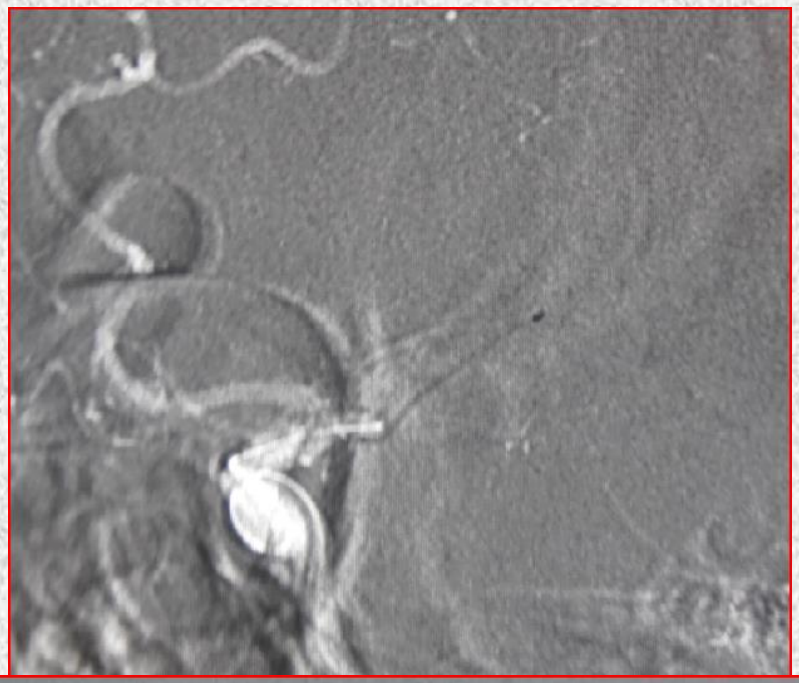
- M, 51 y.o
- h 11.15 aphasia, right hemiparesis
- P.S.: NIHSS 9, full-dose i.v. t-PA, minimal clinical improvement (NIHSS 8) after 40 min. Hospitalised in Stroke Unit
- h 17:10 Clinical deterioration with right hemiplegia and aphasia

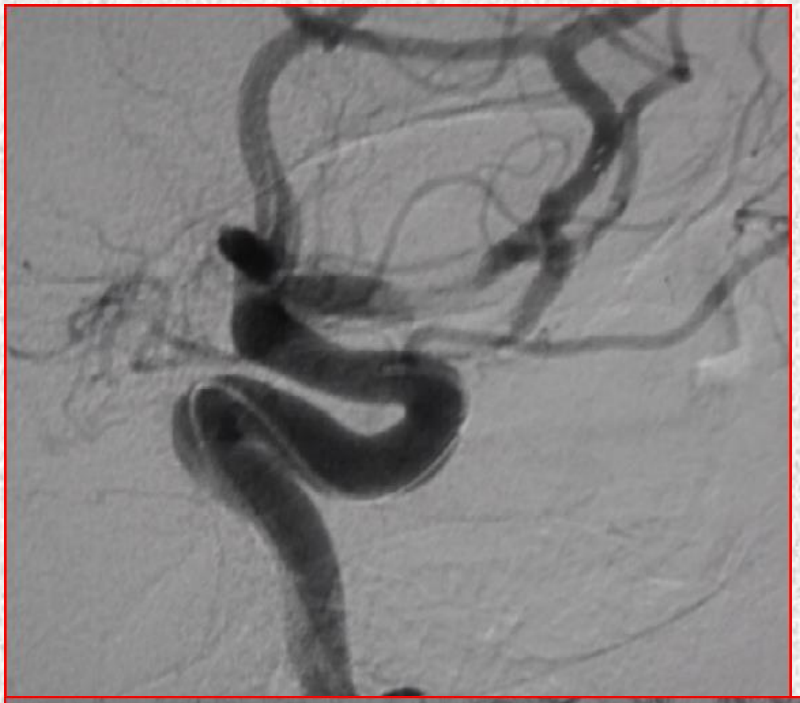


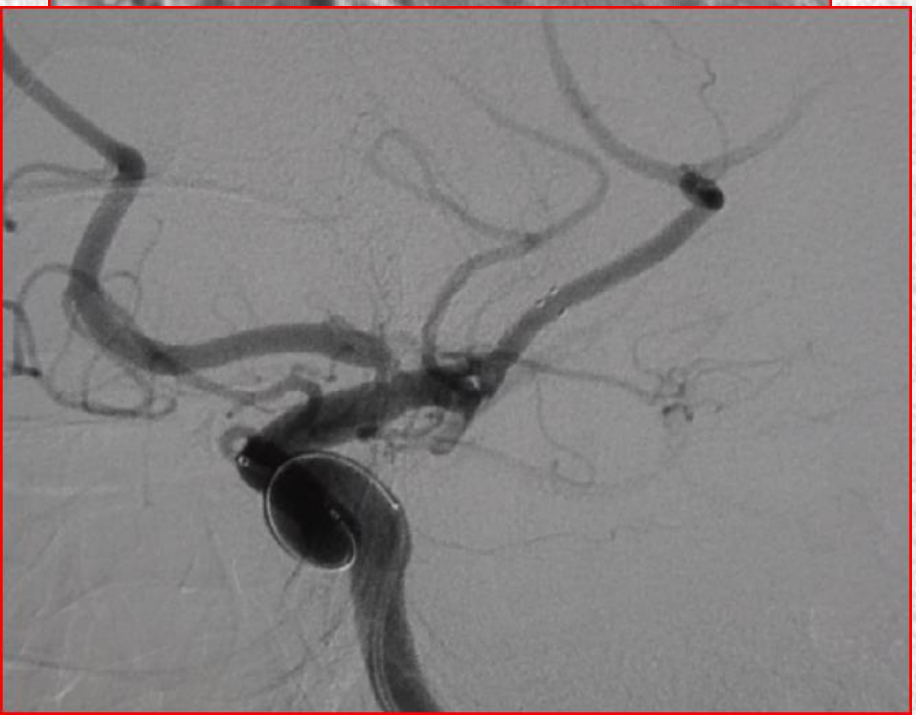


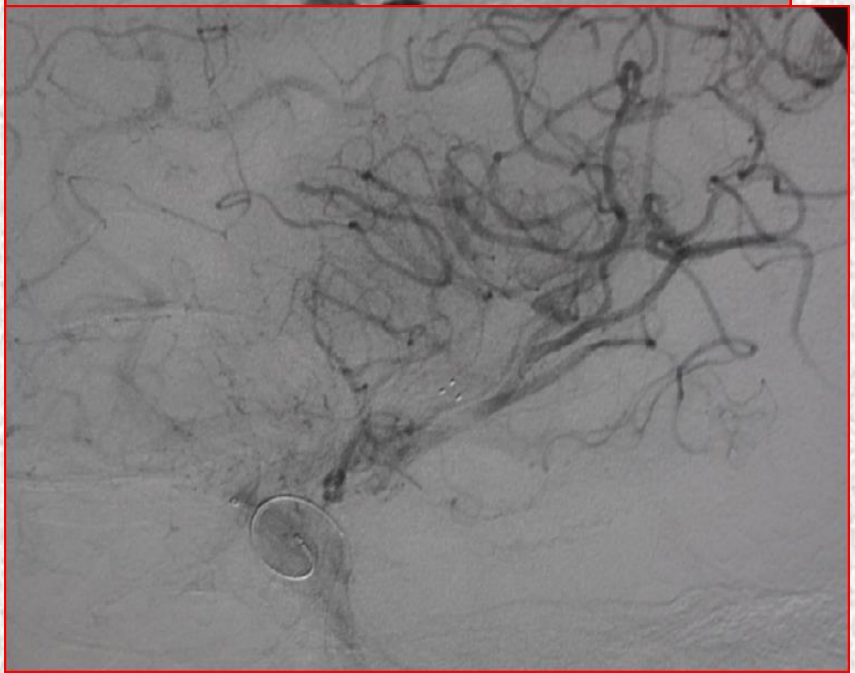


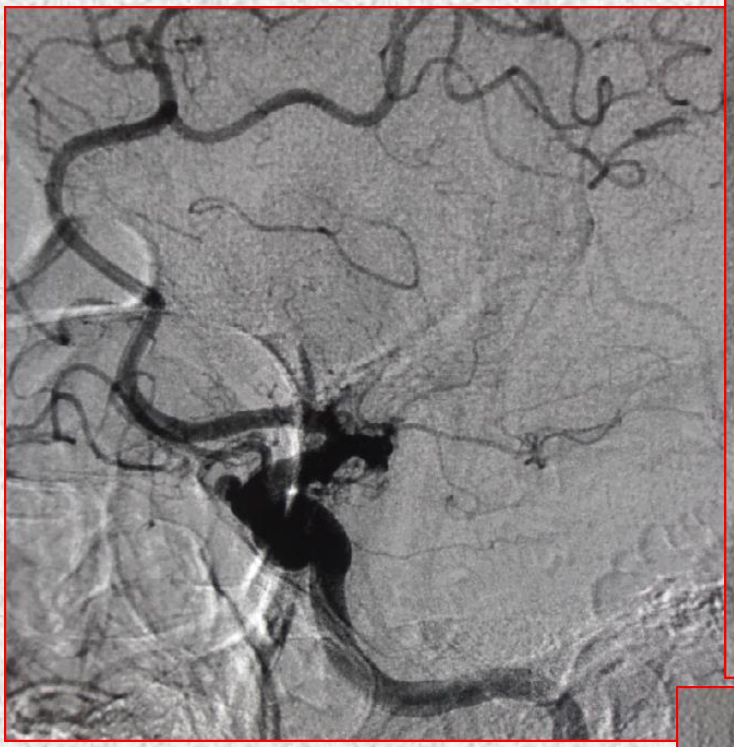




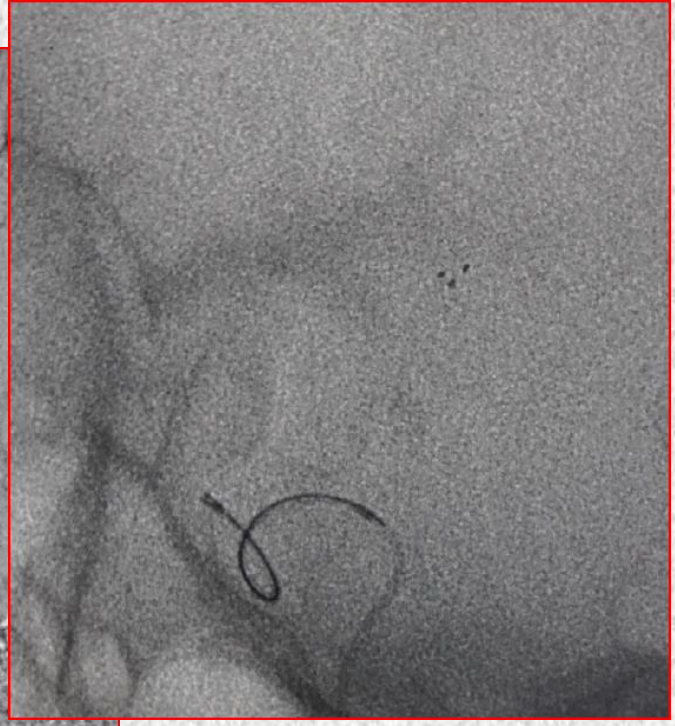


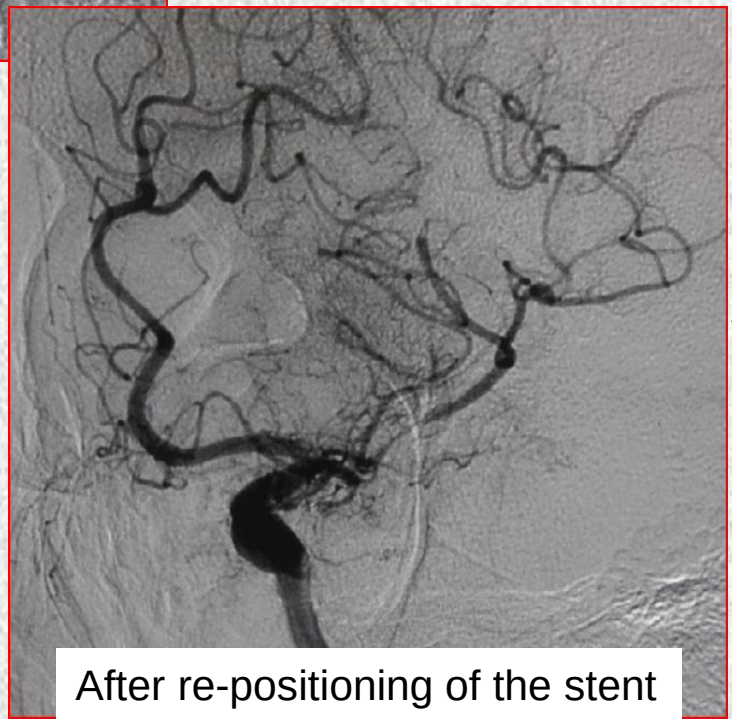






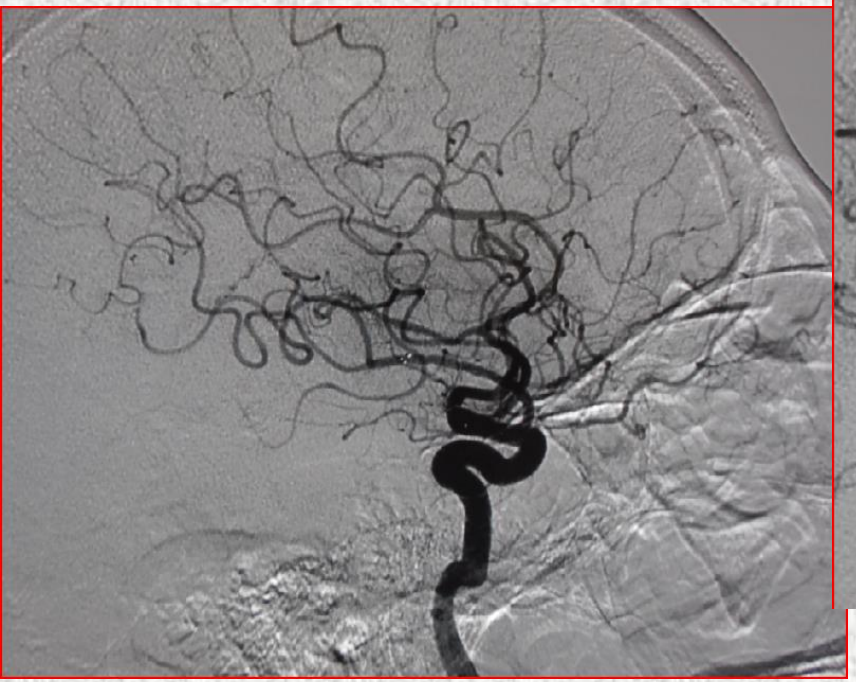
After clot retrieval

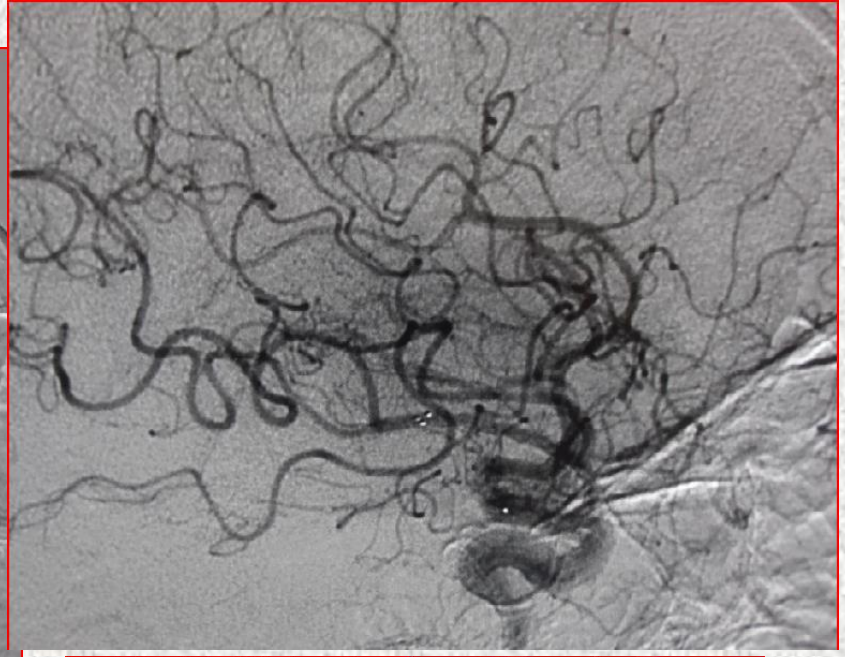




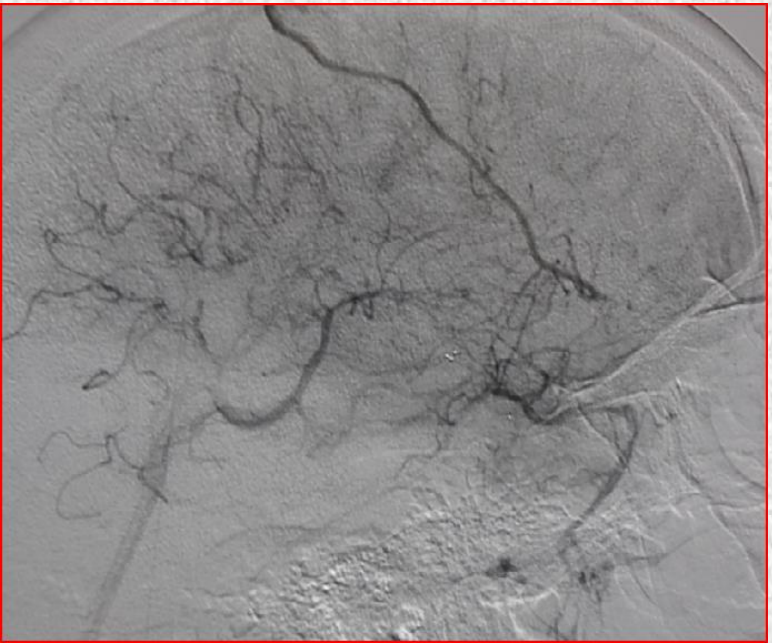
After re-positioning of the stent

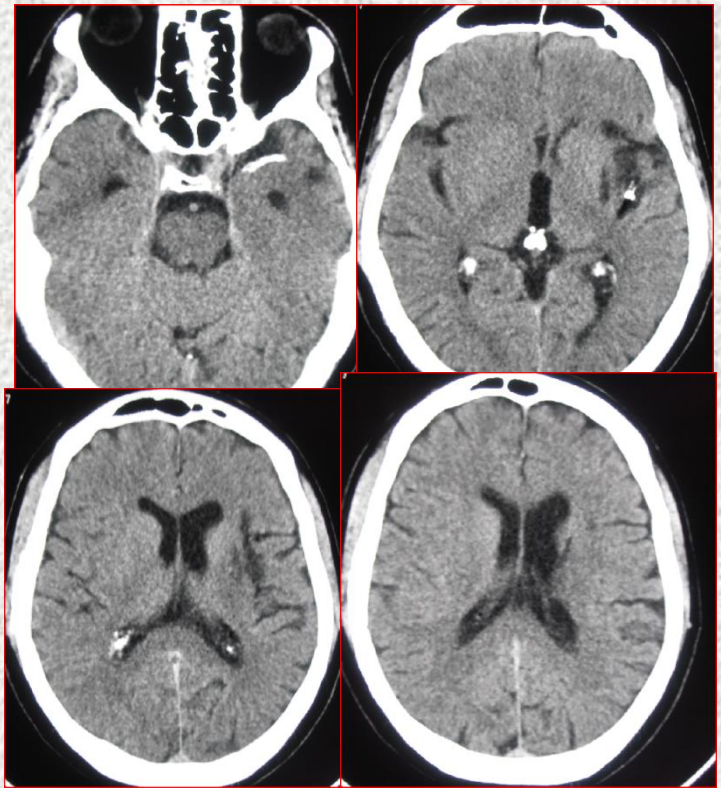
Aggrastat 21 cc i.v.+
10 cc i.a.



