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LA GESTIONE DELLE LESIONI TANDEM NELLO STROKE ISCHEMICO

How to treat stroke tandem lesions

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Introduction

Tandem occlusion

- Acute tandem obstructions/occlusions of the extracranial ICA and intracranial ICA/MCA make-up **10-20%** of major strokes[1,2].
- Acutely symptomatic ICA occlusion cause severe neurological **morbidity** in up to **70%** and **mortality** up to **55%**[3].
- Poor response to trombolyisis t.
- : **low recanalization (~20%), unfavourable outcome in 80-100%**[2,4].
- Different etiologies of cervical ICA lesion: **atherosclerotic** vs **dissection** vs large **thrombembolus**
- Epidemiologic studies have also shown that extracranial artery disease is more prevalent among whites than blacks and Asians
- Endovascular treatment with stent-retrievers with or without concomitant extracranial stenting of the underlying obstructive lesion is an emerging treatment option.

[1]Grau Stroke 2001, [2]Rubiera Stroke 2006, [3]Meyer Ann Surg 1986, [4]Endo AJNR 1998

Introduction

- Relatively few patients with TLs were included in the major randomized controlled trials of EVT, and management of the c-ICA was generally not specified by protocol or analyzed post hoc.

- In the absence of robust randomized trial data, no firm recommendations about optimal management can be forwarded, as reflected in the most recent American and European guidelines.

- Treatment decisions are often complex, and strategies vary according to clinical, anatomic, and technical considerations in addition to physician preference.

Introduction

HERMES Collaborators

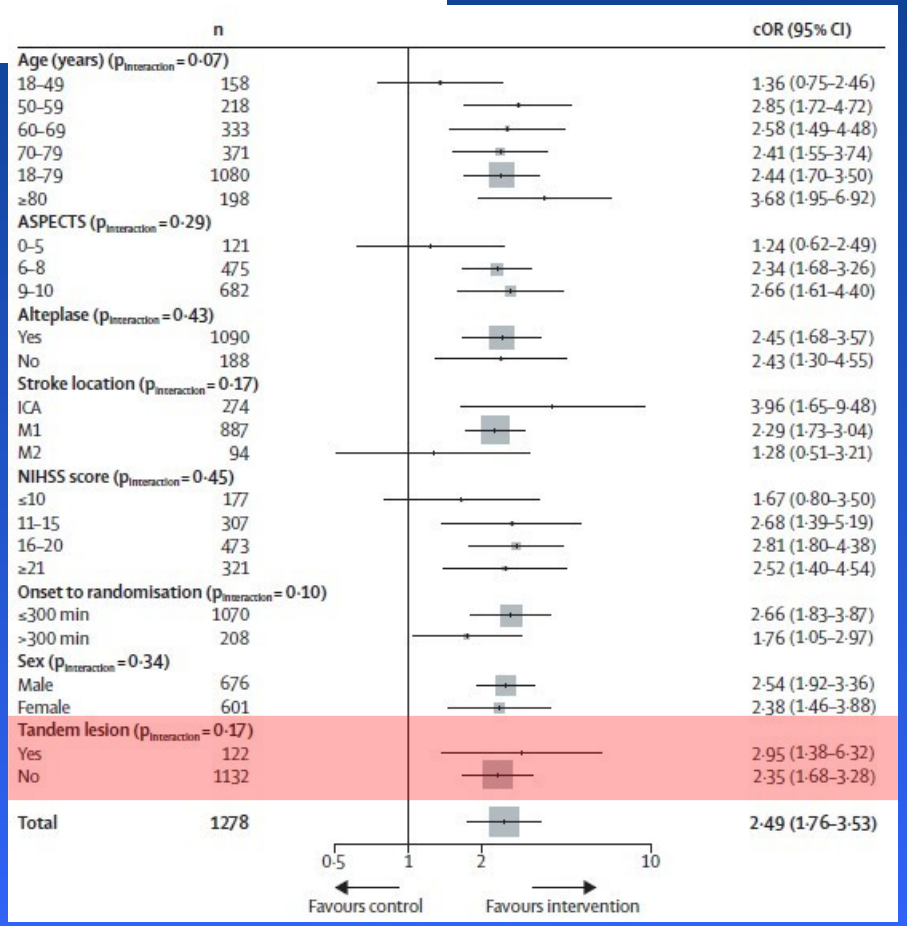
Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

- Pooled patient-level data
- 1287 patients

- **Benefit** from EVT for intracranial occlusion, with or without concomitant (tandem) occlusions of the extracranial ICA

- Patients with tandem occlusions **should not be excluded from treatment**



Introduction

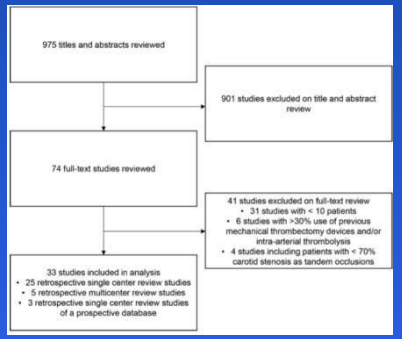
Management of tandem occlusions in acute ischemic stroke – intracranial versus extracranial first and extracranial stenting versus angioplasty alone: a systematic review and meta-analysis

Mitchell P Wilson,[1] Mohammad H Murad,[2] Timo Krings,[3] Vitor M Pereira,[3] Cian O'Kelly,[4] Jeremy Rempel,[1] Christopher A Hilditch,[3] Waleed Brinjikji[3,5]

Table 2 Meta-analysis outcome data for overall tandem occlusions treated with mechanical thrombectomy, intracranial first versus extracranial first approaches, and stenting versus angioplasty-only approaches

Outcome	Overall rate (95 CI, I^2)	Intracranial first (95 CI, I^2)	Extracranial first (95 CI, I^2)	P	Stenting (95 CI, I^2)	Angioplasty (95 CI, I^2)	P
90-day mRS ≤ 0-2	47% (42–51% 48%)	49% (39–60% 31%)	53% (44–61% 11%)	0.58	49% (42–56% 54%)	49% (33–65% 50%)	0.39
90-day mortality	15% (11–19% 48%)	15% (3–32% 41%)	8% (3–15% 22%)	0.28	10% (6–15% 36%)	13% (0–25% 43%)	0.27
TICI 2b/3	78% (73–82% 57%)	79% (60–93% 77%)	79% (69–88% 52%)	0.96	79% (72–86% 59%)	63% (49–96% 34%)	0.38
sICH	8% (6–11% 36%)	7% (2–15% 0%)	8% (3–15% 21%)	0.95	7% (5–30% 24%)	10% (1–19% 0%)	0.38
Procedure Related Complication	9% (4–16% 66%)	8% (1–20% 53%)	20% (9–21% 0%)	0.25	13% (5–22% 71%)	10% (1–18%0%)	0.87
Technical Success Rate of Carotid Revascularization	97% (90–100%71%)	89% (78–98% 0%)	97% (86–100% 71%)	0.31	96% (84–100% 79%)	97% (88–100% 0%)	0.89
TICI 3	36% (26–48% 71%)	26% (6–52% 72%)	18% (2–40% 75%)	0.55	27% (17–39% 41%)	NA	NA
Any ICH	23% (15–32% 82%)	NA	24% (2–54% 82%)	NA	19% (8–33% 84%)	20% (0–40% 60%)	0.39
Procedure Time in minutes	79 (70–88% 93%)	78 (54–101% 90%)	75 (53–97% 95%)	0.67	74% (62–87% 95%)	73 (64–82% 80%)	0.98

- 33 studies
- 1102 pts.



Overall treatment results and outcome similar to isolated large vessel occlusion!