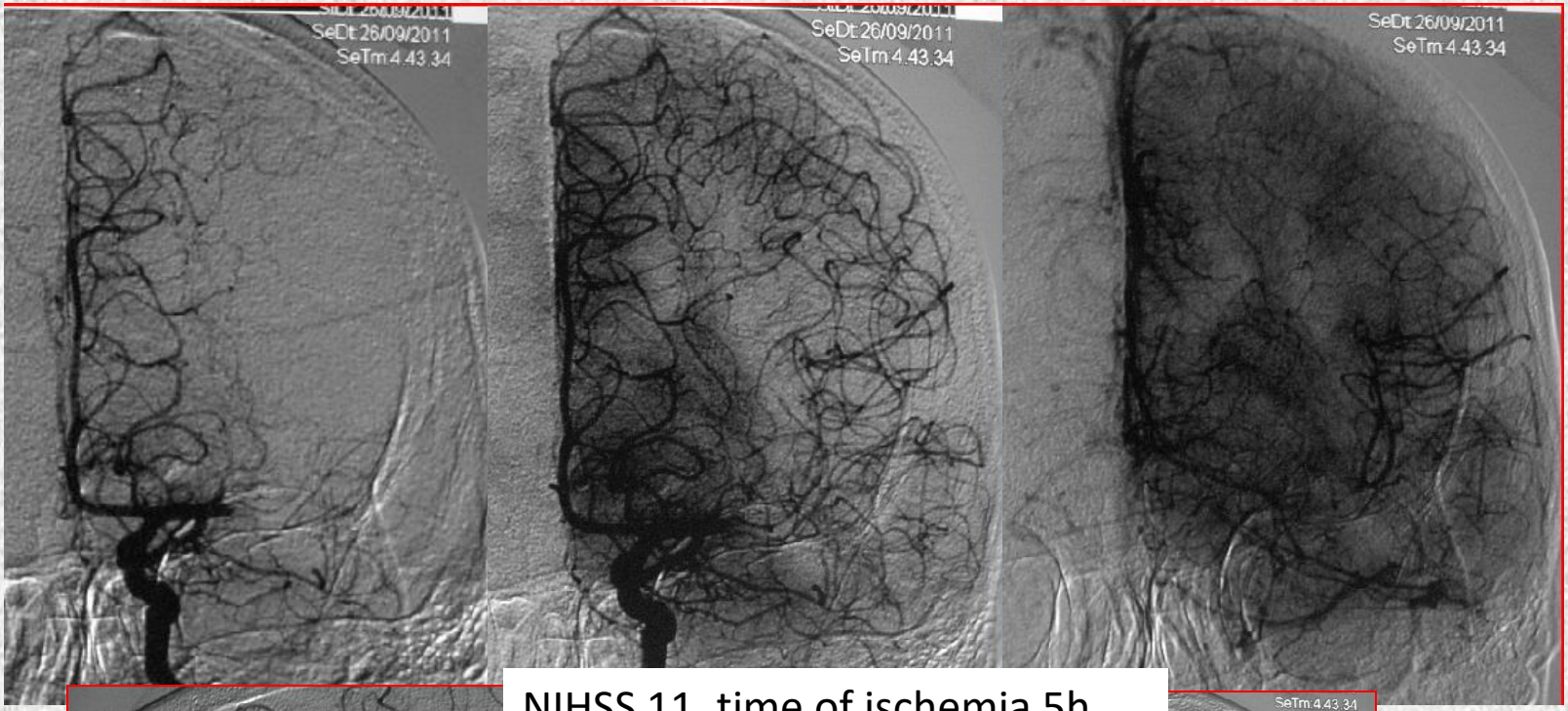


Final DSA, **deployed stent**

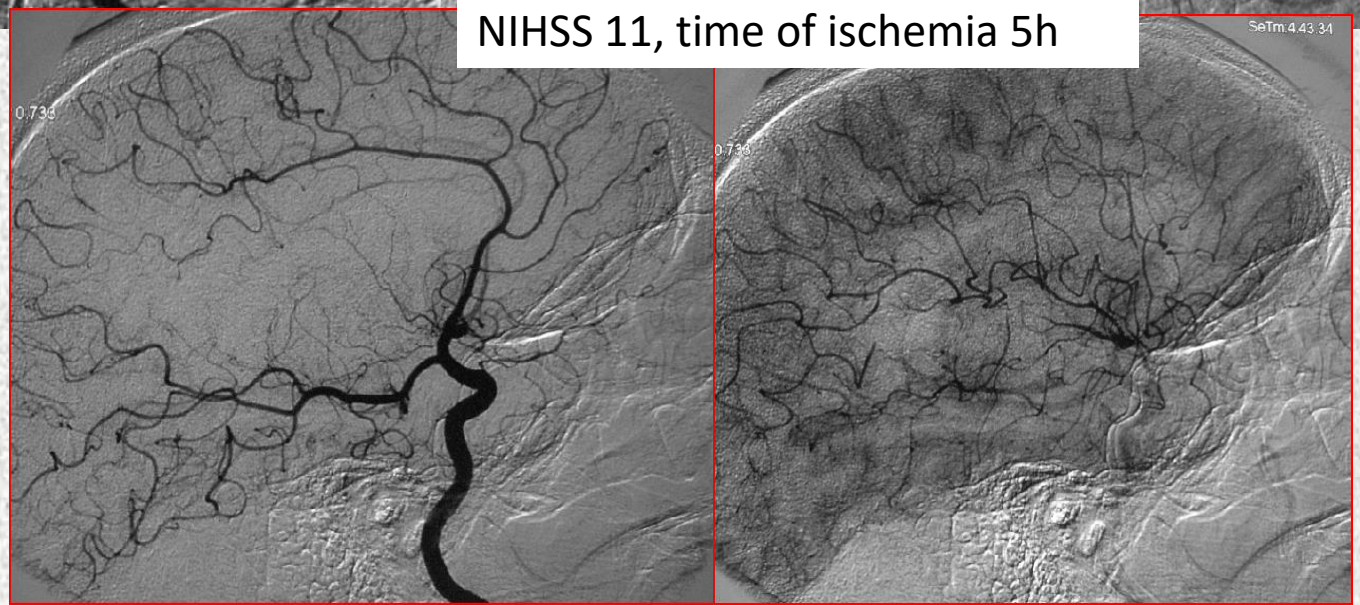


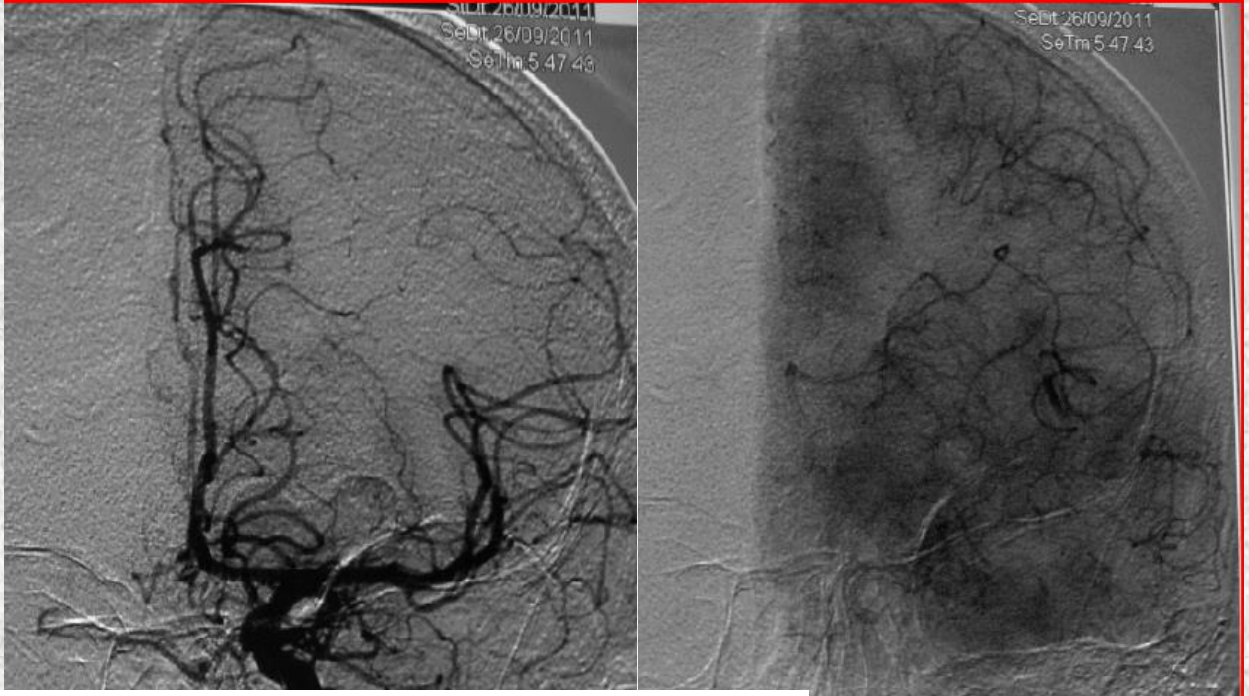


ICA–M1 occlusion, CCS4

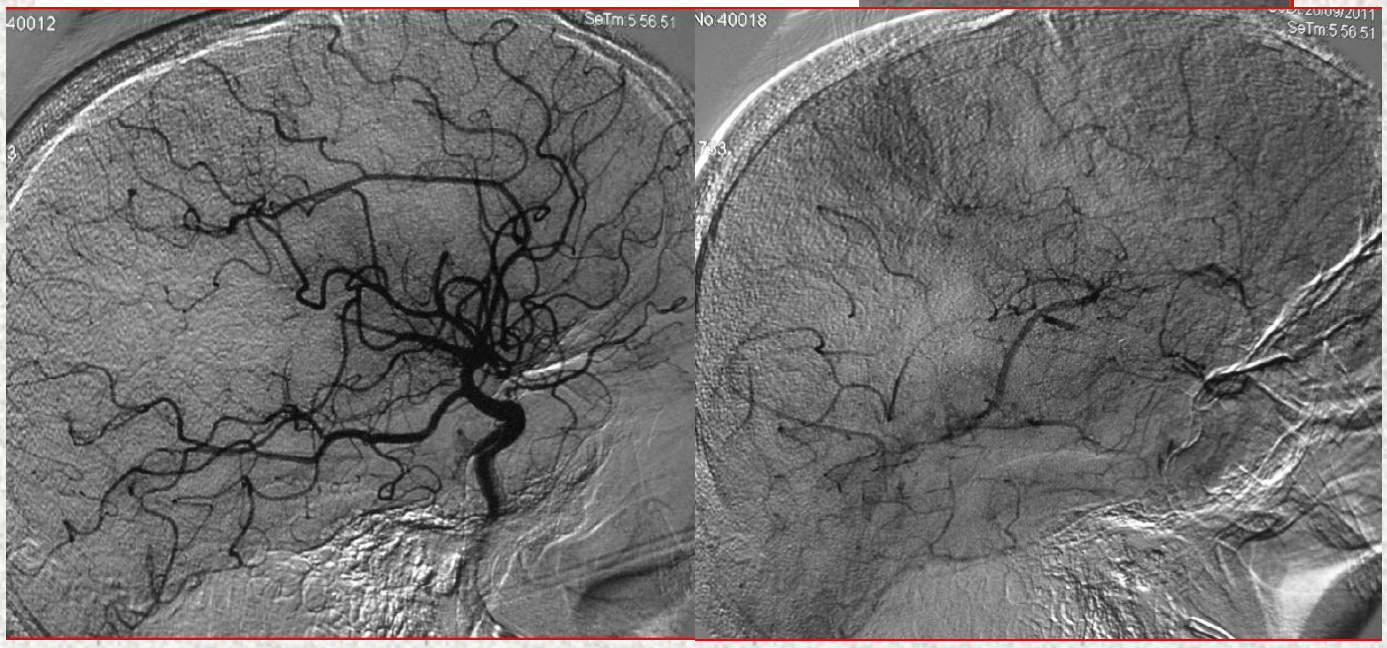


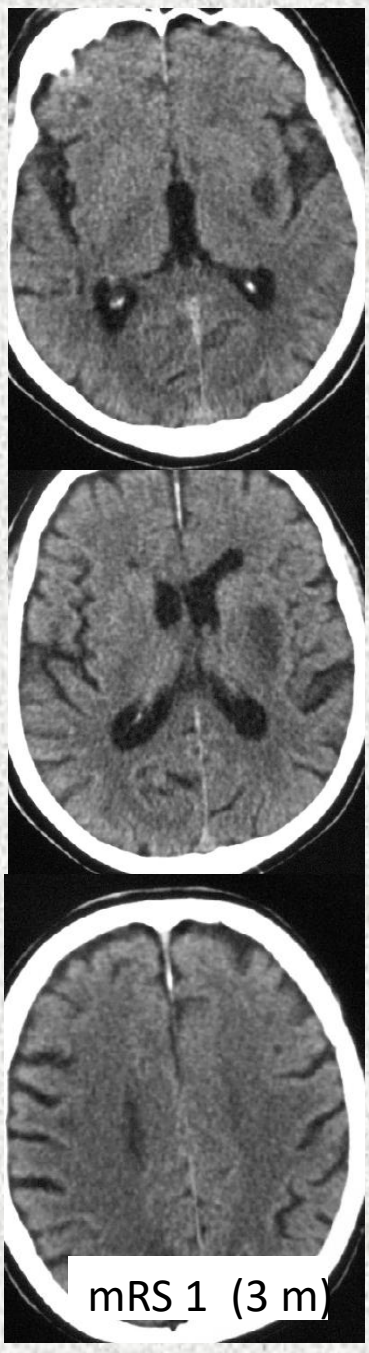
NIHSS 11, time of ischemia 5h





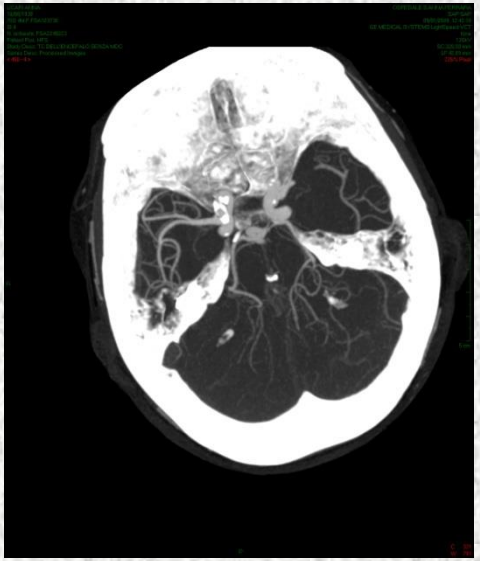
Thrombectomy: recanalization TICI 2b

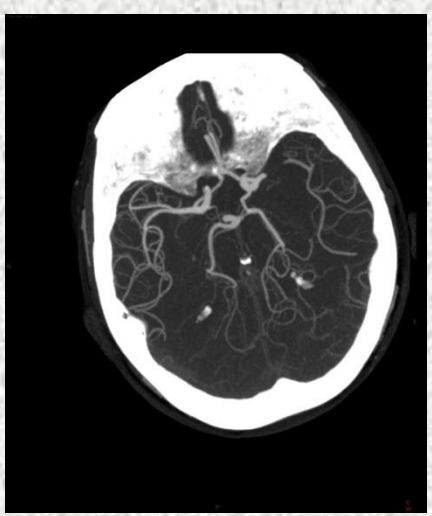


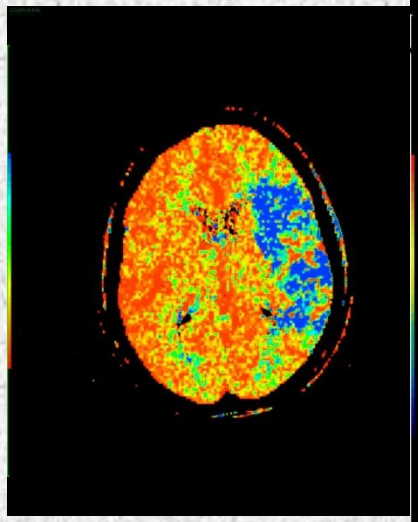


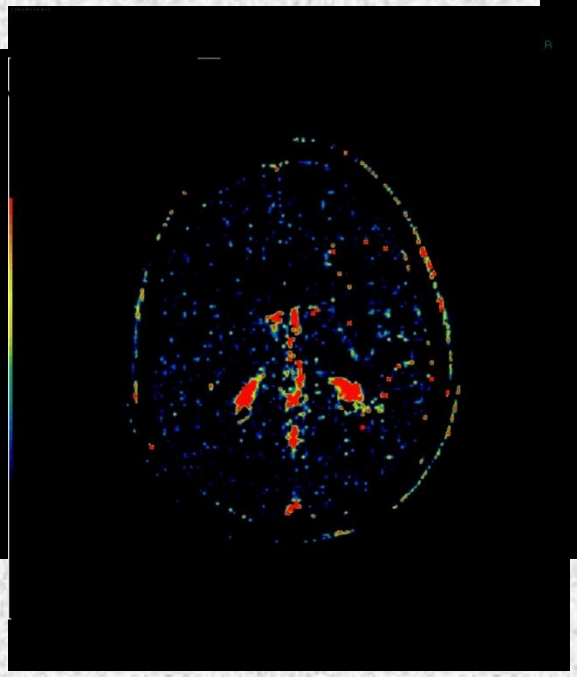
mRS 1 (3 m)

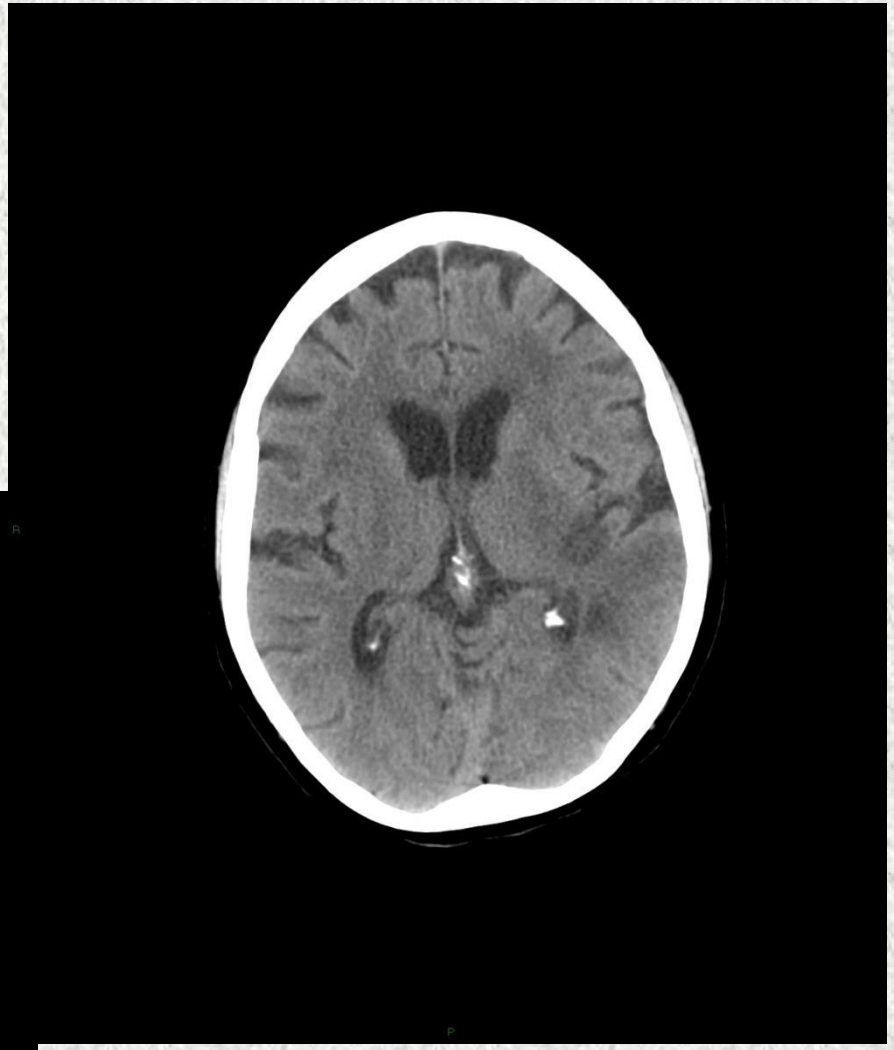
MAP of PERMEABILITY









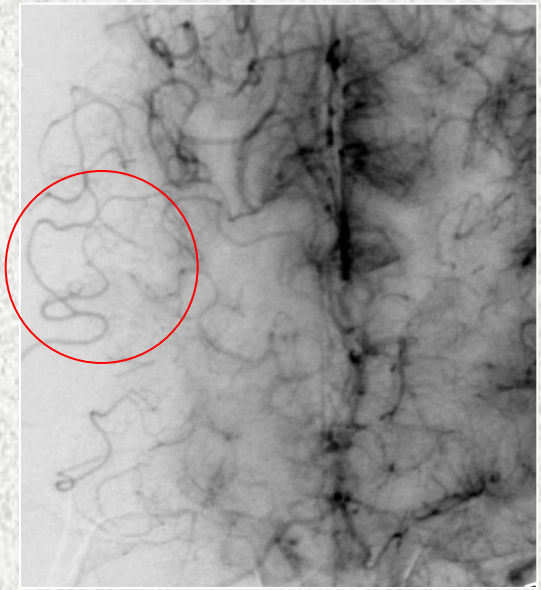


Curtesy dott E.Fainardi

Pharmacological profile

- In patients with small score, wide mismatch and good collaterals it is possible to administer fibrinolytics (i.v. rT-PA) or Antiplatelets without increasing th risk of hemorragic transformation
- Platelet inhibitors in case of extra or intracranial stenting do not increase the hemorrhagic risk, even after i.v. t-PA

Three different types of perfusional profiles



Type B: Poor collaterals

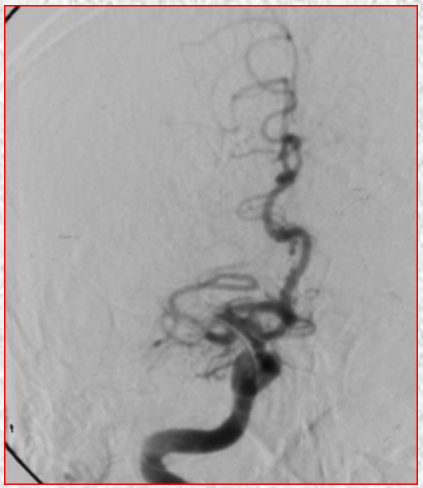
The retrograde perfusion by the microcirculation is poorly effective to slower the evolution of the ischemic core, the expansion of the core is rapid and the integrity of the BBE is not assured

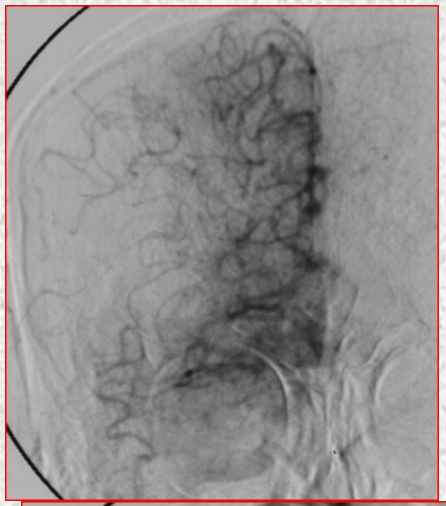
The expansion of the ischemic core is probably rapid (time-dependent)

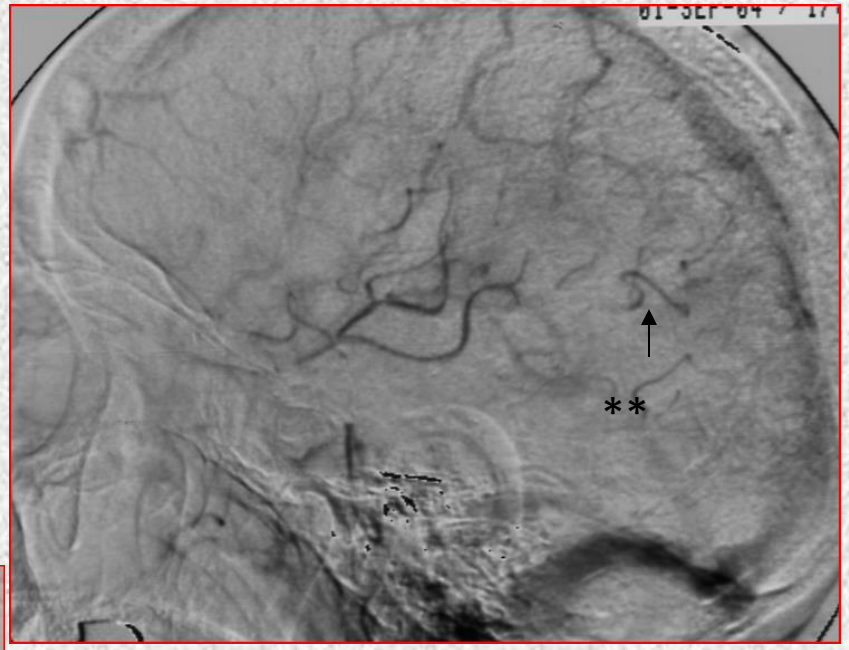
BEE alterations are early

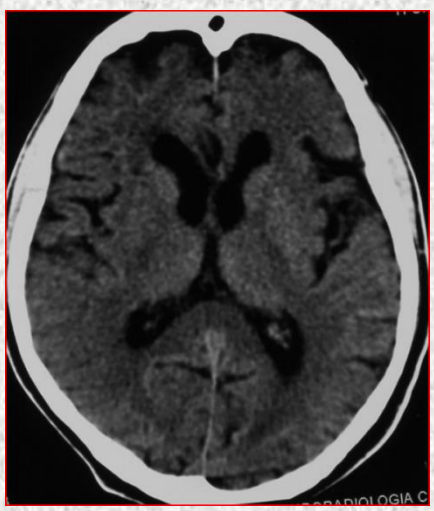
Risk of hemorrhage has to be considered more carefully

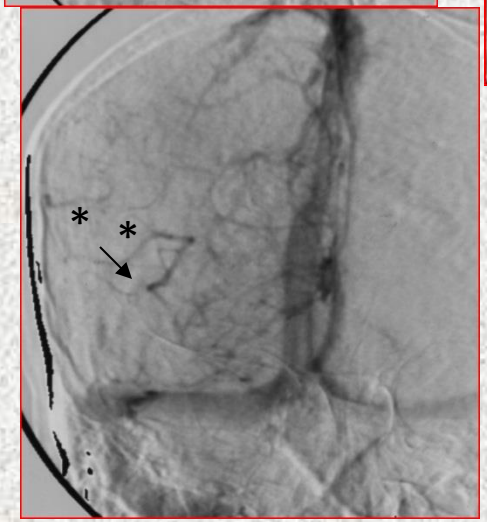
perfusione collaterale povera (CCS2)



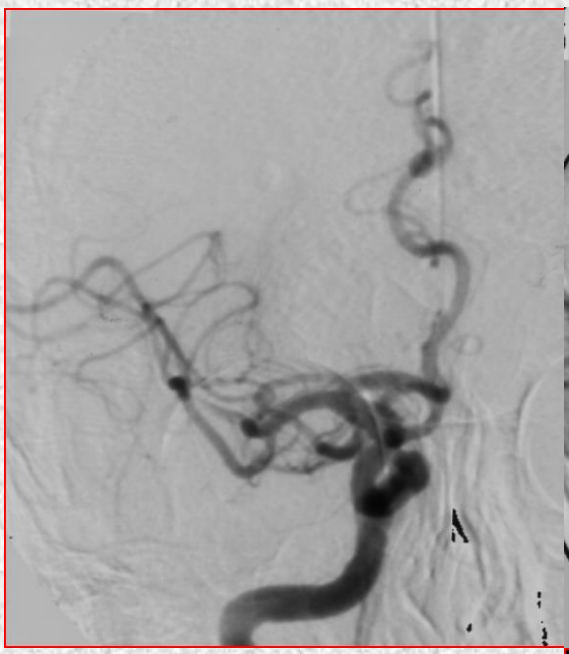


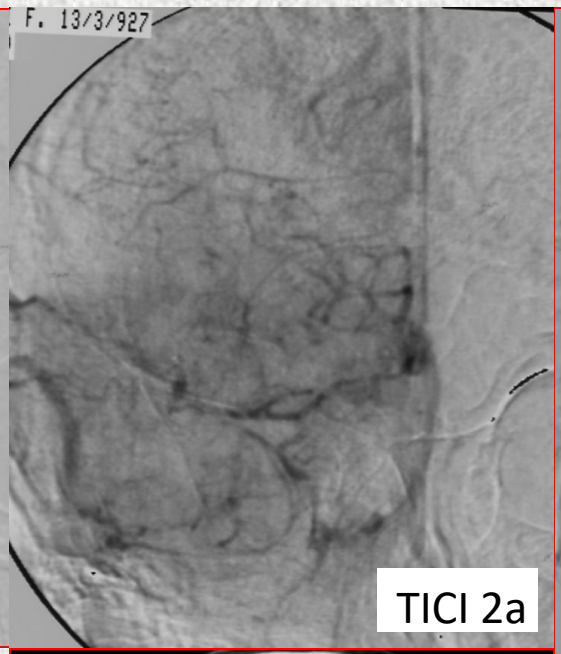




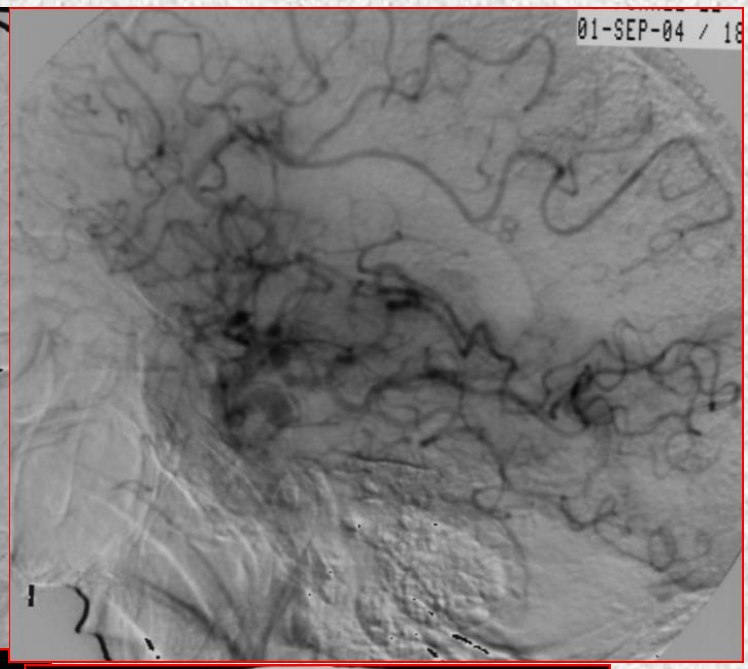


- Pial collaterals do not supply all the cortical territory fo the MCA
- Cortical avascular areas
- Insular arteries visualised only in late venous phase *
- Suspended artery **

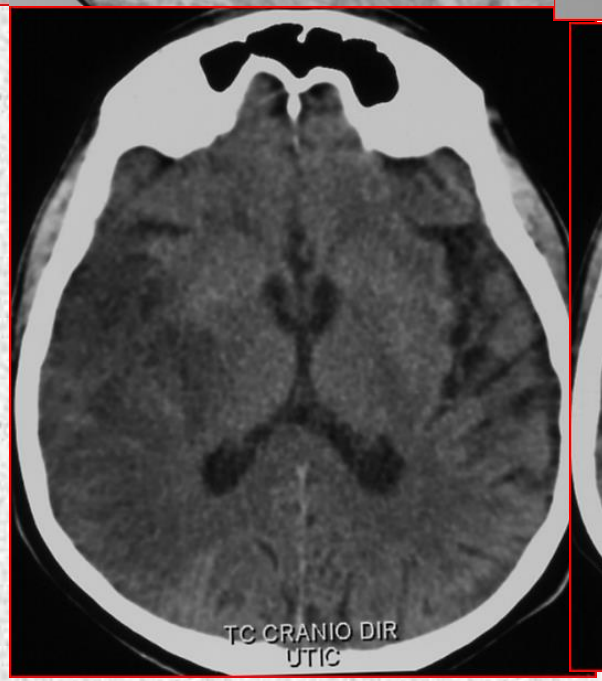


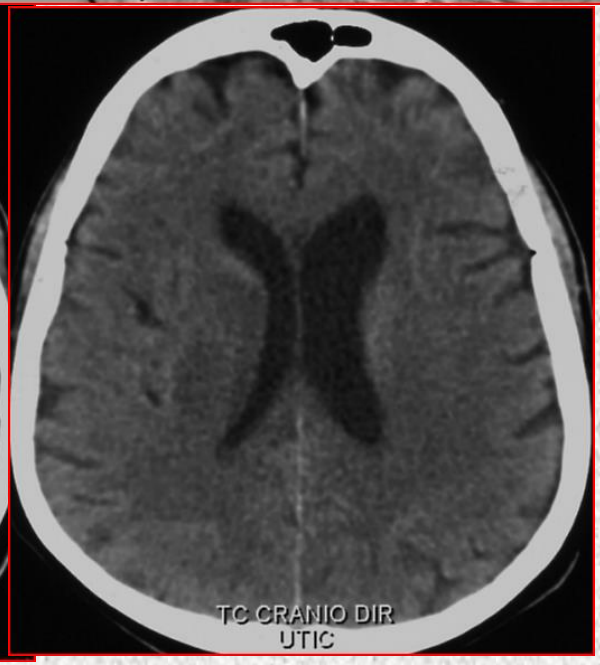


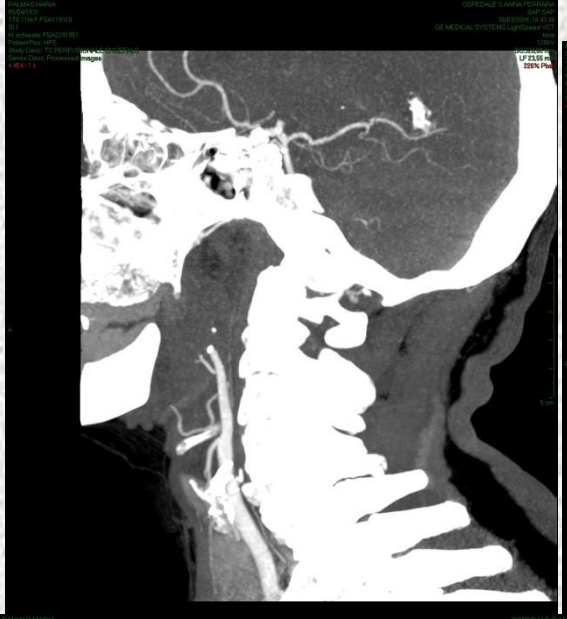
TICI 2a

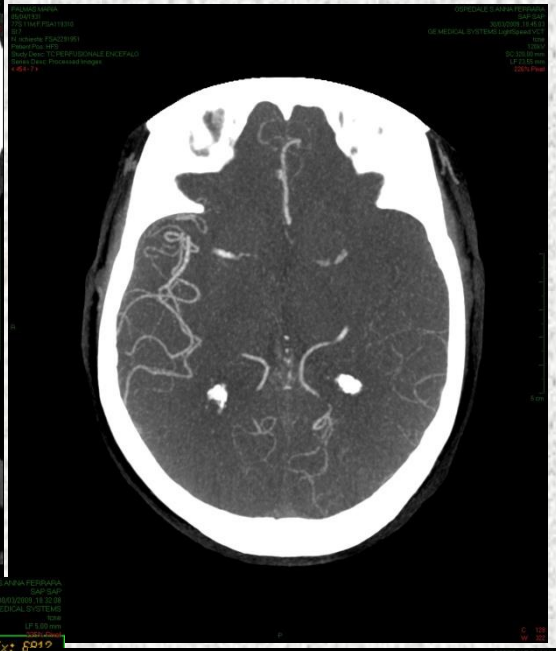


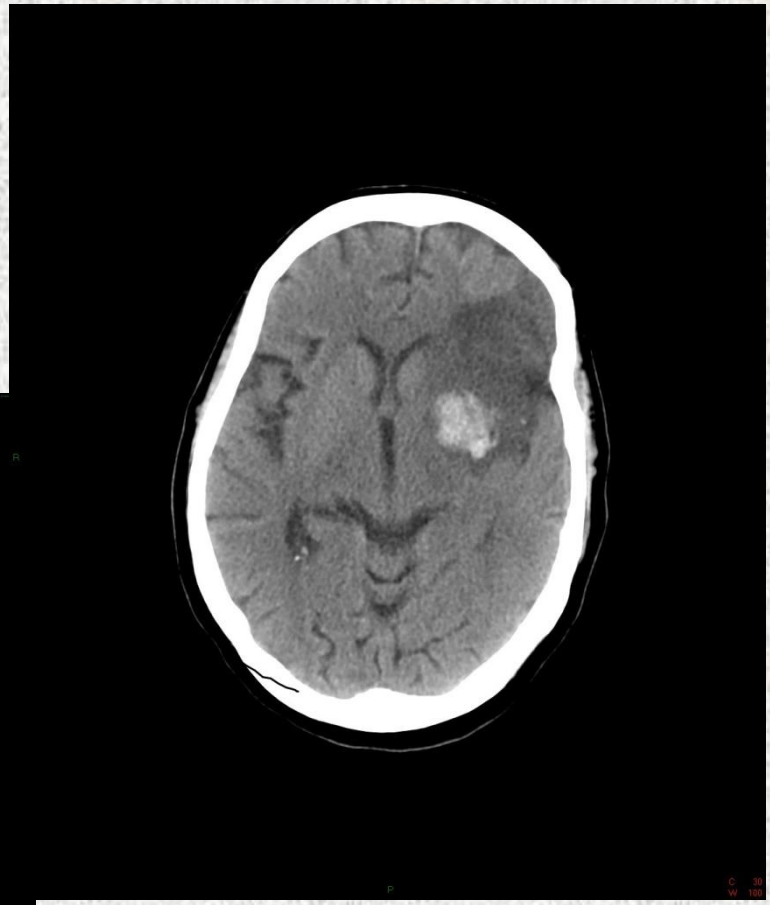
A partial recanalization (TICI 2a) could be insufficient

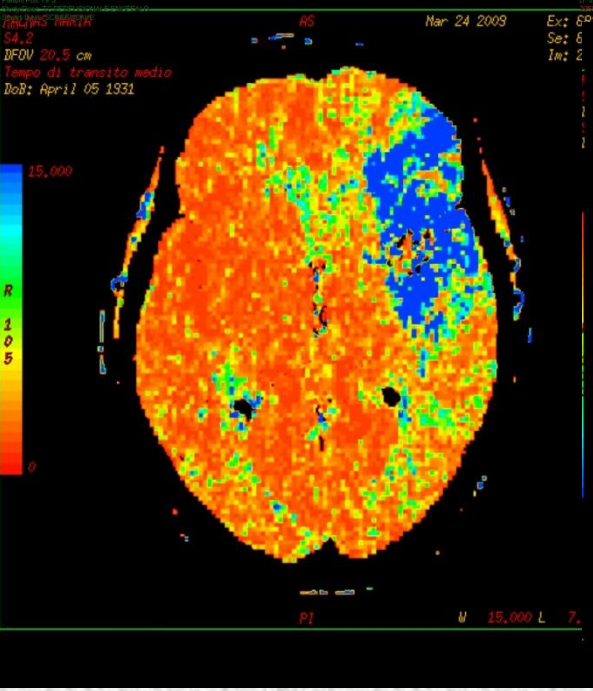


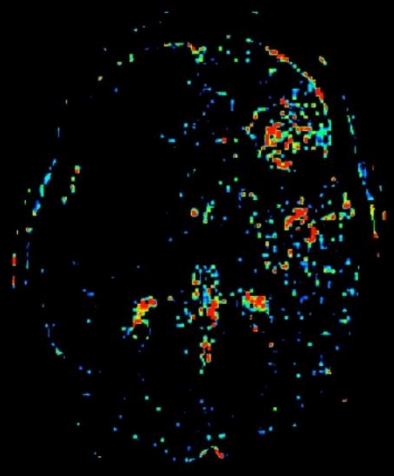












PERMEABILITY MAPS

Curtesy Dott E. Fainardi

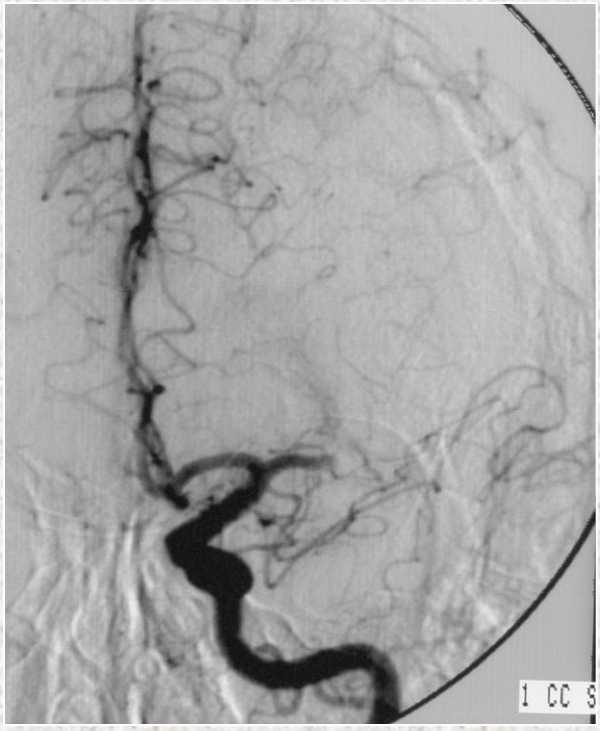
Pharmacological profile

- In patients with wide core, small mismatch and poor collaterals, the loco-regional administration of fibrinolytics is contraindicated

- The hemorragic risk is increased if the patient received i.v. rt-PA

- Platelet inhibitors in case of extra or intracranial stenting is contraindicated because the hemorrhagic risk is increased, particularly after i.v. t-PA

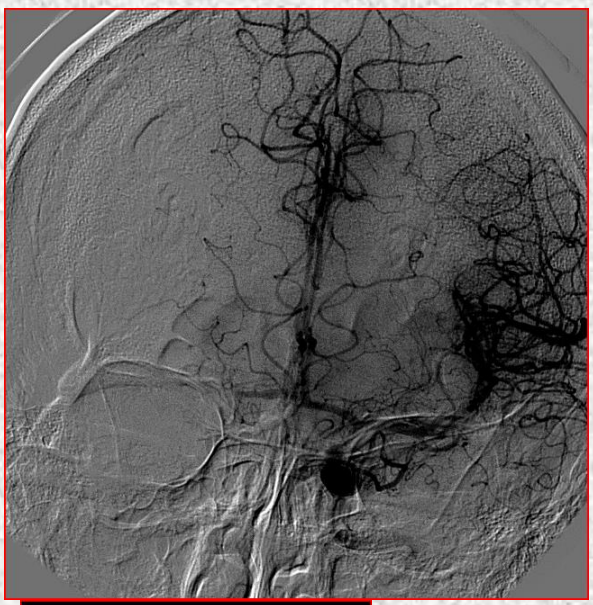
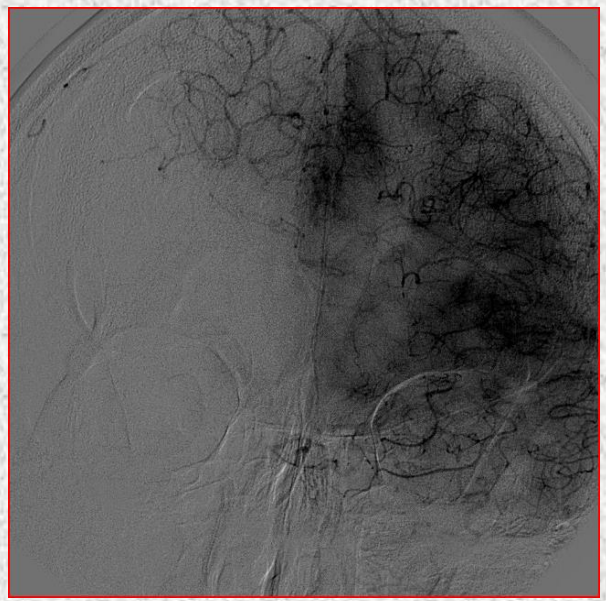
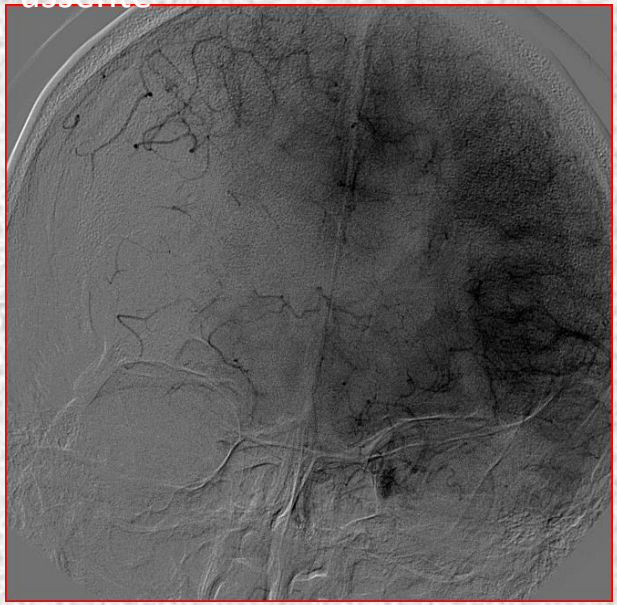
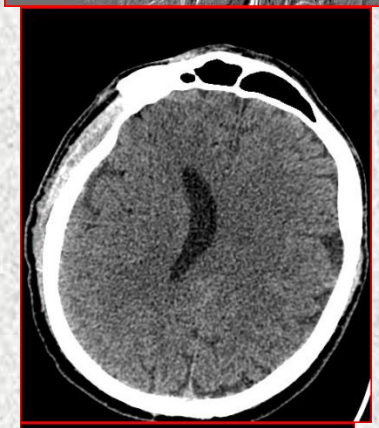
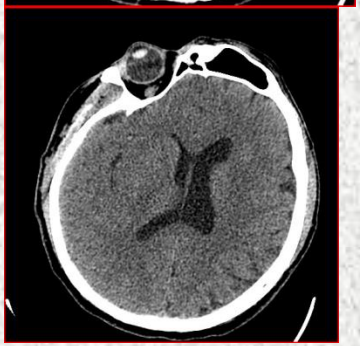
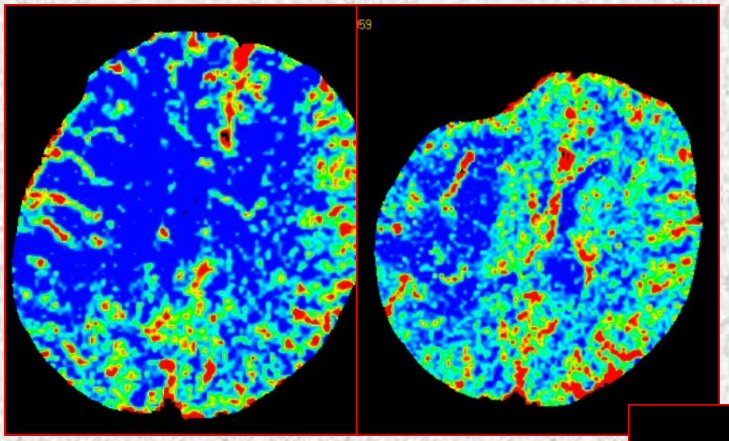
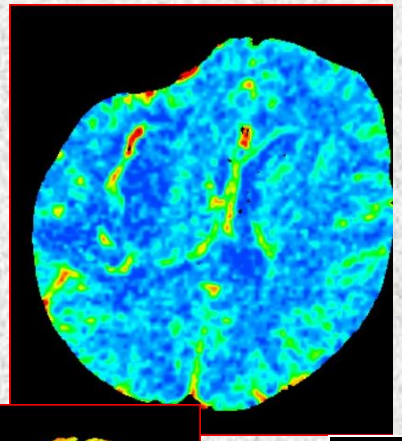
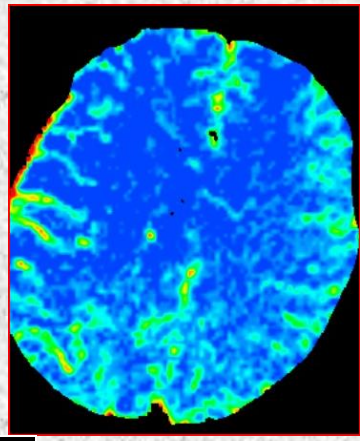
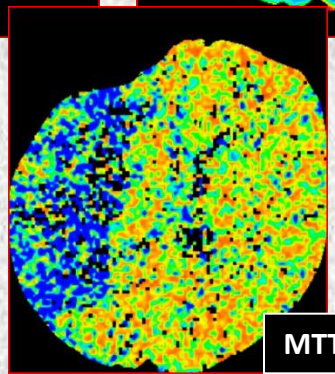
Type c: absent collaterals