Atherosclerotic Plaque versus *Dissection*

In paints with TLs, the mechanism of stroke usually involves artery-to-artery embolization of the clot from:

Atherosclerotic plaque

Dissection

Atherosclerotic Plaque *versus* ***Dissection***

- Atheromatous lesions and dissections in most studies pooled as ‘tandem occlusions’[1,2].
- Different **disease entities**, patient **population** and **pathophysiologic origin**:

- Atherosclerotic lesion	- ‘vulnerable’ plaque - older patients - more prone to have good leptomeningeal collaterals[3], larger mismatch? - high stroke recurrence rate[4] - navigation through high grade stenosis and stenting
- ICA dissections	- intramural hematoma - younger patients - less prone to have good leptomenigeal collaterals, lesser mismatch? - stroke recurrence rate seems low[5] - navigation in true lumen, mobilisation of in-situ thrombus during stenting

[1]Behme AJNR 2015, [2]Lescher Cardiovasc Intervent Radiol 2015, [3]Rebello Eur J Neurol 2017, [4]Arauz Cerebrovasc Dis 2006, [5]Lovett Neurology 2004

Atherosclerotic Plaque *versus* ***Dissection***

Tandem lesions are most often atherosclerotic in nature, with an underlying plaque becoming unstable, rupturing, and triggering local thrombus formation with distal embolization of thrombus fragments.

Published series of acute TLs suggest that about:

- **60%–70%** are due to atherosclerotic plaque;
- **20%–30%** due to dissection
- The remainder, attributable to carotid webs and cardiac emboli.

Dissection

Patients with TLs due to carotid dissection tend to have more favorable demographic profiles, being younger with fewer comorbidities than patients with atherosclerotic lesions.

Acute stent placement for an ICA dissection is less commonly performed than for atherosclerotic lesions

Likely due to anatomic considerations (dissected segments may be long and tortuous) and the generally more favorable natural history of dissection, which involves spontaneous vessel wall healing with recanalization in up to 70% of patients.

Addressing the intracranial occlusion first and avoiding routine c-ICA stent placement in patients with dissection appears to be a safe approach

Atherosclerotic Plaque

Atherosclerotic lesions represent an important technical challenge, highlighted by longer procedural times, lower recanalization rates, and more procedural complications in some series.

If stent placement is performed for carotid lesions due to atherosclerotic plaque, angioplasty before and sometimes after stent placement may be required, particularly in calcified plaques

Traversing a complete occlusion may be more challenging and must often be done “blindly” because the distal lumen cannot be opacified.

However, outcomes appear similar regardless of whether cervical ICA pathology is occlusive or stenotic

Atherosclerotic Plaque

- A distinct subgroup comprises patients with isolated acute c-ICA occlusion presenting with symptoms of ipsilateral hemispheric ischemia, with no intracranial occlusion (hemodynamic stroke)

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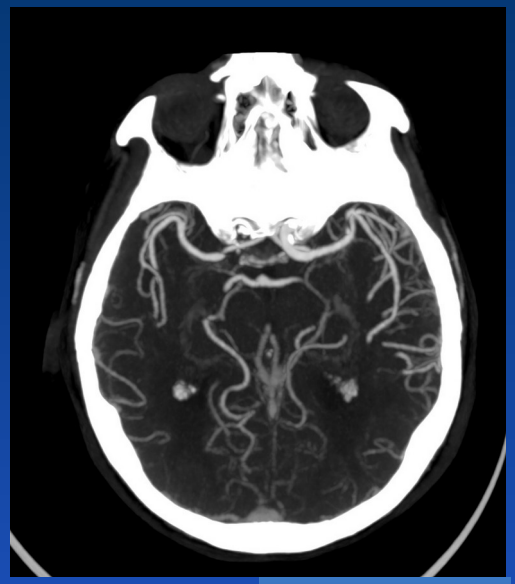
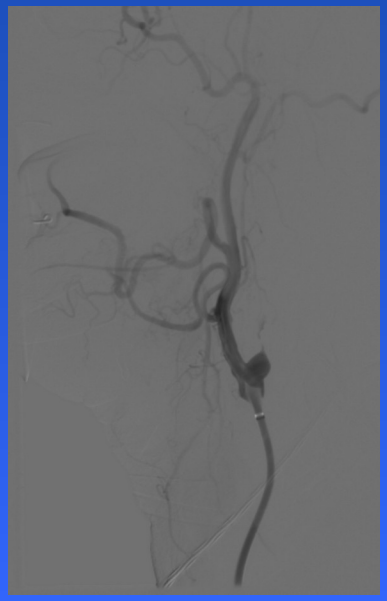
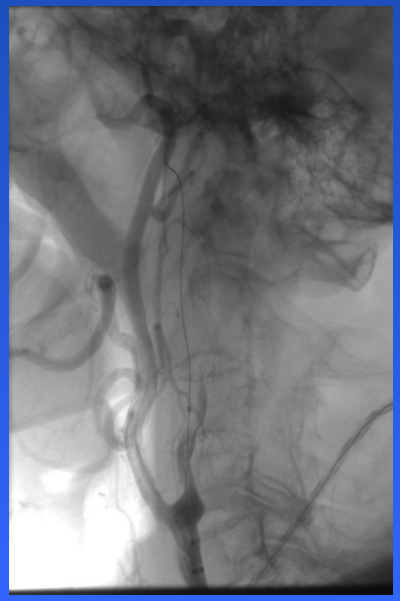
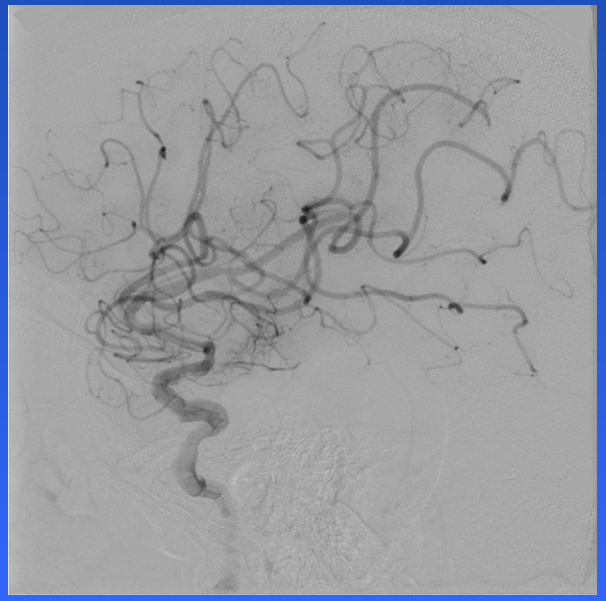


NIHSS 18







True Carotid Occlusion versus Pseudo-Occlusion

It is sometimes difficult to reliably identify patients with true TLs on CTA.

About one-third of patients with presumed c-ICA tandem occlusions using this technique actually have **intracranial carotid terminus occlusions (so-called ICA pseudo-occlusions)** with delayed opacification of the c-ICA due to slow anterograde flow and a stagnant column of nonopacified blood.[17,18]

In such cases, the pseudo-occlusion is usually only confirmed on angiography; however, delayed-phase CTA of the neck may be helpful in confirming true c-ICA occlusions.

Identifying a true tandem occlusion before EVT is helpful to properly plan the angiographic procedure, including determining how to traverse the c-ICA occlusion and permitting sufficient forethought regarding the need for c-ICA stent placement or angioplasty.

Treatment Strategies and Challenges

The optimal management of patients with AIS and TLs undergoing EVT remains uncertain, being subject to multiple clinical, anatomic, and technical considerations.

- **stenting vs PTA alone?**
- **antegrade vs retrograde approach?**
- **antiplatelet strategies?**
- **risk of sICH?**
- **risk of complications, e. g. distal emboli?**