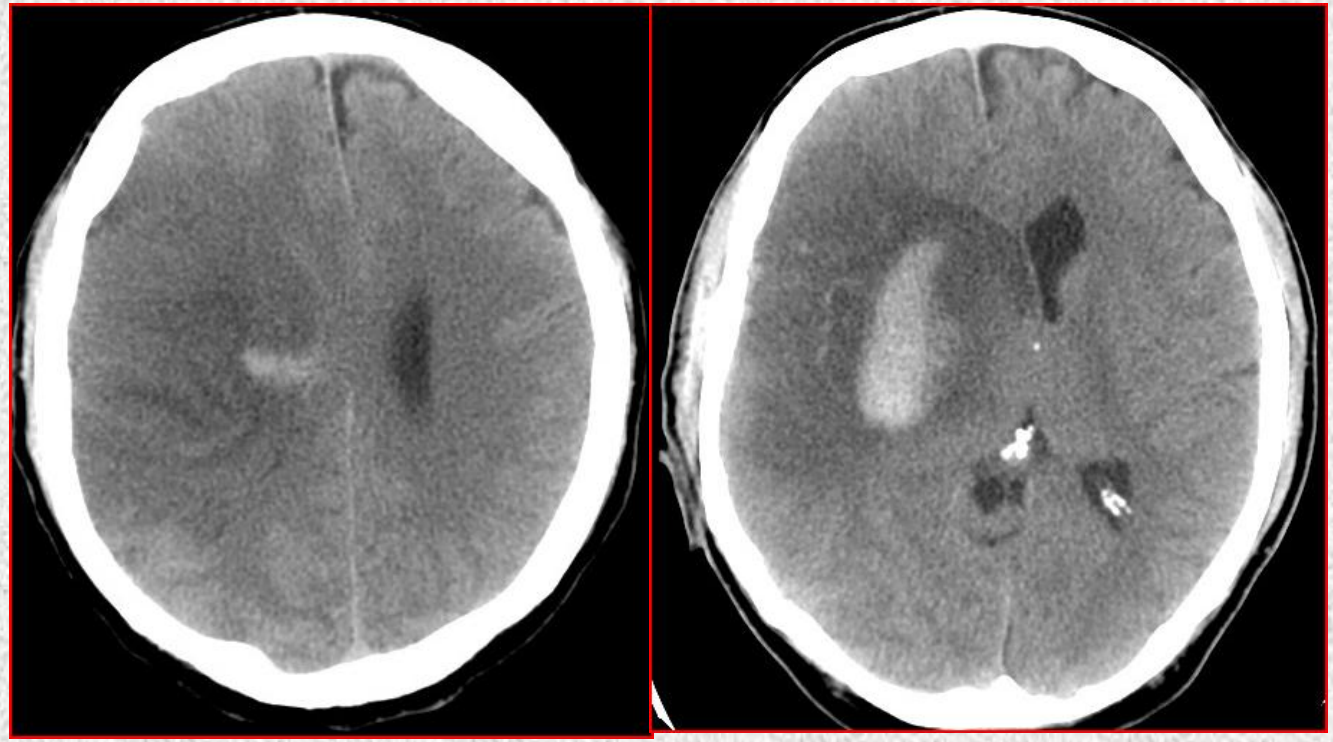
- Collaterals do not supply the ischemic territory
- The extension of the ischemic core is rapidly at the maximum
- Any recanalization grade (partial or complete) will not modify the extension of the ischemic core
- Therapeutic window is closed

No indication to endovascular treatment

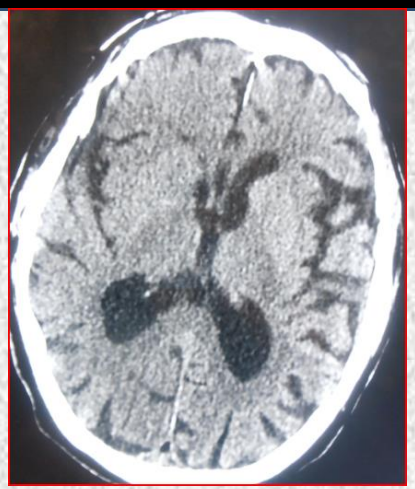
Perfusione collaterale povera :Circolo colaterale assente

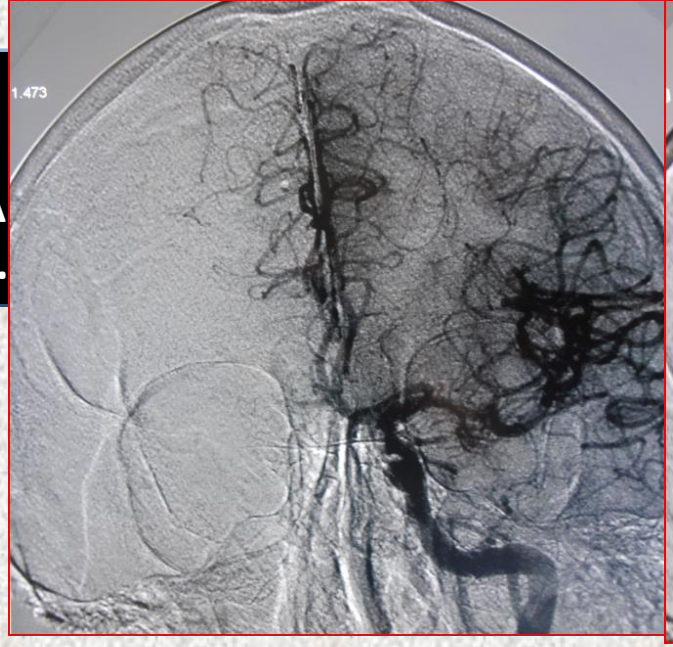






CBF


CBV

MTT

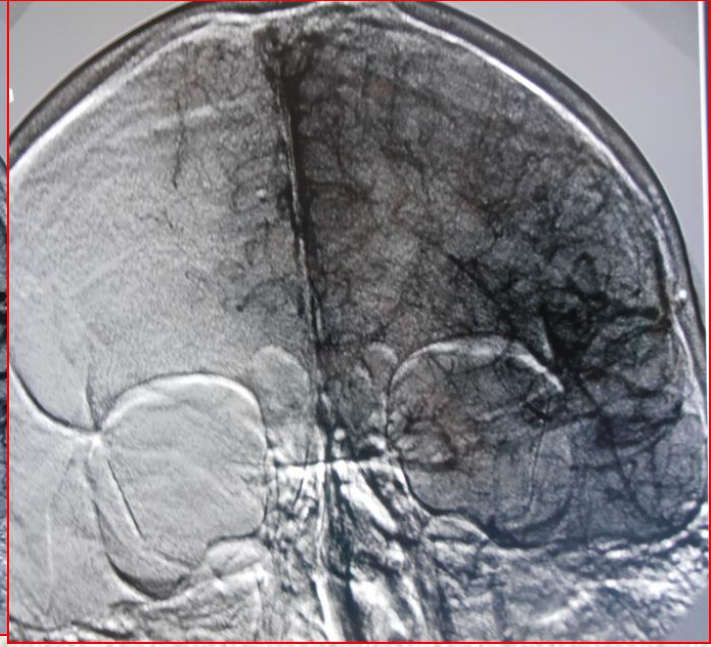
No recanalization achieved

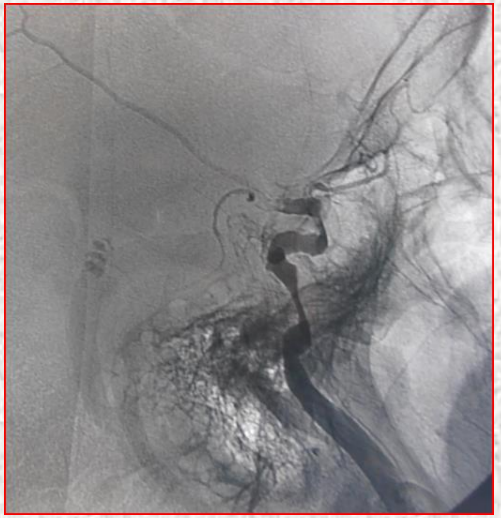


85 yo M
13.00 Left hemiplegia
TC : Hyperdensity of MCA
Time to groin ; h3.30 (16.

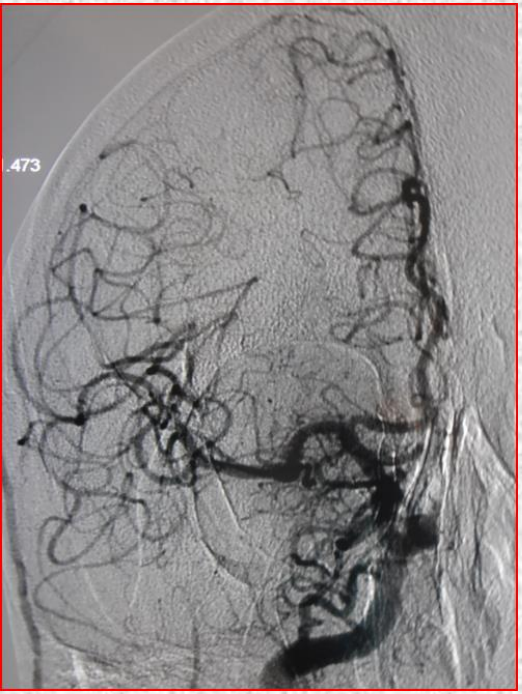


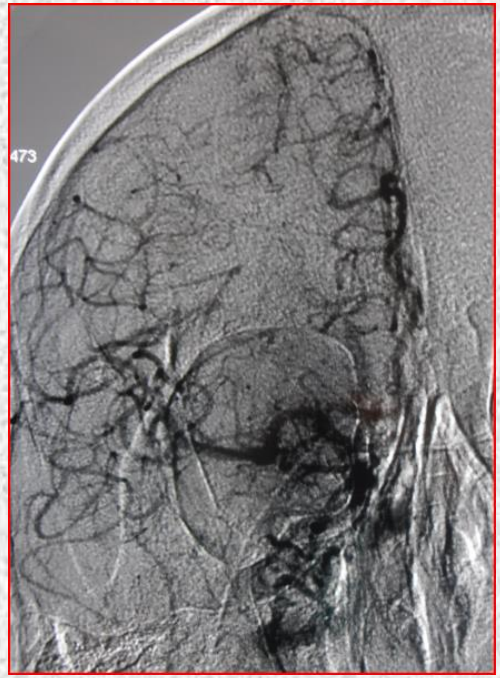


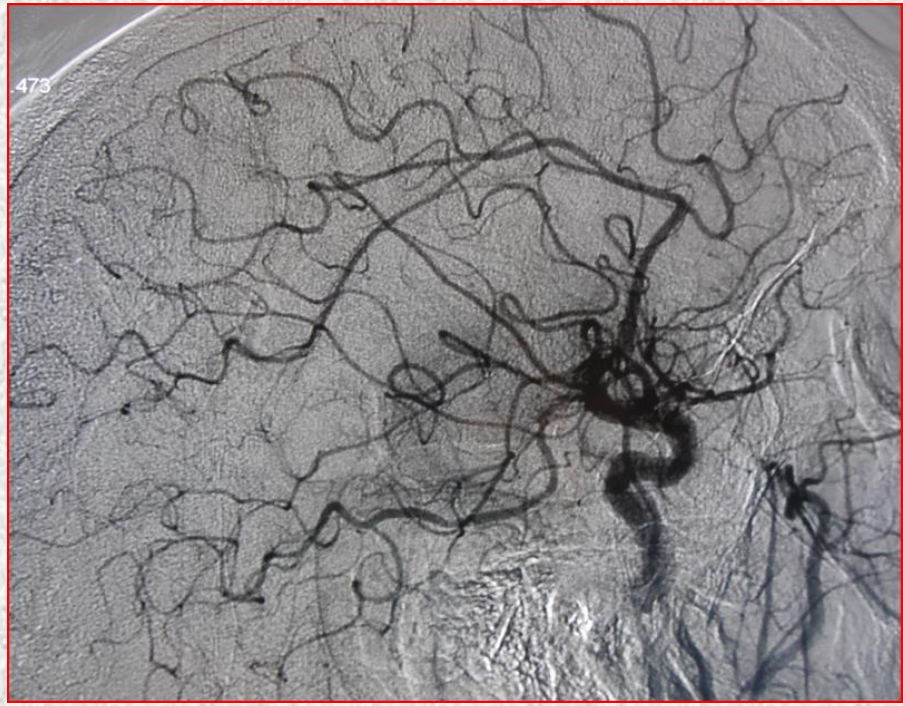


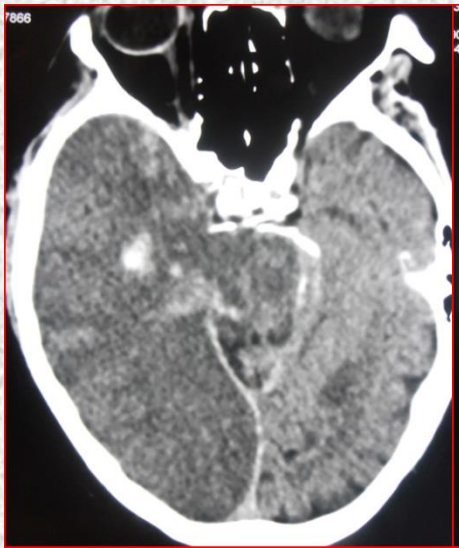


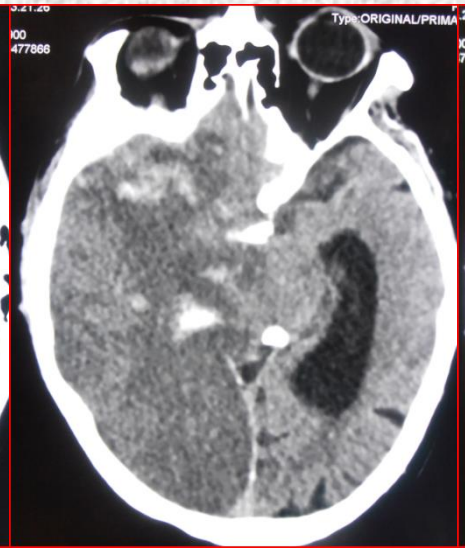
TOR: h4.30 min

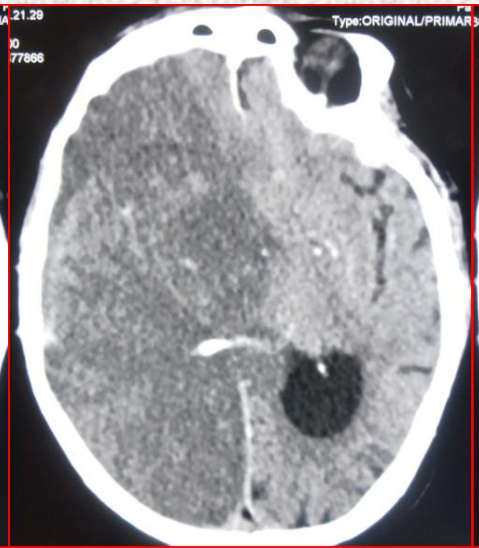


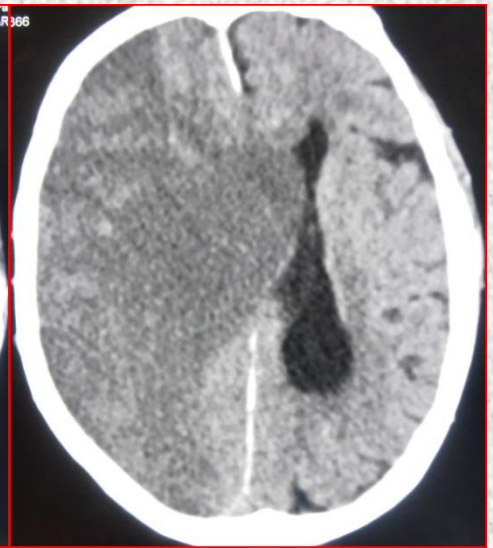


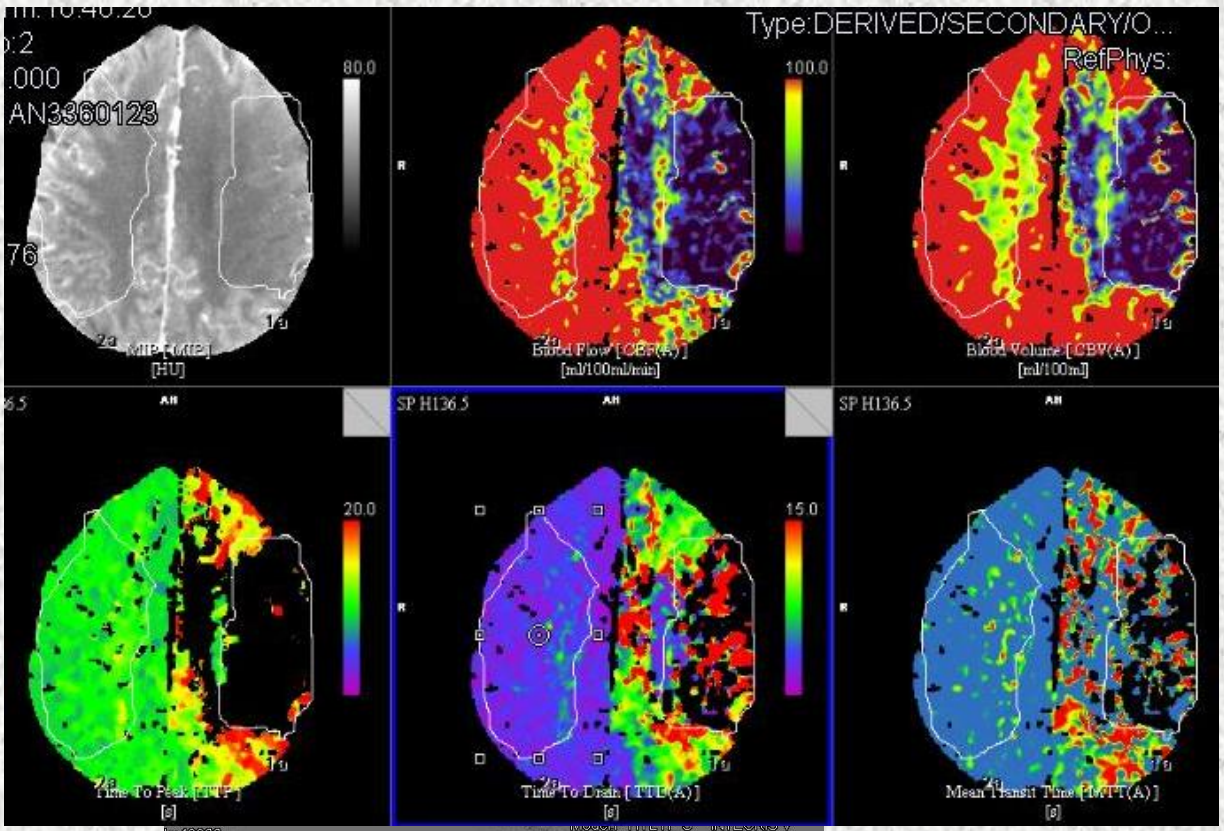


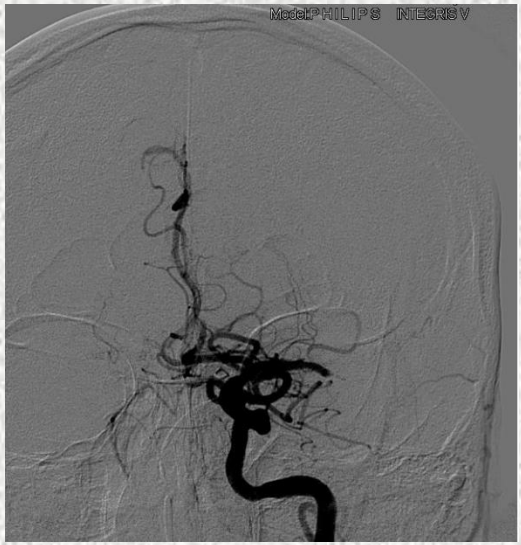


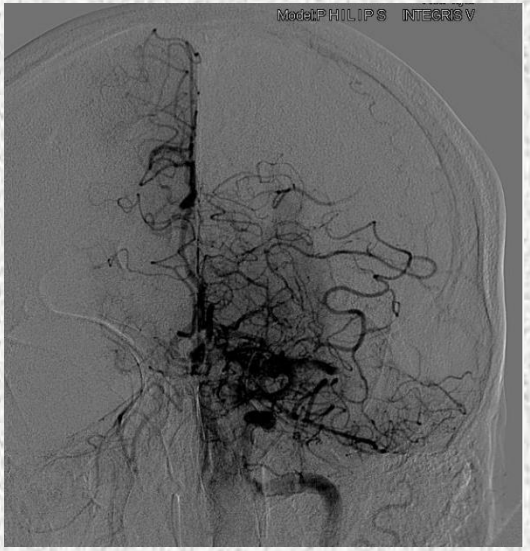


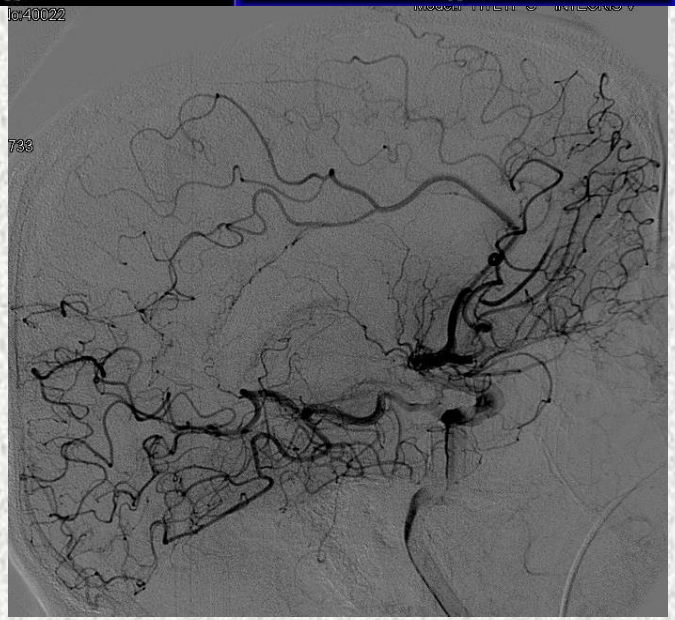












Not treated

DSA: 4.5 h from onset
Poor collaterals (CCS0)
Correlation with CT-P!