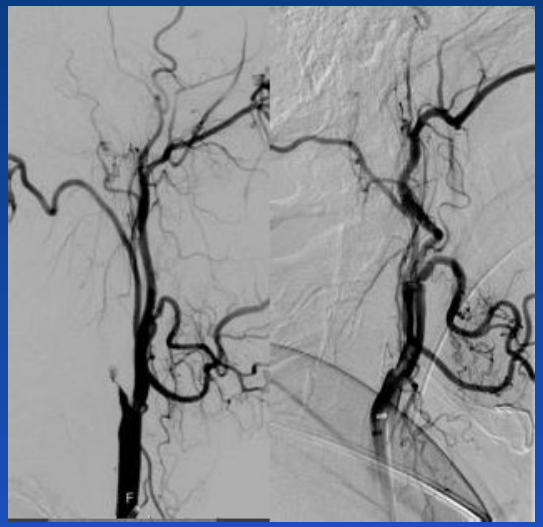
Stenting vs PTA only

	Stenting	PTA
pros	- Protection of symptomatic lesion/plaque ▼ decreased risk of recurrent stroke - Treatment of hemodynamic impairment - «one-stop-shop» treatment	- Treatment of hemodynamic impairement - No need for anti-platelet / anticoagulation medication - Deferred treatment by CEA or stenting under «optimal» conditions
cons	- Risk of sICH ▼ need for anti-platelet / anticoagulation medication - Risk of stent occlusion	- Risk of re-occlusion - Risk of recurrent stroke

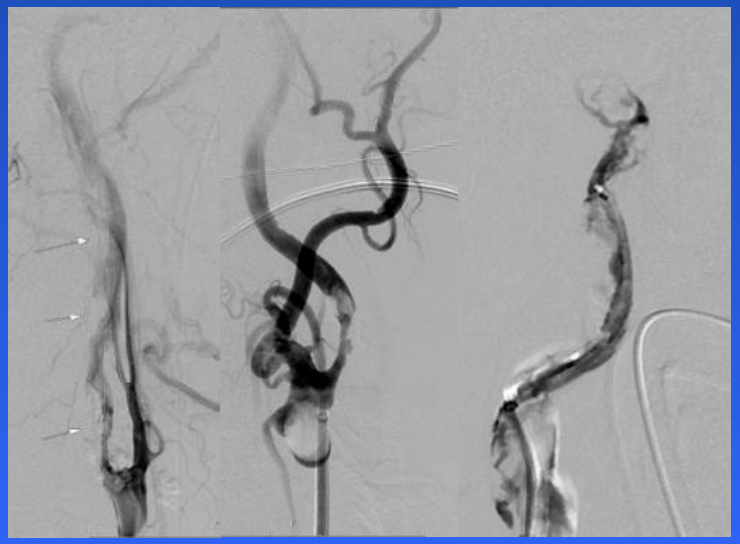
Brinjikji JNIS 2018

Rationale to stent

- **Intracranial access** not possible without stenting/P



- **Stroke recurrence** due **to intracranial re-embolization** or **hemodynamic impairment** in case of ICA occlusion / stenosis



To stent or not to stent? That is the question…

Issues with Stenting in the acute setting: Factors to be considered

- Infarct core volume
- Time to reperfusion
- Received IV tPA or not
- Antiplatelet to be tailored to above
- Need for Abciximab in case of in-stent thrombosis (increases bleeding risk)
- Risk of stent occlusion

Hemorrhage on imaging and worsening of NIHSS score of ≥4[1]
natural course ~1-2%

Thrombotic / thromboembolic complications
Recurrent stroke, stent occlusion

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Brinjikji JNIS 2018

Should the Intracranial or Extracranial Lesions Be Treated First?

Stent placement may be performed either before intracranial thrombectomy (“anterograde”) or after thrombectomy (“retrograde”).

Published series have shown that both approaches are commonly used and suggest that both yield similar functional outcomes **despite differences in recanalization times.**

Anterograde

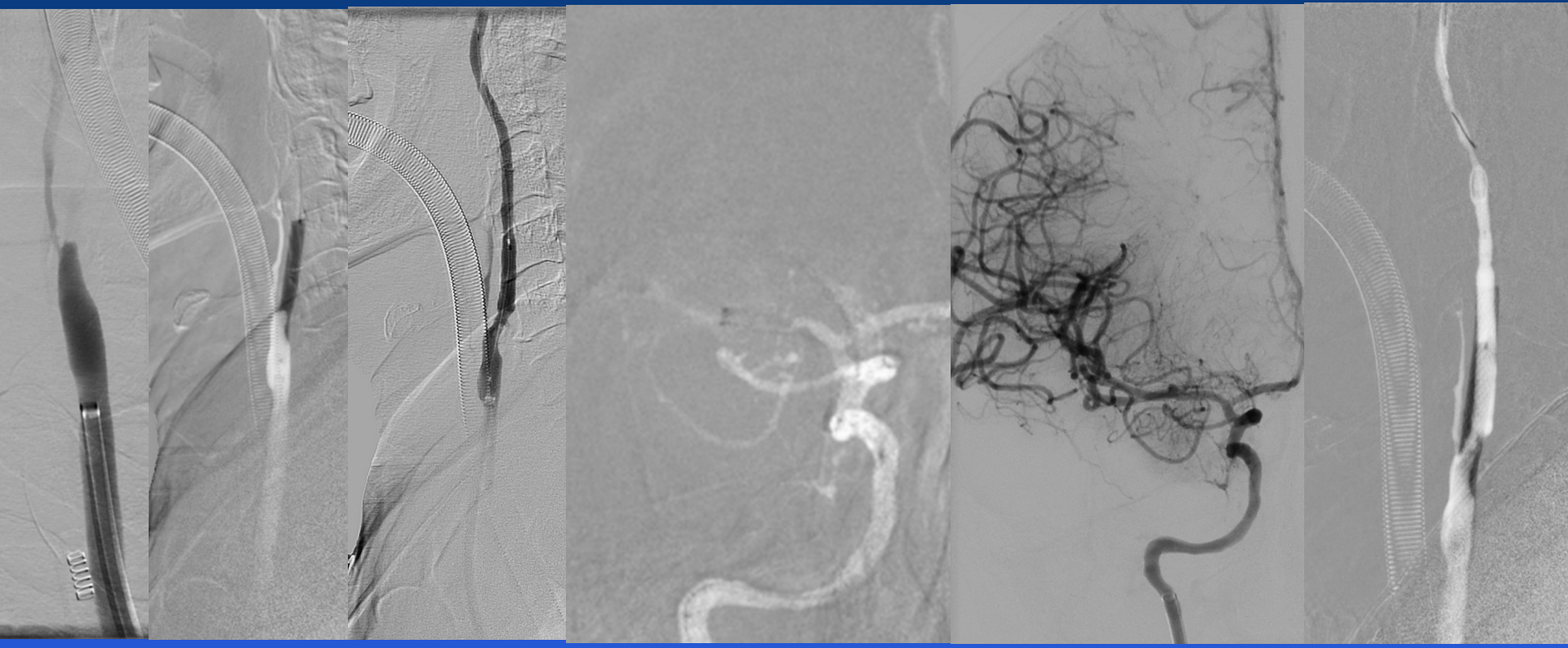
Retrograde

Revascularization Technique
Antegrade Approach ('proximal-to-distal')

Advantages:
- Not necessary distal protection against emboli (intracranial occlusion)
- Re-establish flow in ICA to enhance collateral circulation and efficacy of thrombolytics

Disadvantages:
- Target lesion, i. e. intracranial lesion not treated first
- Time delay in intracranial recanalization due to ICA recanalization, e. g. multiple PTA, stent thrombosis, dissection etc.

Revascularization Technique
Retrograde Approach ('distal-to-proximal')



Advantages:

- Target lesion, i. e. symptomatic intracranial lesion treated first to restore perfusion
- Intracranial recanalization under flow arrest

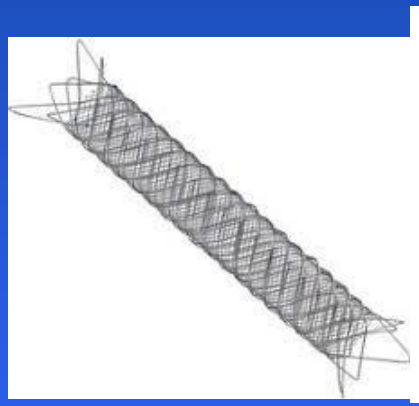
Disadvantages:

- Need for protection for treatment of ICA lesion
- ICA lesion may impede distal delivery of devices for intracranial recanalization
  - ⇓ need for antegrade approach

What Type of Stent Should Be Used?