Pharmacological profile

- In patients without mismatch and collaterals, the loco-regional administration of fibrinolytics and platelet inhibitors is contraindicated
- The endovascular treatment should not be performed
- The hemorrhagic risk is increased if the patient received i.v. t-PA

THERAPEUTIC PROTOCOL

- **After rt-PA i.v. and Thtombectomy** no Anticoagulants and antiplatelets for 24 h

- **After carotid PTA**, only i.v. aspirine 500 mg ev from the day of the procedure

- **After carotid PTA-Stenting or intracranial stenting**:

Aggrastat (Tirofiban) i.v. bolus 2/3 of the dose at the moment of the deployment

Clopidogrel and ASA since the day after the procedure (If CT rules out BBB alterations or initial hemorrhagic transformation)

Medical therapy Post stenting in patients without systemic IV tPA

- No heparin for 24h
- Administration of IV tirofiban (½ dose in base PC/h) for six hours

only if control TC scan shows

- no hedema
- no pathological enhancement of Basal Ganglia

only if DSA shows

- Good and efficient Collateral circulation before treatment
- a partial recanalization (TICI 2a- 3)

only if TC Perfusion shows

wide mismatch

Post stenting medical therapy in case of A. Carotid occlusion Previously treated wirh i.v. t-pa

Double platelet inibition (Clopidogrel and Aspirin) is given after 24 h from the end of intervention (after CT negative for hemorrhagic conversion)
In case of altered BBE only aspirine (150 mg die) since normalization of BBE

In alternative, immediate PTA followed by PTAS (after 1 week) from clinical onset ONLY if ECHO doppler EXAMINATIONS show stability of the initial recanalization

The devices : action on the clot

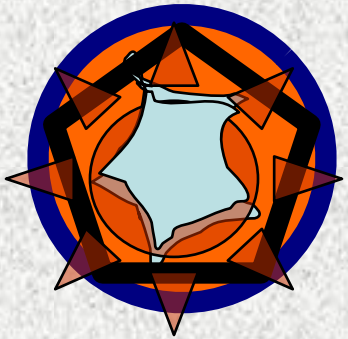
Clot

- **Mechanical Retraction Thrombectomy**
- **Thromboaspiration**

- Mechanical Interaction with the clot
- Trapping
- Fragmentation

- Nature of the clot
- Extension of the clot
- Clot burden
- Localization of the clot (bifurcation)

TEMPORARY BY:PASS



Clot trapping

STENT-CLOT interaction

Stent

Stentriever

Retriever

Engineering of stentriever

Flow restoration (by-pass)

Wall apposition

- Radial Force
- Close cell
- Small cell area

Clot trapping

- Inhomogeneous cell design
- Small cell area
- Struts Orientation

Clot traction, Conformability

(clot fragmentation, vessel wall damage)

- Cell design: closed or Hybrid design, deformation
- Equilibrated radial force
- Spiral cell orientation
- Length of working zone
- Tapered (close) distal end

Technical features

- **Cell design**
- **Cell geometry and width**
- **Strut orientation**
- Radial force
- Distal guide wire
- Distal end

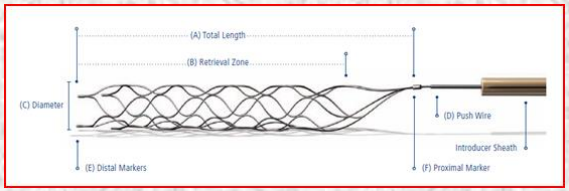
- **Cell design, geometry and width**:
- closed cells: increase stability, no deformation in curves
- Variability of cell design/area vary the force applied on the thrombus (linear proportion force applied-number of cells), homogeneous cell design/area: same force applied
- Large cells: increase stability; more trapping capabilities?
- **Strut orientation**
- horizontal and thin (stent-like) not designed for thrombectomy
- vertical arrangement could **help clot-stent integration**
- Helical/oblique arrangement could **help clot retrieval**

Technical features

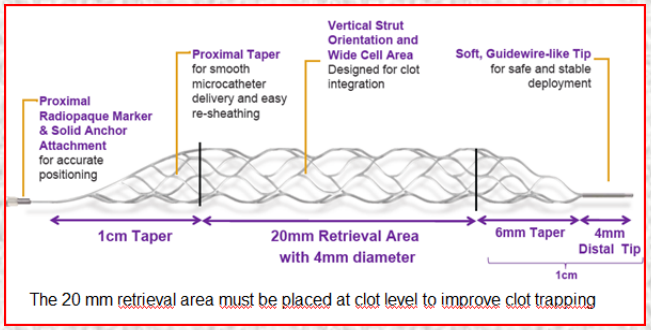
- Cell design
- Cell geometry and width
- Strut orientation
- **Radial force**
- **Distal guide wire**
- **Distal end**

- **Radial force:**
- High radial force: immediate reopening of the vessel (temporary by pass) and may improve stent-clot interaction; constant: reduces vessel wall trauma
- **Distal guide wire:**
- May provide stability and help the positioning
- Risk of perforation
- **Distal end:**
- Closed: theoretical reduction of clot migration

SOLITAIRE FR (EV3, Covidien)

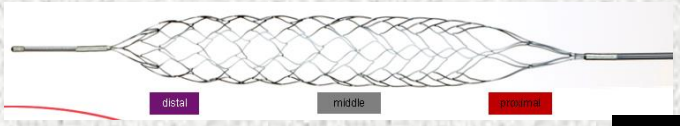


TREVO PRO (Concentric, Stryker)

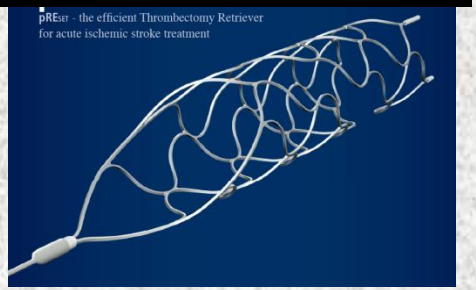


CAPTURE (Mindframe, Covidien)

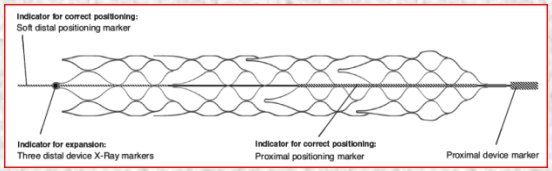
Revive (Codman)



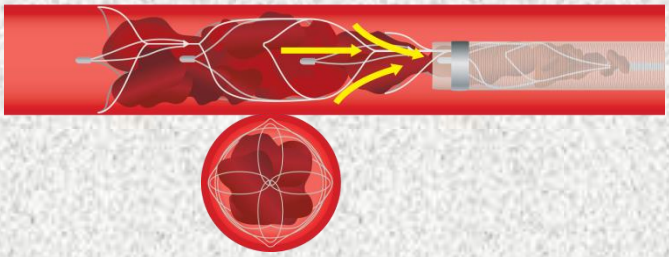
phenox - pREset



APERIO (ACANDIS)

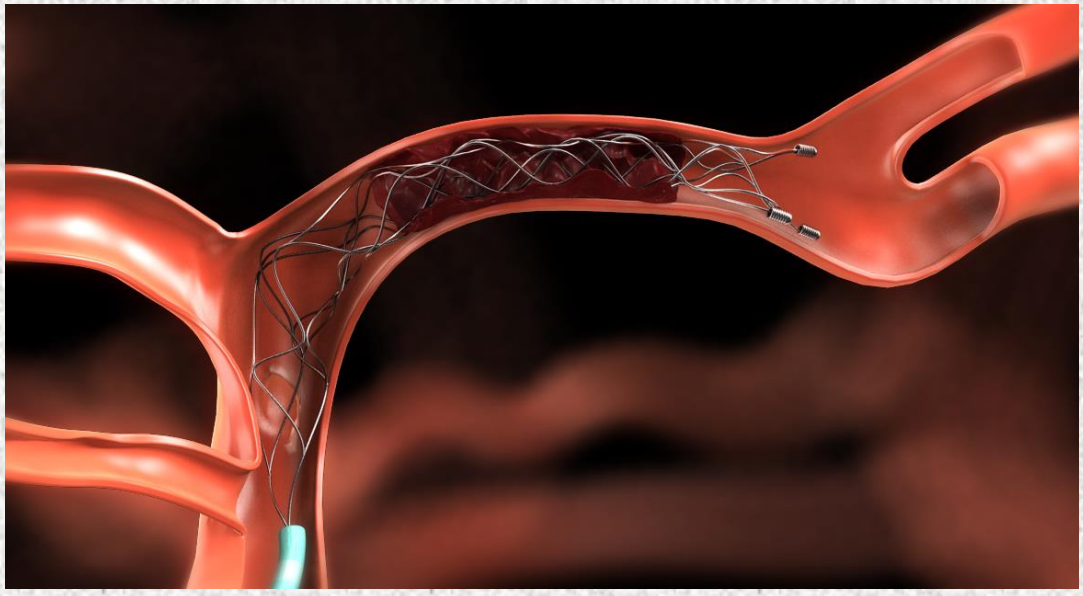


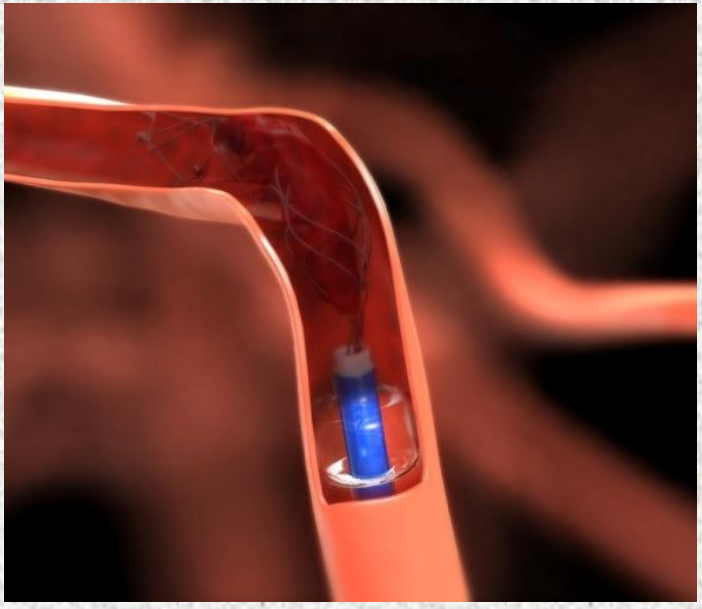
Penumbra 3D



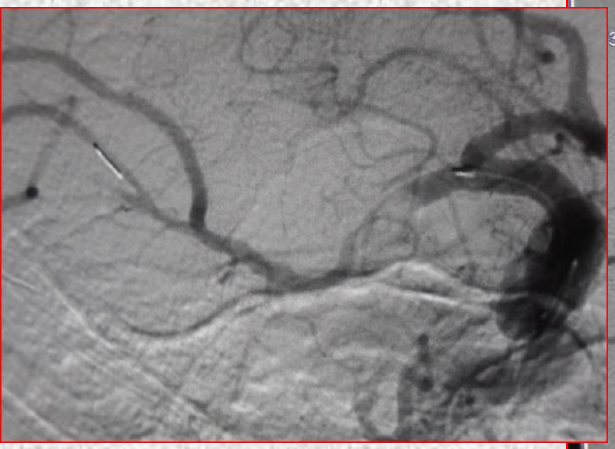
STENTRIEVERS (Stent like retrievers)

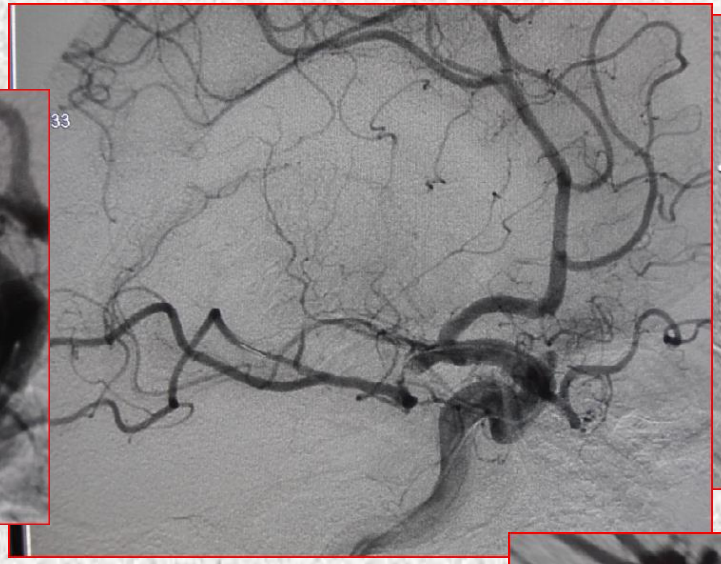
- Stent-like structure
- Retrieval of the clot
- "Endovascular by-pass" effect with immediate flow restoration
- Mechanical action of clot fragmentation

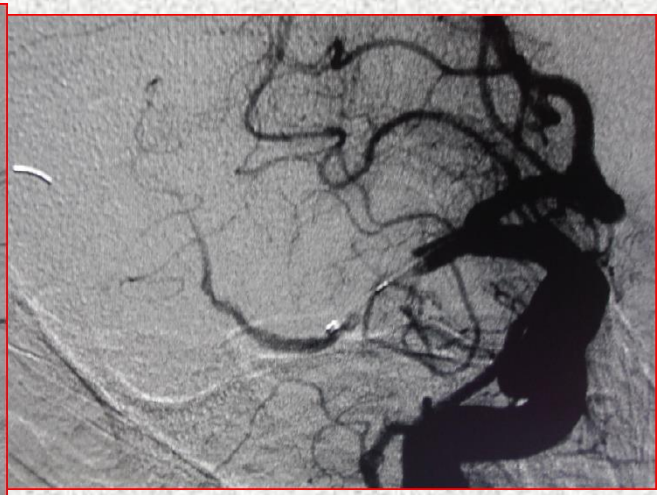


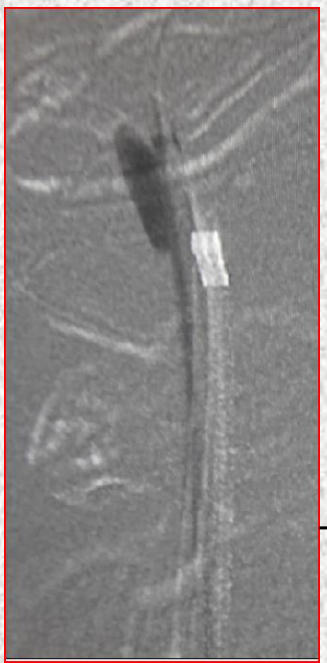


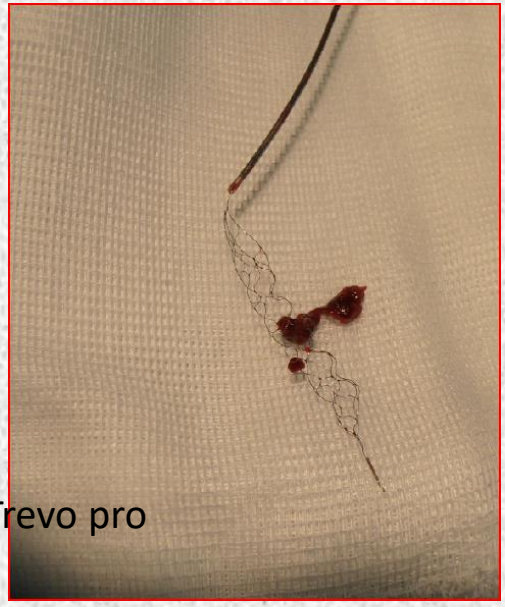
M, 67 yo. Atrial Fibrillation H 13:15 left hemiplegia, confusion
CT scan negative H 15:30 i.v. tPA (full dose) (NIHSS 18),
No clinical improvement After 1 h
H16:15 arrive at Angiosuite



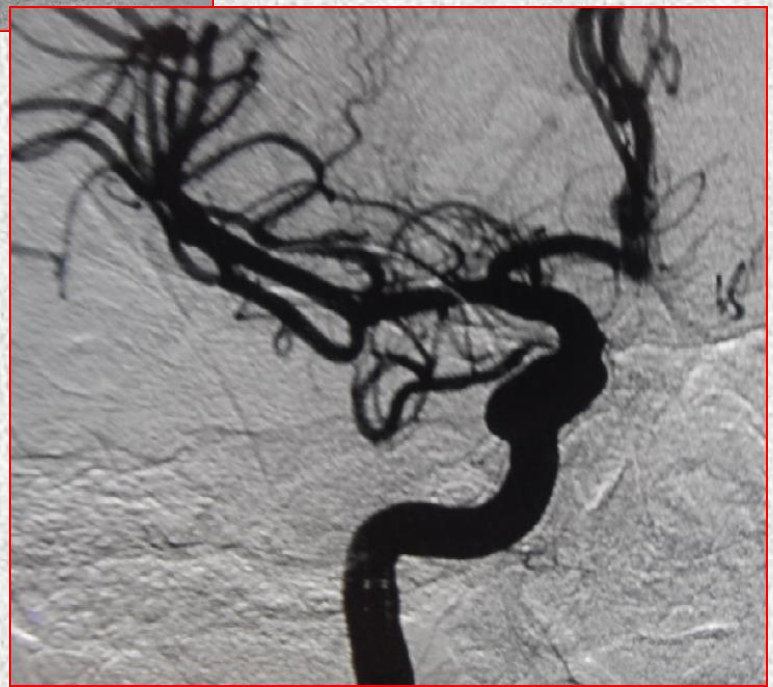






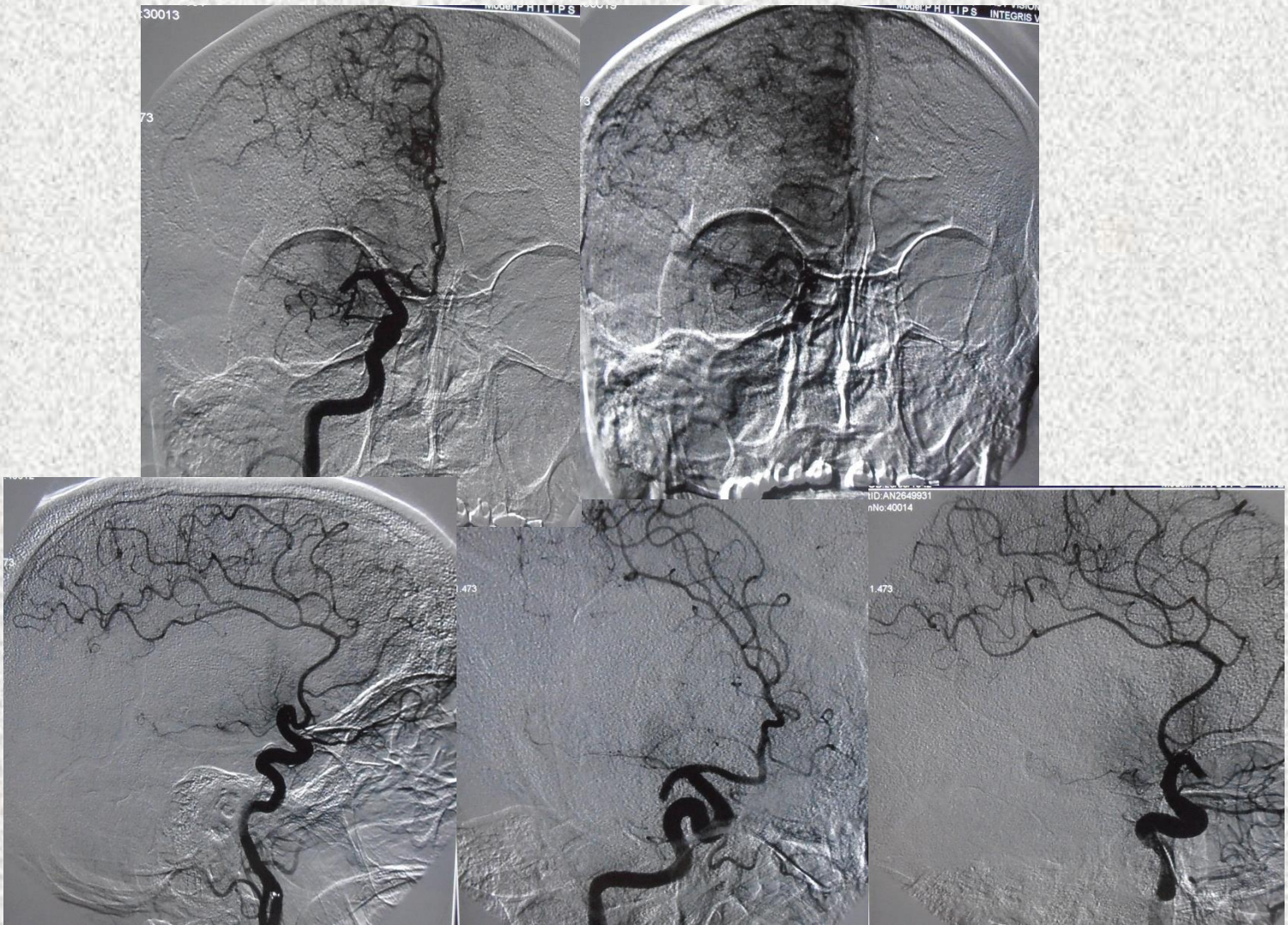


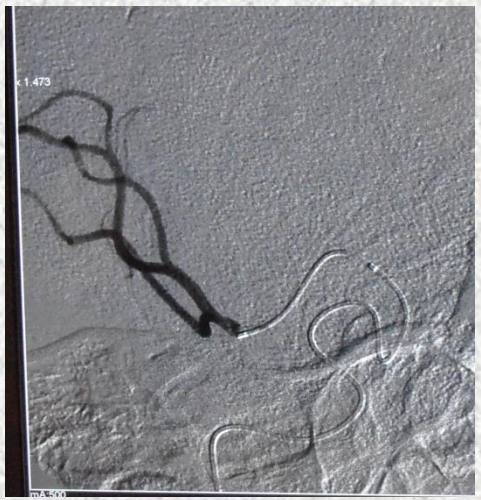
Trevo pro

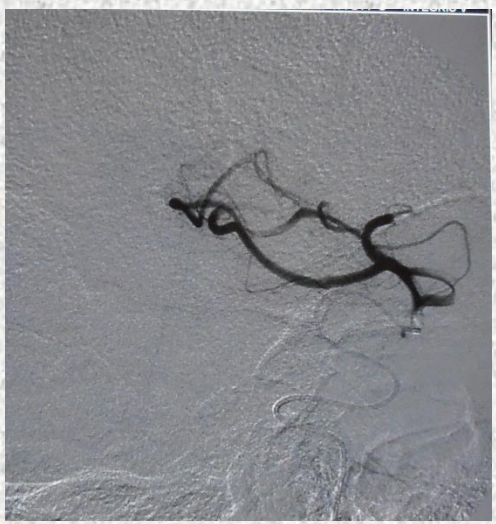


Technique : thrombectomy (Mechanical Clot Disruption)

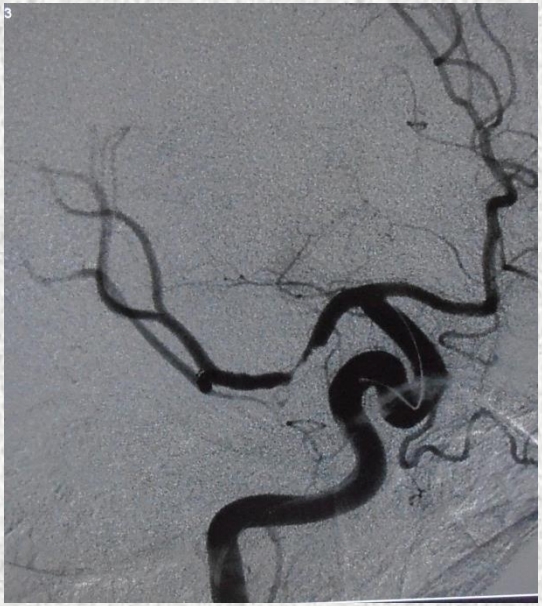
F, 70 y.o., left hemiparesis , dysarthria (NIHSS 16)
Time of ischemia 5 h

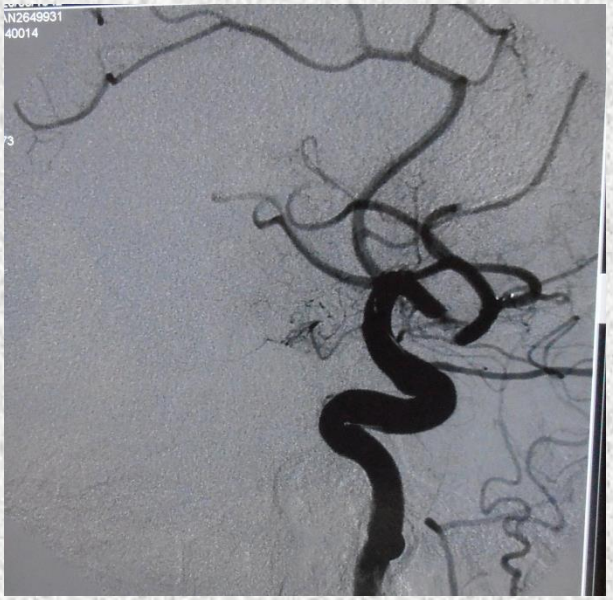




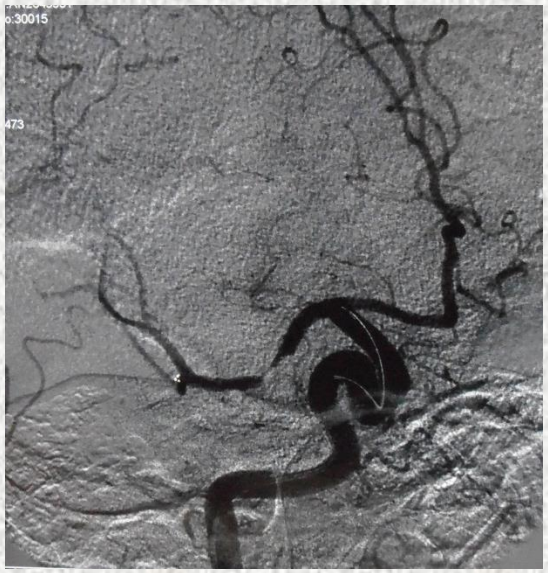


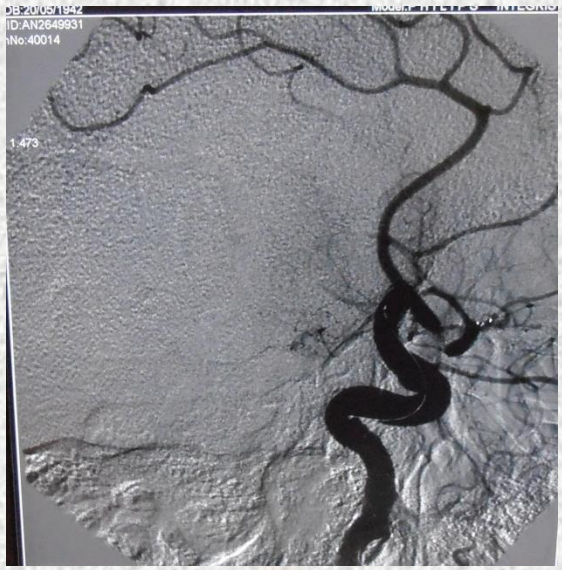
Envoy 6F
Prowler Select Plus
Terumo .012
Solitaire 4x20



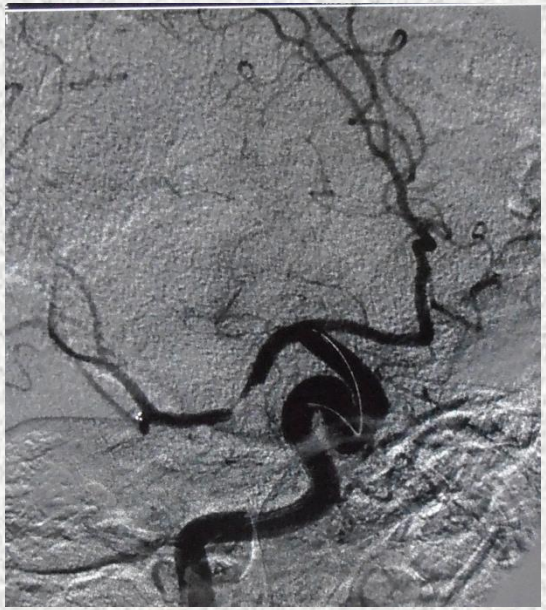


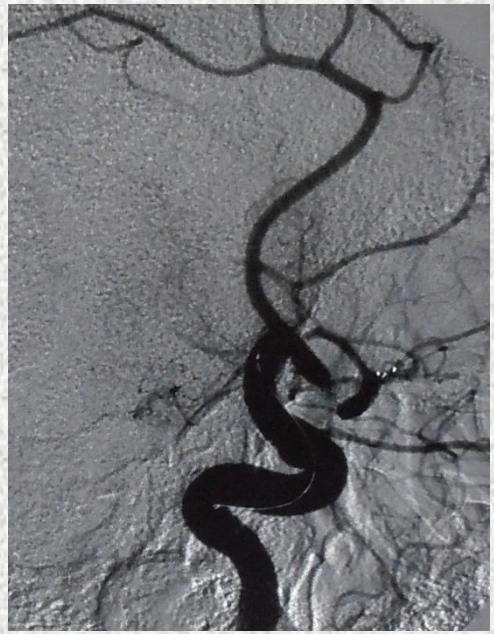
After positioning of the Solitaire





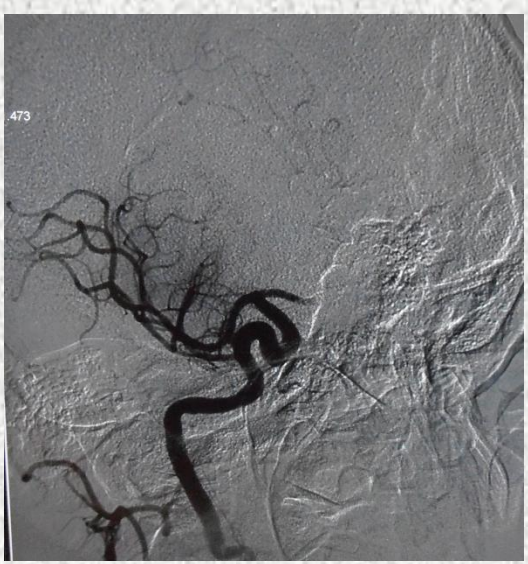
Watch and wait…

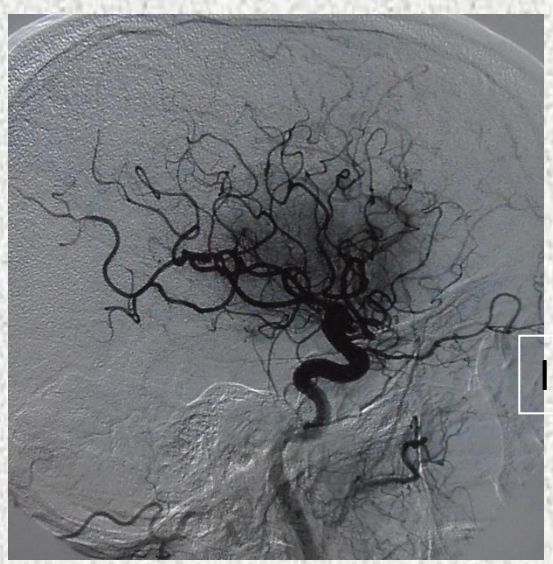




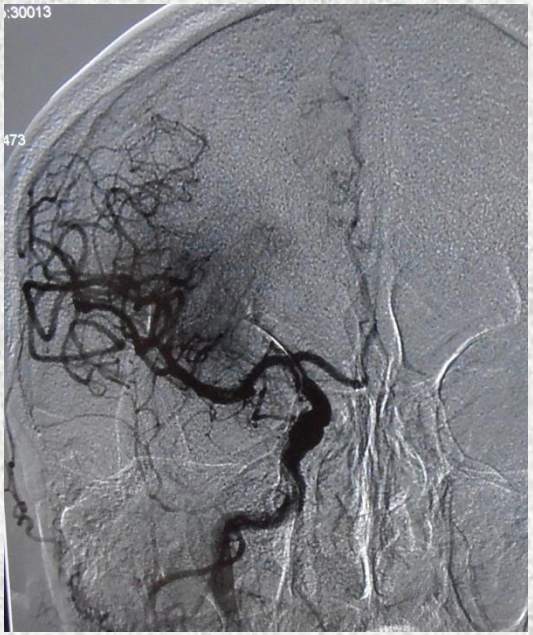
5 min control:
Stent opened within the clot
Control after other 5 min

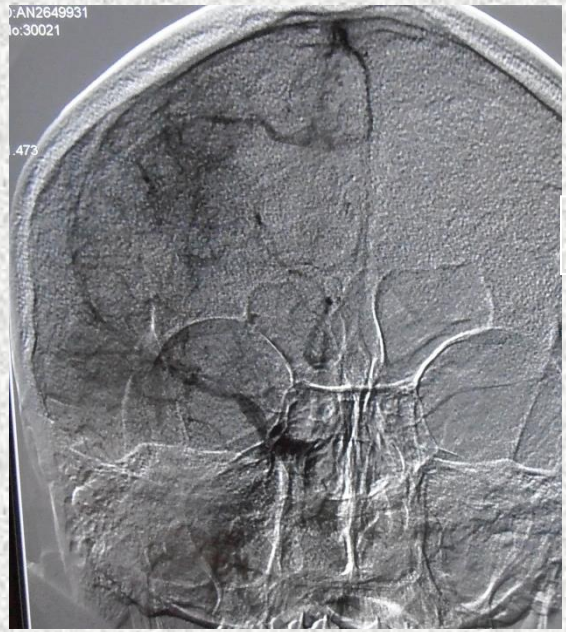
10 min Time of Interaction stent clot



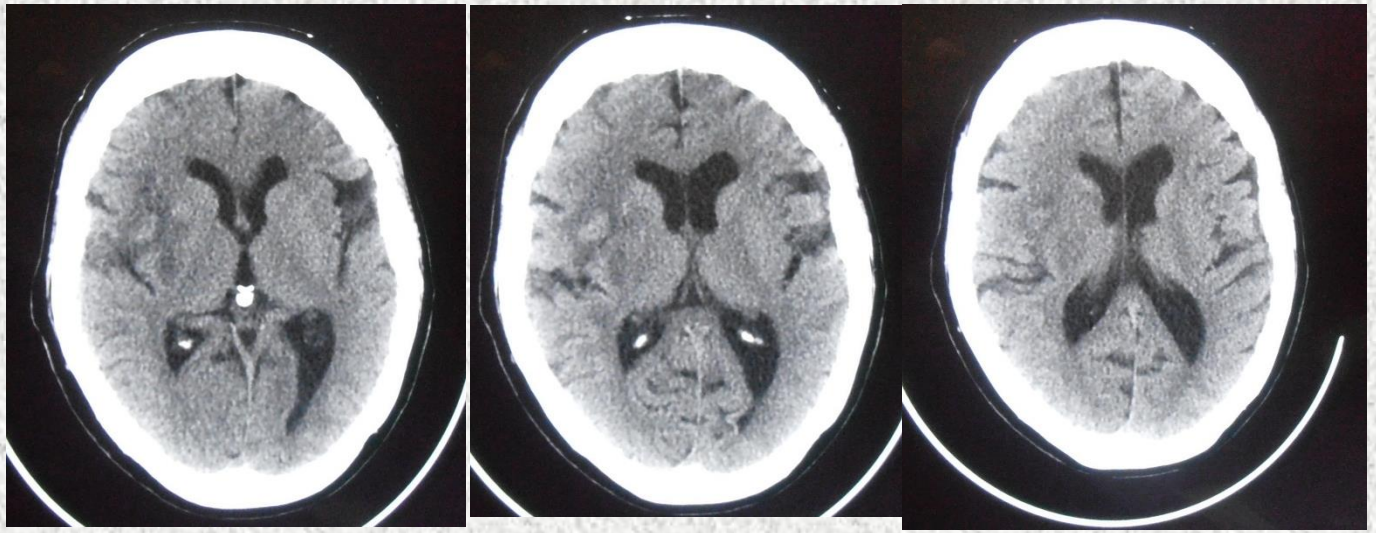


Immediately after retrieval





Final DSA (after 5 min.)

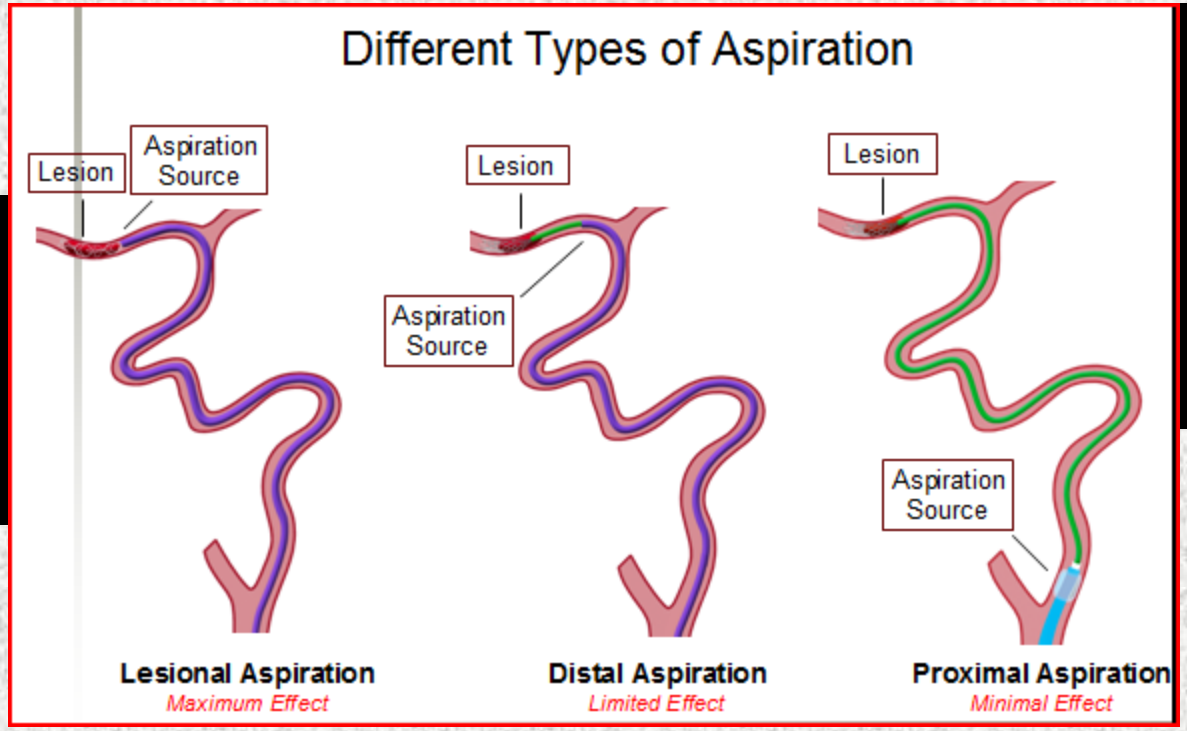


TC 24 h
NIHSS 0 at the discharge

thrombus-aspiration
(3 different techniques)

Lesional Aspiration

Microcath.
In contact with the clot



Proximal aspiration

- BOC (balloon occlusive guiding catheter)
- Prepetrosal internal carotid)

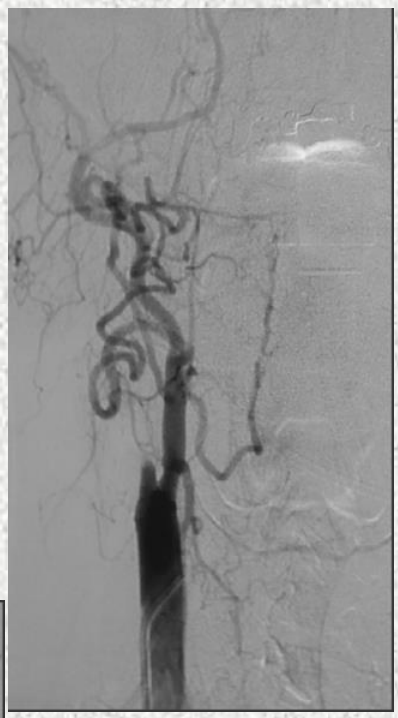
Distal aspiration

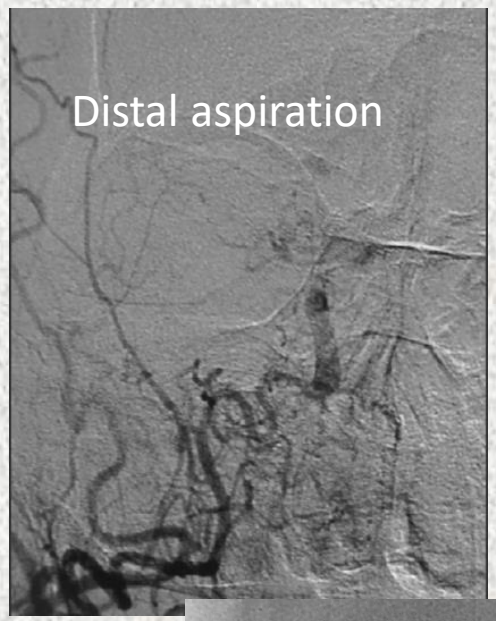
- Intermediate Catheter (4F)
- Distal Navigation with micro
- The closest to the clot to aspire

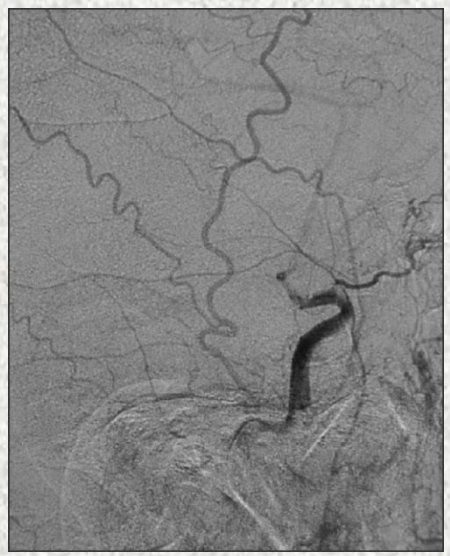
F, 71 aa.,

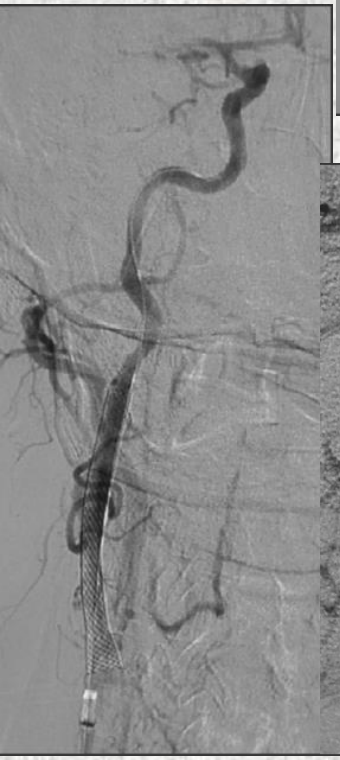
NIHSS 19

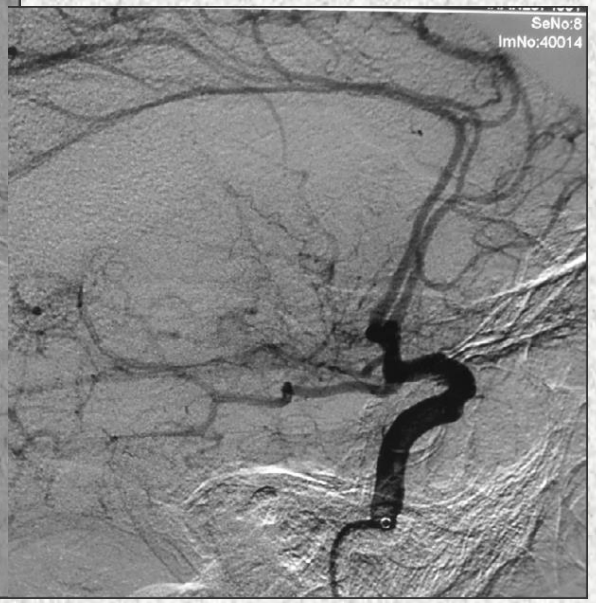
OTT 5 h

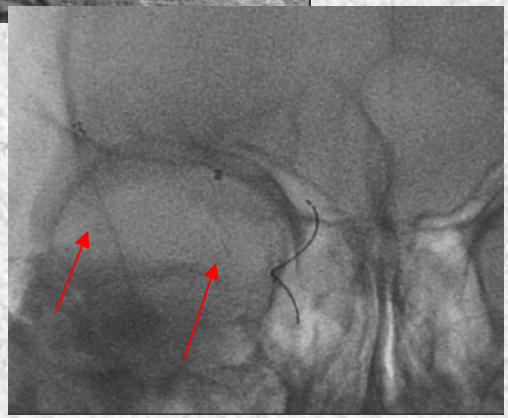


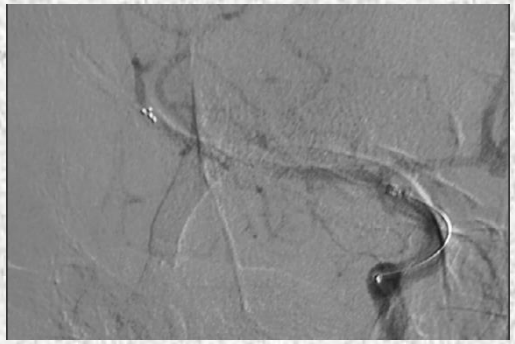


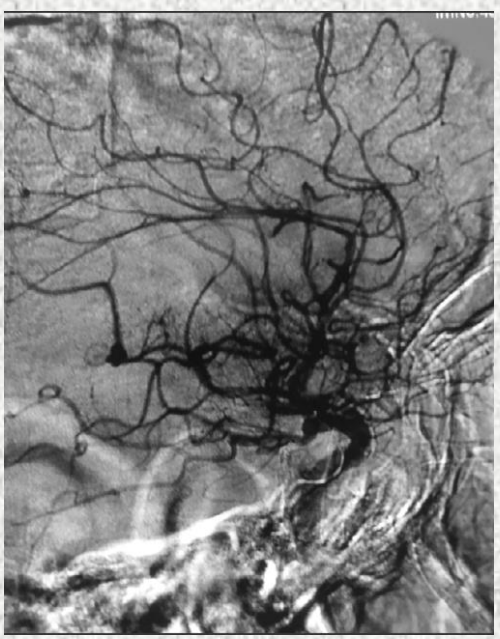












Proximal Thromboaspiration

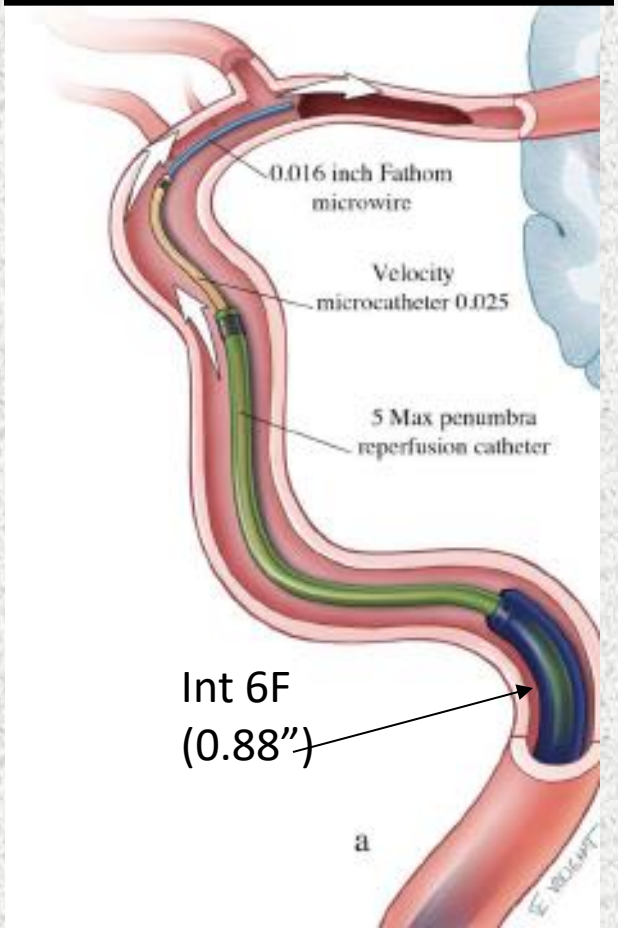
Direct thrombus aspiration
(**ADAPT** technique: removal through thrombo aspiration)

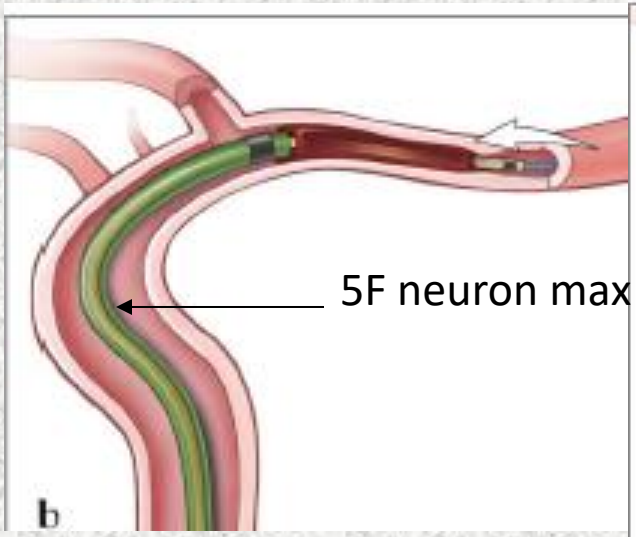
new technique utilizing a direct aspiration first pass technique with a large bore aspiration catheter as the primary method for vessel recanalization.