- **Differences of implanted stents**
  varying percentage of metallic surface, closed-cell, open-cell, mesh size, stent length
- In most series **laser-cut stents** (open cell, closed cell,
  hybrid) used (Precise, Wallstent, Protégé etc.)
- Stent **sizing**, **subnominal or nominal diameter dilatation / vessel wand adaptation**, use of **overlapping** stents
- Introduction of **dens mesh stents** (braided or nitinol mesh) for carotid stenting (double layer, high mesh density, small pore size) [1,2]:
  - improved carotid plaque coverage

↓ > rates of thrombosis / occlusion ?!



What Type of Stent Should Be Used?

Management of intra-procedural stent thrombosis / occlusion:

- **angiographic evaluation of collateral status** (COW, leptomeningeal)[1,2] may guide **„aggressiveness“ of treatment** (peri-procedural, post-procedural)
  - **Mechanical problem**: thrombus aspiration, PTA, additional stent
  - **Pharmacological problem**: anti-platelets (ASA, clopidogrel, GPIIb/IIIa inhibitors), heparin, additional iv tPA / urokinase

- Angiographic surveillance at the end of procedure (10-15 min)
  - peri-procedural thrombosis is important risk factor for delayed thrombosis!

[1]Marnat et al. AJNR 2018; [2]Eker et al. Front Neurol 2018

What Antithrombotic Regimen is Preferred?

If ICA stent placement is performed, antithrombotic medication must generally be given to prevent acute in-stent thrombosis and its associated potential risks of distal embolization or stent occlusion.

However, the choice of optimal antithrombotic therapy in the setting of acute ICA stent placement during EVT remains unknown.

The risk of in-stent thrombosis must be balanced against the risk of hemorrhagic transformation of infarcted cerebral tissue, with this latter risk of particular concern in patients having IVT or having a large core of infarction.

What Antithrombotic Regimen is Preferred?

Impact of stent occlusion

Predictors and Clinical Impact of Delayed Stent Thrombosis after Thrombectomy for Acute Stroke with Tandem Lesions

R. Pop, I. Zinchenko, V. Quenardelle, D. Mihoc, M. Manisor, J.S. Richter, F. Severac, M. Simu, S. Chibbaro, O. Rouyer, V. Wolff, and R. Beaujeux

- 73 pts. stented, **delayed stent thrombosis** in **19.1%** (14/73)
- 13/14 stent thrombosis **within 24 hrs**, 1/14 after 5 days
- Stent occlusion rates **28.2%** for periprocedural **ASA** and **8.8%** for **ASA + clopidogrel** (p=0.04) (impact of stent design?)
- **No re-embolization**
- **21.5%** (3/14) **aggravation of neurological deficits** that could be attributed to stent occlusion; 35% lower flow velocities in MCA
- mRS 0-2: stent occlusion **7.1%** vs patent stent **55.9%** (p=0.001)

Multivariable regression analysis of predictors for delayed stent thrombosis and clinical outcome at discharge[a]

Predictors	OR (95% CI)	*P* Value
Delayed stent thrombosis		
Admission NIHSS (per 1-point increase)	1.1 (1.01–1.28)	.03
Diabetes	6.07 (1.2–30.6)	.02
In-stent thrombus on final angiographic run	6.2 (1.4–27.97)	.01
Unfavorable clinical outcome at discharge (mRS > 2)[b]		
Delayed stent thrombosis	19.78 (2.78–296.83)	.001
Admission NIHSS (per 1-point increase)	1.27 (1.12–1.51)	<.001
Symptomatic hemorrhagic transformation	23.65 (1.85–3478.94)	.012

Pop et al. AJNR 2019

Platelet aggregation inhibitors for emergency carotid artery stenting in stroke

Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage

Donald V Heck, Morry D Brown

- N = 23
  Aggressive anti-platelet therapy: aspirin, abciximab, clopidogrel
- sICH: 22% (5/23), all died
- Mortality: 39% (9/23)

- Incidence of sICH may be associated with the use of abciximab and advanced patient age