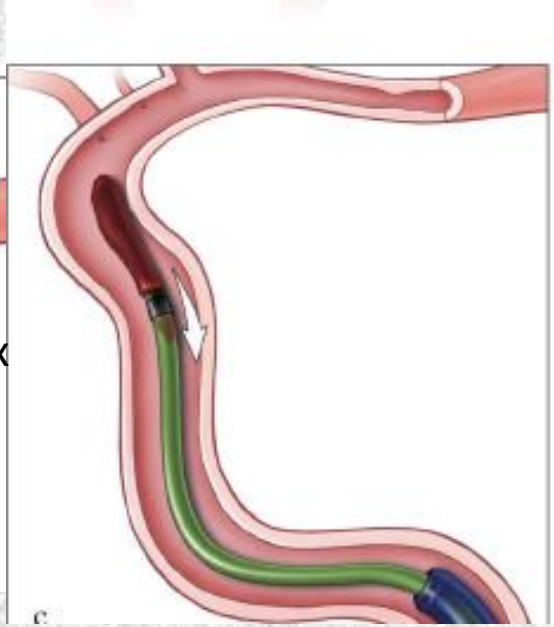
ORIGINAL RESEARCH

Initial clinical experience with the ADAPT technique: A direct aspiration first pass technique for stroke thrombectomy

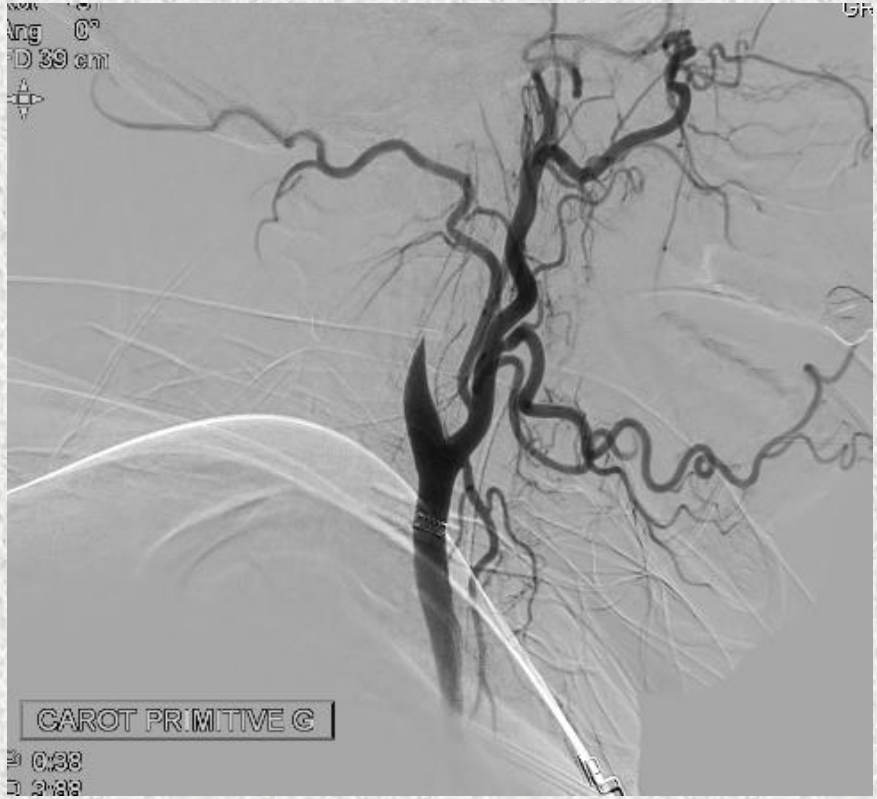
Aquilla S Turk,[1] Alex Spiotta,[2] Don Frei,[3] J Mocco,[4] Blaise Baxter,[5] David Fiorella,[6] Adnan Siddiqui,[7] Maxim Mokin,[7] Michael Dewan,[4] Henry Woo,[6] Raymond Turner,[2] Harris Hawk,[1] Amrendra Miranpuri,[1] Imran Chaudry[1]

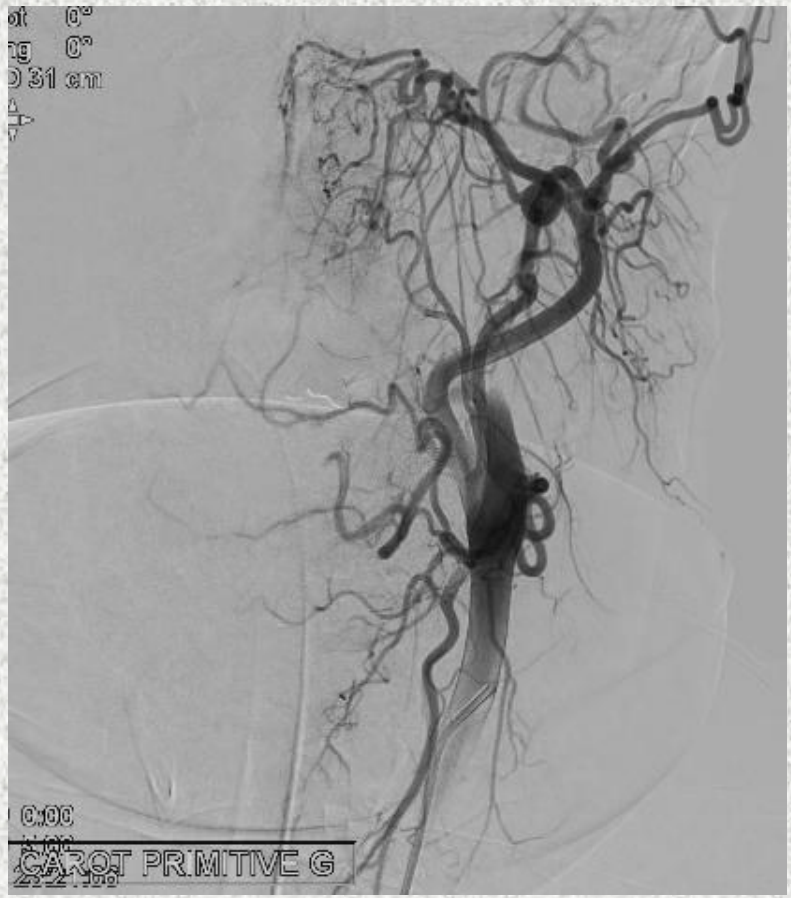


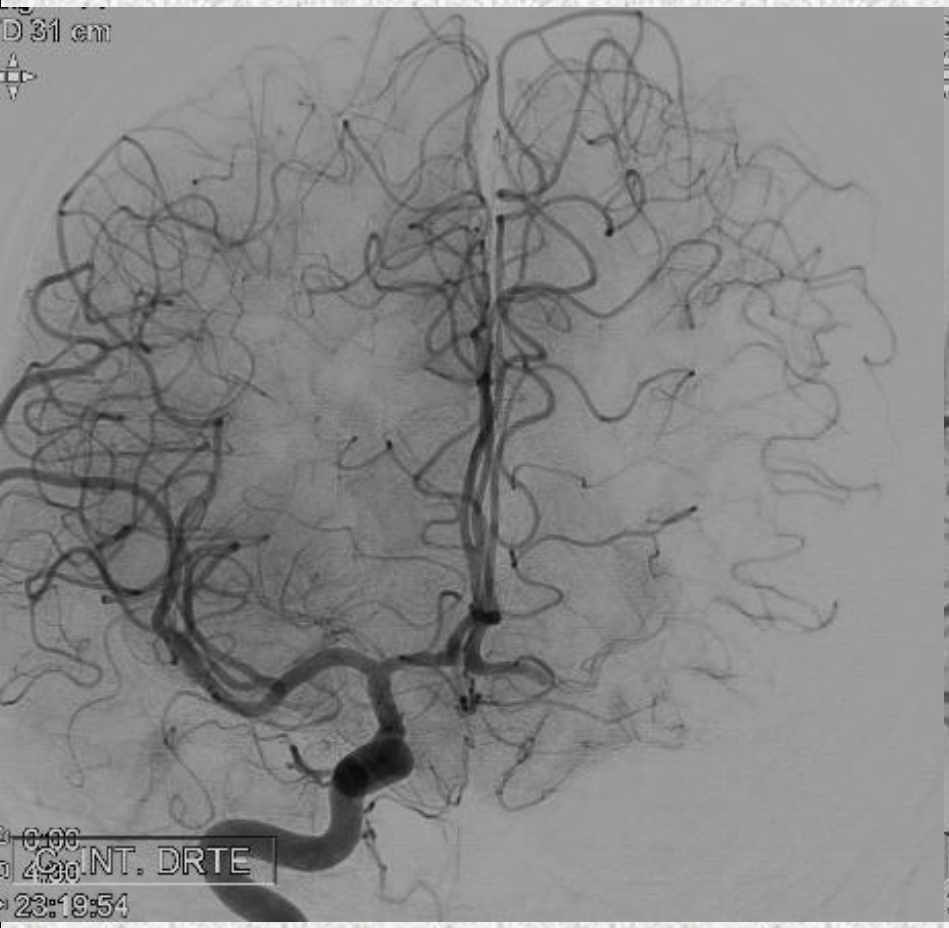


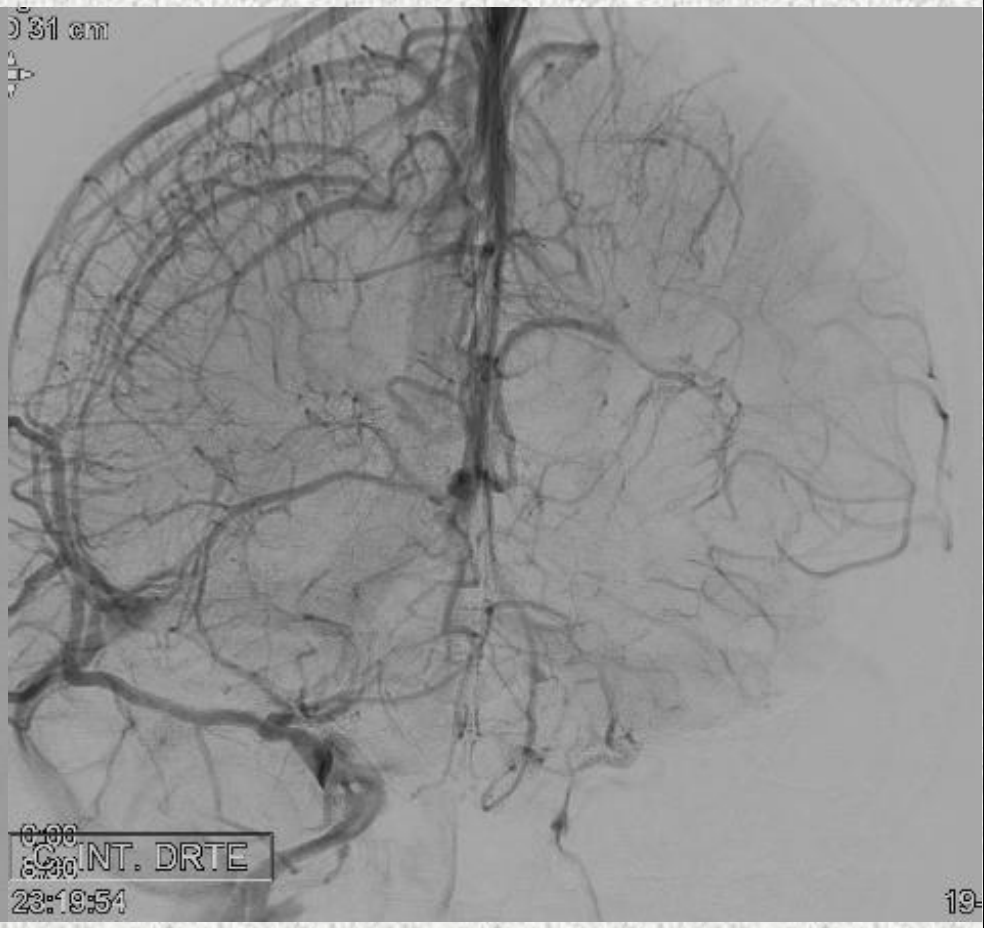


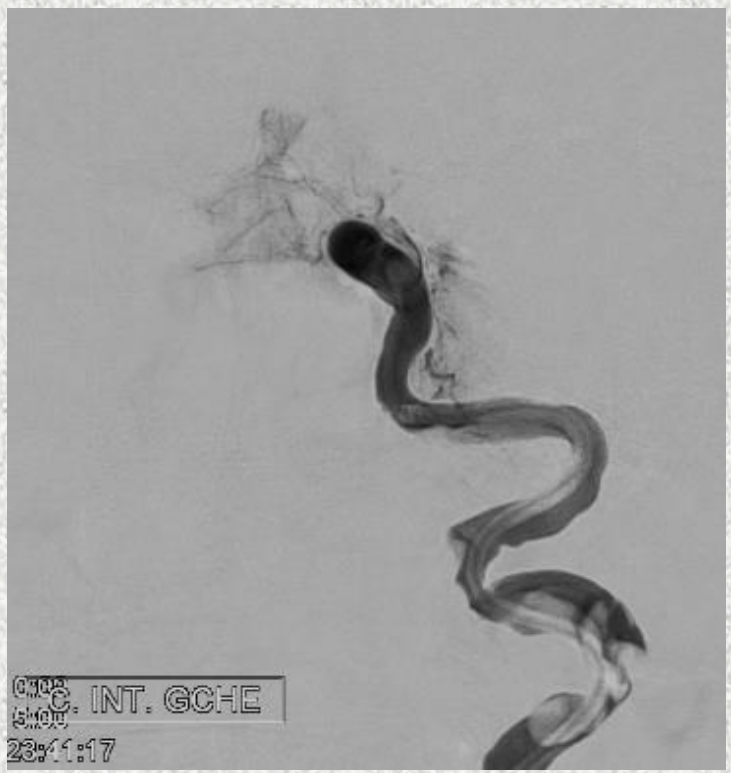
F, 40
NIHSS22
Fibrinolisi i.v.
Onset to groin: 5h15…

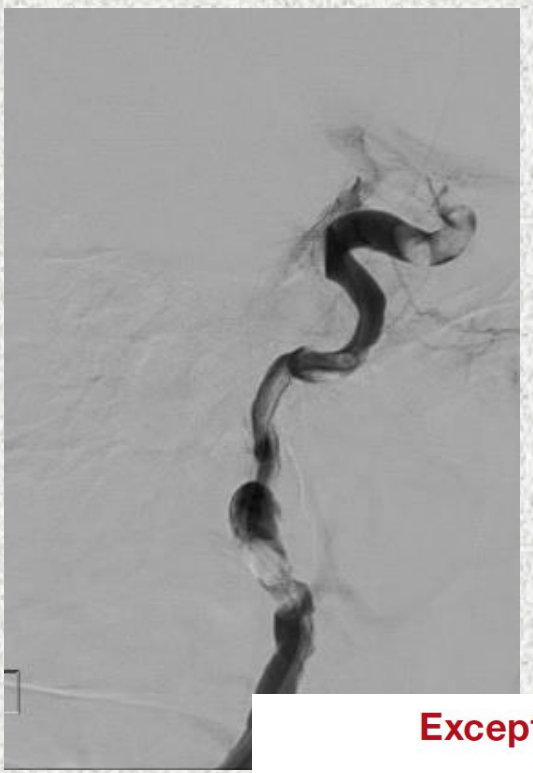




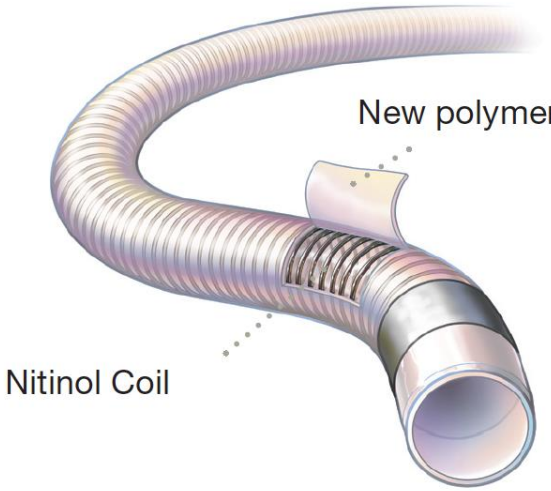

D 31 cm
CONT. DRTE
23:19:54

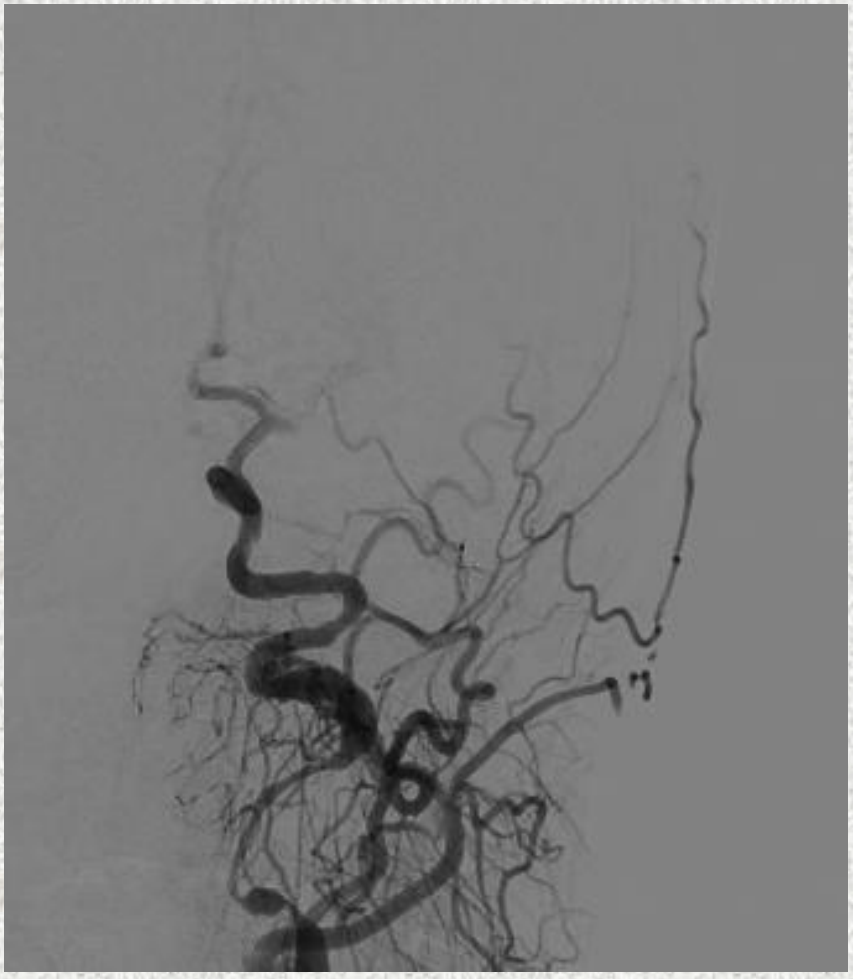

D 31 cm
CONT. DRTE
23:19:54

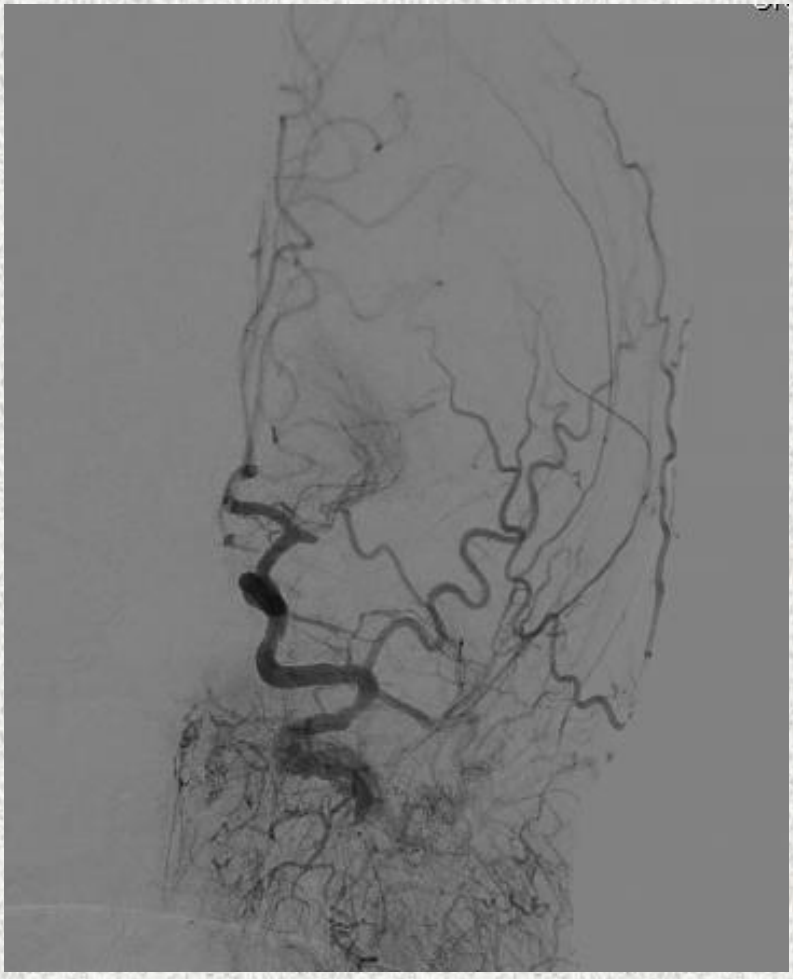


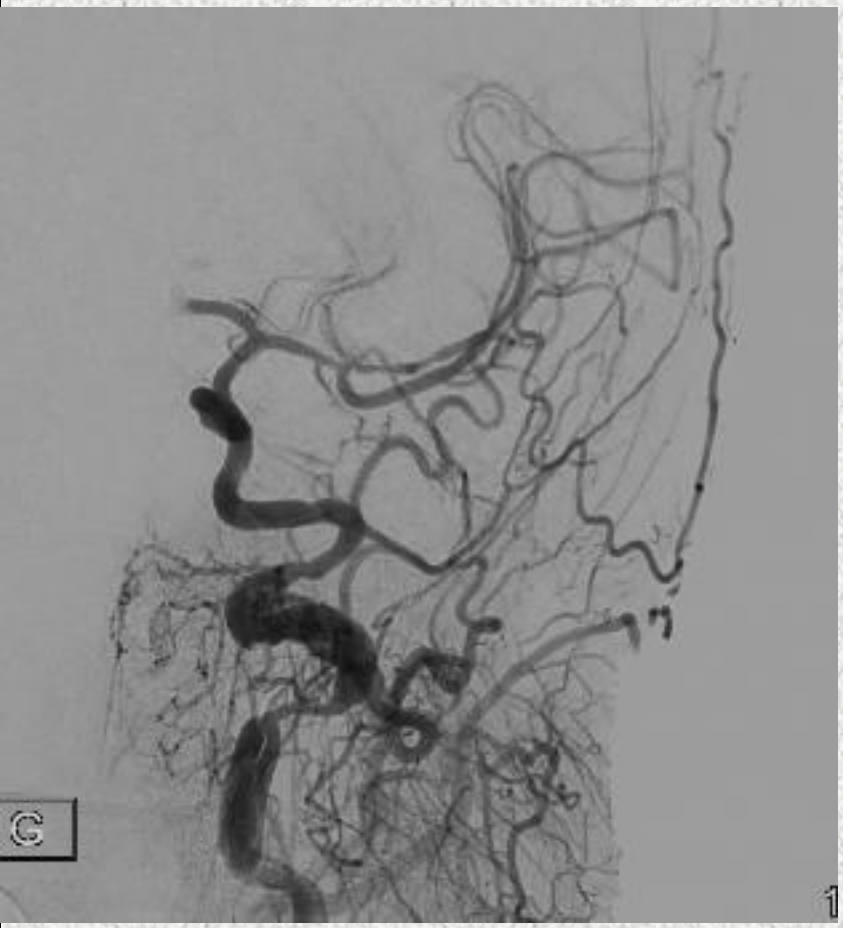


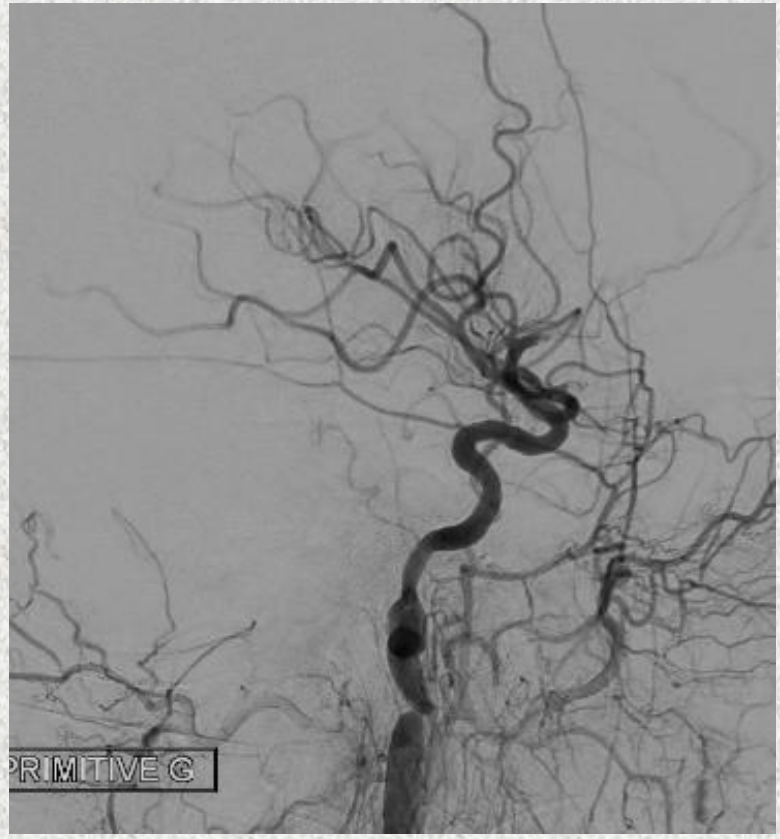
Exceptional Trackability







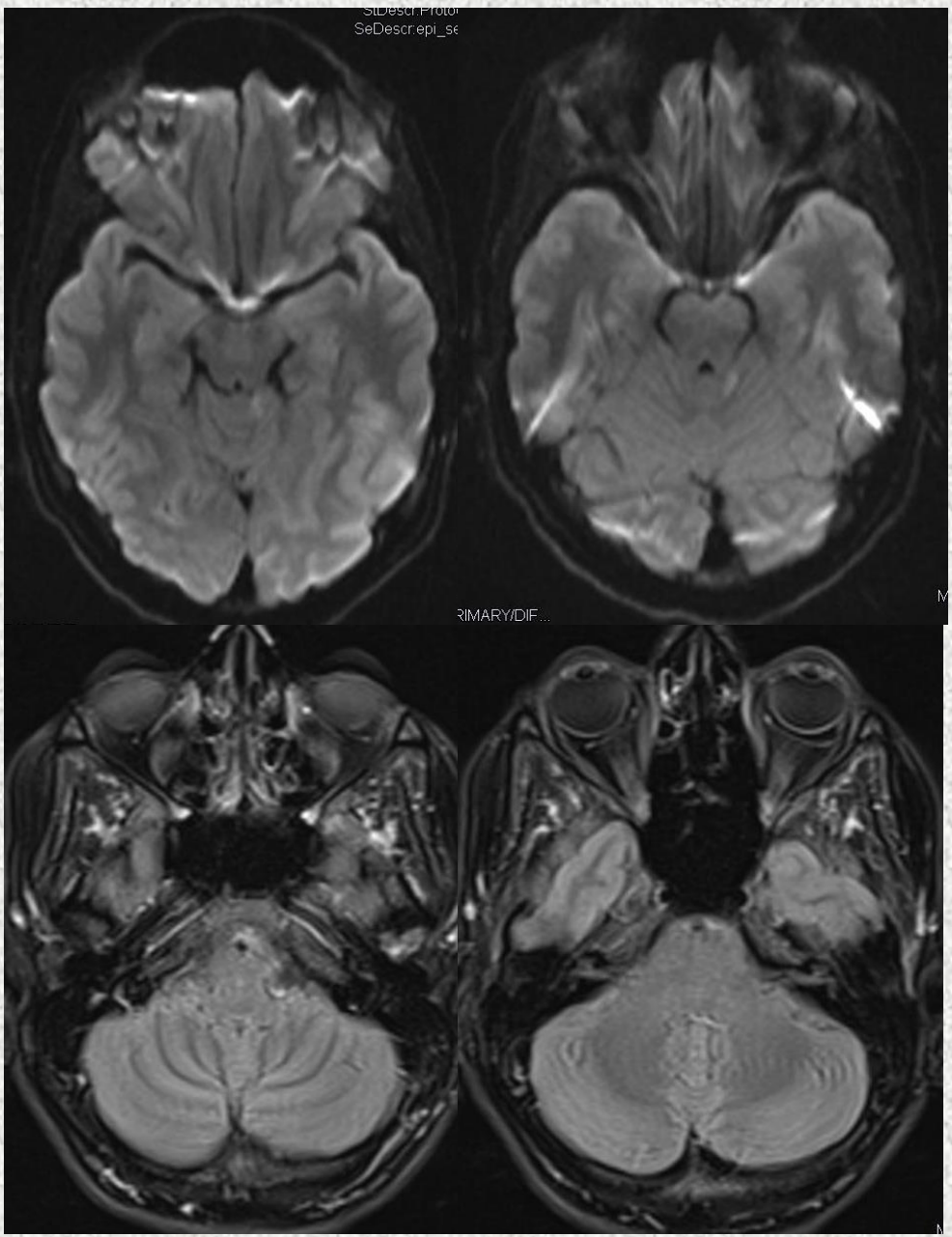




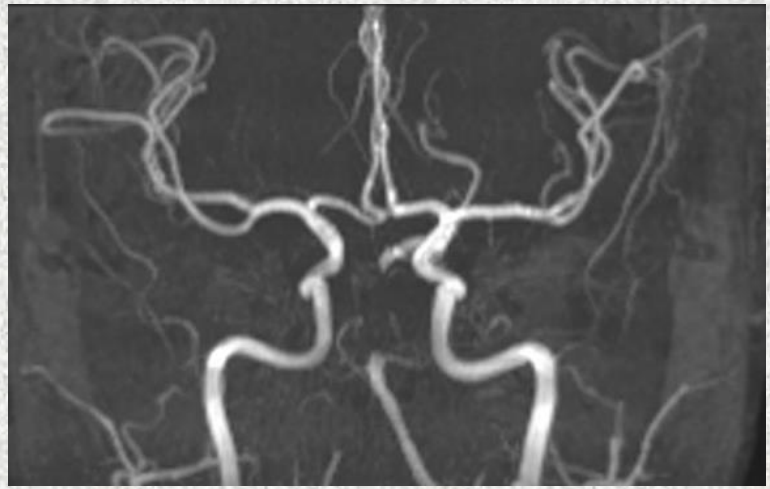
TTR 5h50

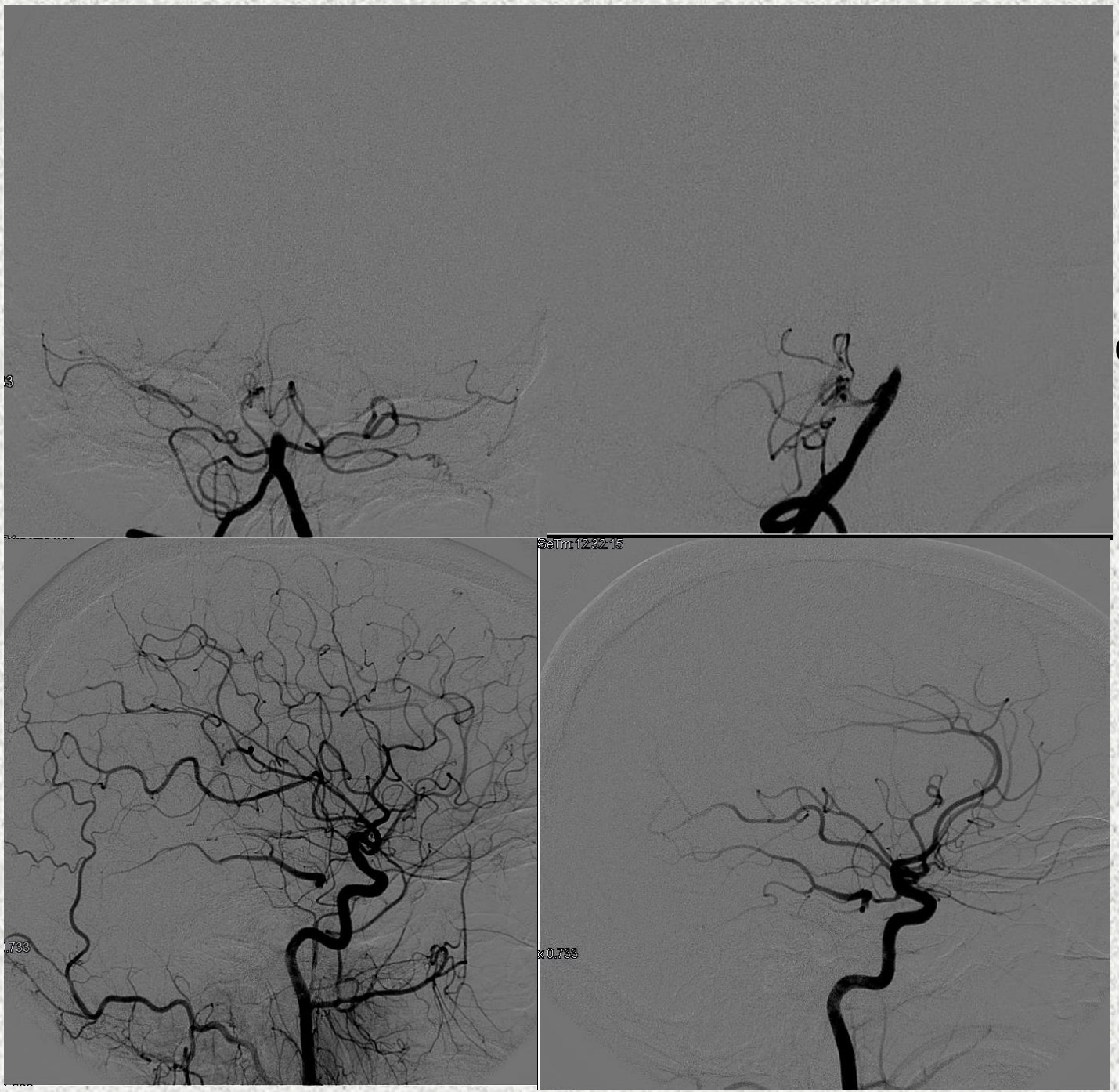
Time of procedure 35 min

Combination of thecniques

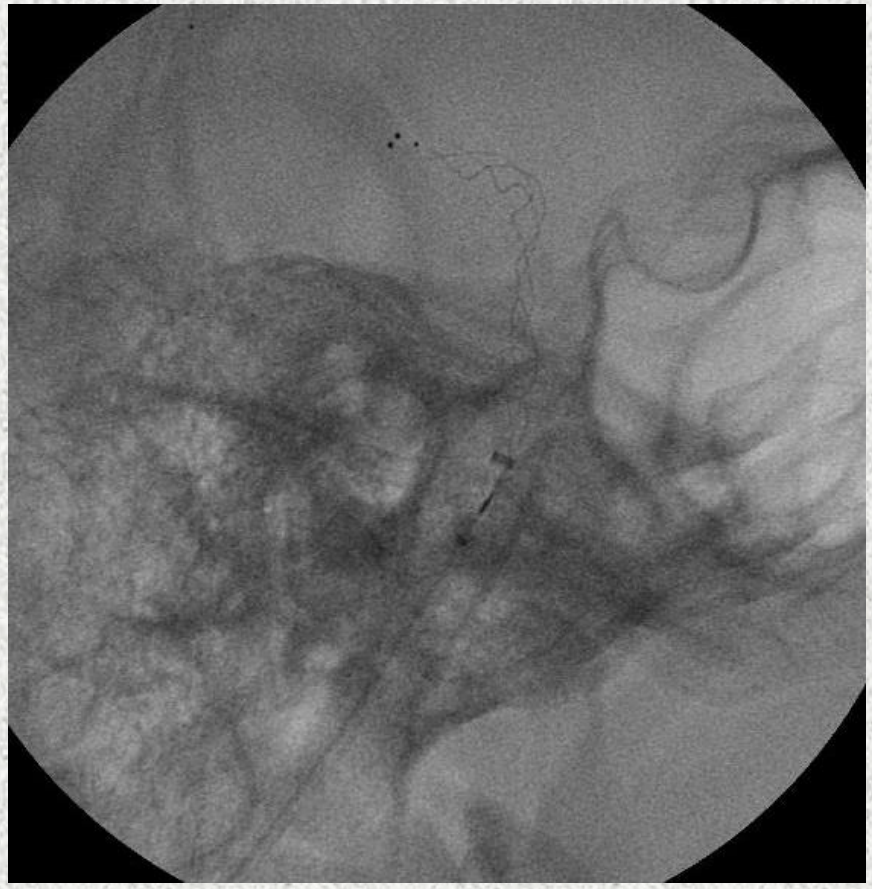


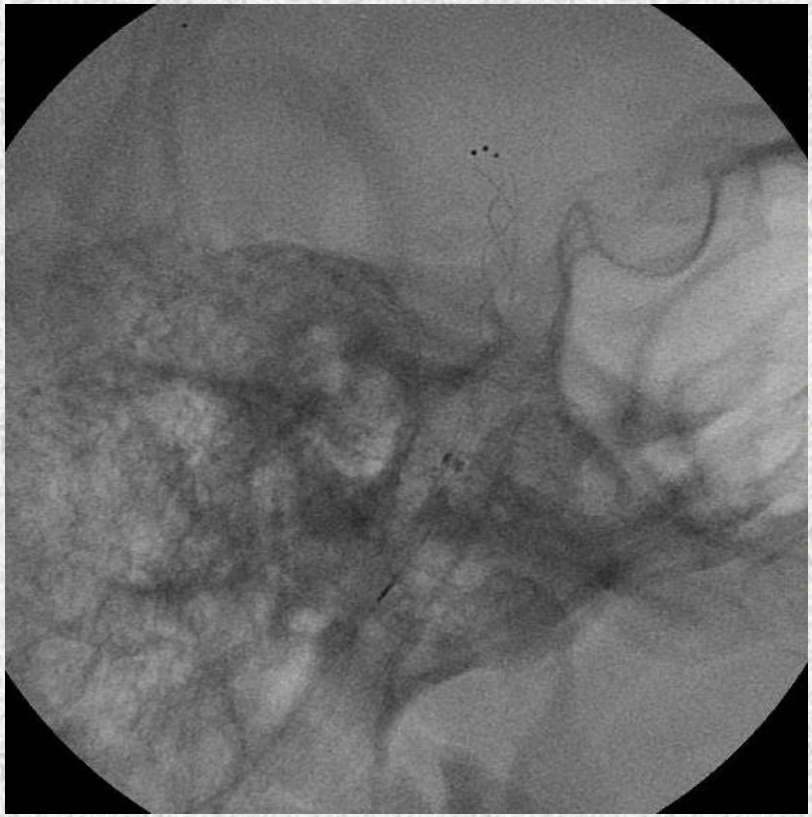
F, 34 yo
X week of pregnacy
GCS9





Onset to groin 4h45 min





Trevo Xp Provue + Revive IC
Rimosso il microcatetere

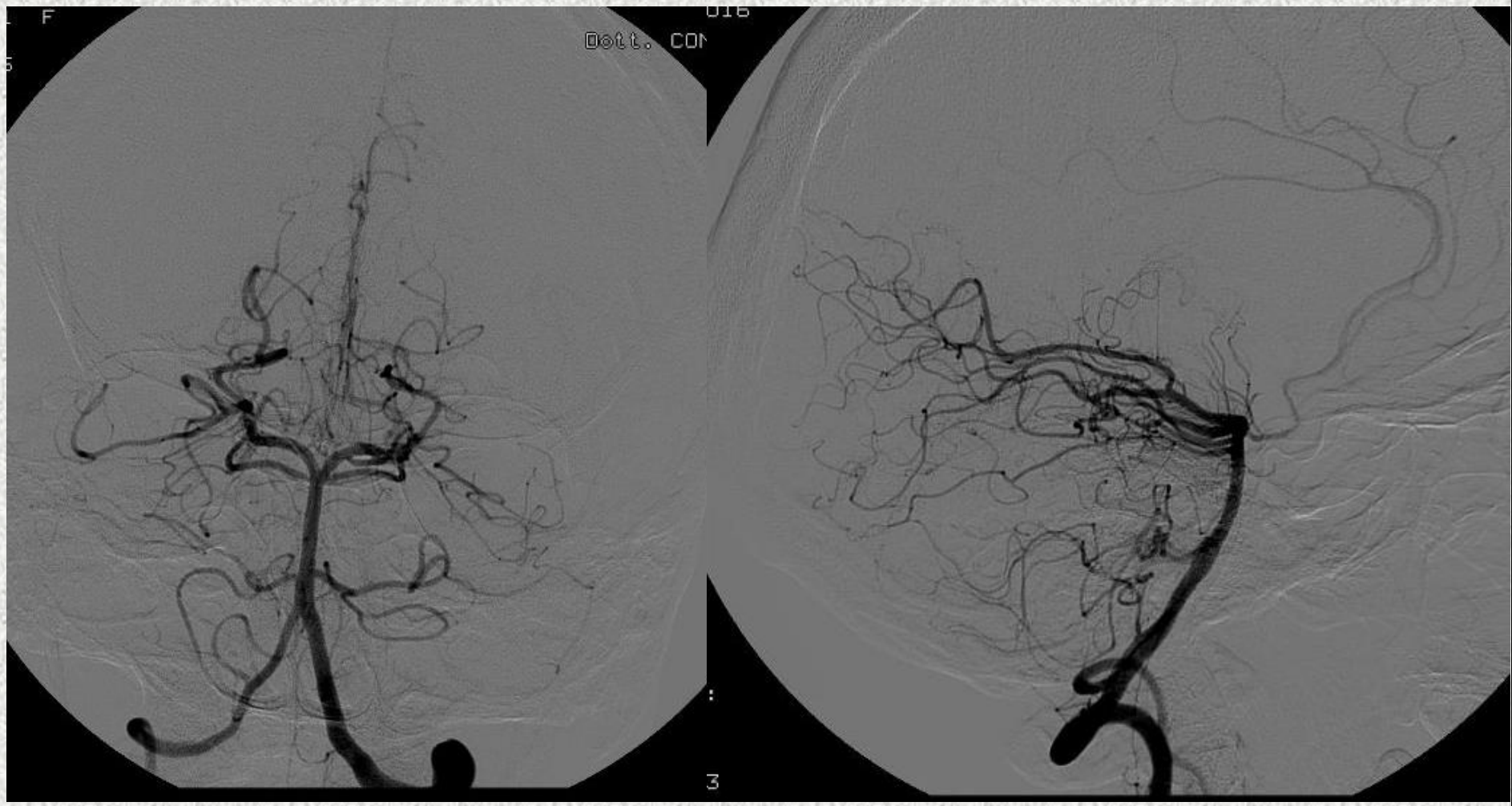
Pince tecnique

1 passage

TTR: 5h

16 min of proceture

, 5.6 min of Xray exposition , 24786 mGcm^2



rationale use of device

- High clot burden (ACI + MCA occlusion) ADAPT technique first
- M1 , M1-M2 BA : stetntriver with proximal thrombus aspiration first
- Distal occlusion (P2, P3 A2-A3, Cortical arteries) Thrombus aspiration First

Conclusion

- **To treat stroke is not a matter of techniques**
- **To treat a stroke is a matter of understanding the clinical status, the perfusional profile , the collateral circulation , the clot stucture , the extension and localization of the occlusion**
- **All these are the points on the base of which it is possible to have a tailored and rationale approach to the stroke pathology**

Trattamento endovascolare dell'ictus ischemico cerebrale in fase acuta

RELAZIONE FARMACI e DEVICE Nelle COMPLICANZE EMORRAGICHE

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