Heck J Neurointervent Surg 2015

Impact of intra-venous thrombolysis

Impact of intravenous thrombolysis and emergent carotid stenting on reperfusion and clinical outcomes in patients with acute stroke with tandem lesion treated with thrombectomy: a collaborative pooled analysis

- **TITAN** collaboration (**T**hormbectomy **I**n **TAN**dem lesions), prospectively collected data
- 395 pts. with tandem lesions ondergoing mTE with or without stenting; ≥1 anti-platelet agent

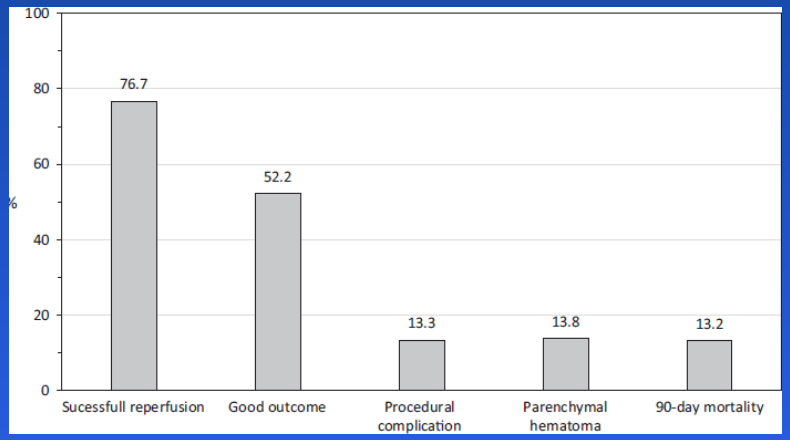


Table 2 Multivariable regression analysis of predictors for successful reperfusion and good 90-day outcome

Predictor	OR (95% CI)*	*P**
Successful reperfusion (mTICI 2b–3)		
Admission NIHSS score (per 5-point decrease)	1.26 (1.07–1.48)	0.004
ASPECTS ≥7	2.00 (1.07–3.43)	0.011
Extracranial ICA stenting	1.63 (1.04–2.53)	0.030
Prior use of IV t-PA	1.47 (1.01–2.12)	0.042
Current smoking	1.63 (0.92–2.88)	0.091
Good 90-day outcome (mRS score 0–2)		
Admission NIHSS score (per 5-point decrease)	2.04 (1.53–2.72)	<0.001
Age (per 10 year decrease)	1.58 (1.26–1.97)	<0.001
ASPECTS ≥7	2.75 (1.24–6.10)	0.013
Absence of hypercholesterolemia	1.77 (1.10–2.84)	0.018
Intracranial MCA occlusion	1.59 (1.03–2.44)	0.035
Onset to groin puncture ≤180 min	1.96 (0.87–4.38)	0.099

- Prior iv tPA and emergency stenting with anti-platelet administration was associated with higher reperfusion rates
- Pre-treatment iv tPA was not associated with increased risk of hemorrhagic complications

Gory et al. Eur J Neurology 2018

What Antithrombotic Regimen is Preferred?

Acetyl salicylic acid (aspirin) and IVT:

- low but significantly elevated risk of sICH (OR: 2.08, 95% CI: 1.46–2.97)
- *no* impact on the overall neurological outcome (impact in the Artis Study)
- recommendation: not be given within 24h after IVT

Dual therapy with aspirin and clopidogrel and IVT:

- elevated risk of sICH?
- probably affecting neurological outcome (small patient numbers

Diener et al. Lancet 2013; Zinkstok et al. Lancet 2012; Cucchiara et al. Stroke 2009;Diedler et al. Stroke 2010

Revascularization Technique

Our anti-platelet regimen

- Aspirin 500 mg bolus IV on the table after intracranial recanalization prior to stenting
- No routine use of clopidogrel, glycoprotein IIB/IIIA receptor inhibitors or systemic heparin
- Control CT after 12 hours to exclude hemorrhage
- ECD: if stent is opened
  - Loading dose of clopidogrel (300 mg), following by DAPT for 3 months

What Antithrombotic Regimen is Preferred?

New antiplatelets

Only limited data exist regarding the use of **ticagrelor or prasugrel** in carotid stent placement, and their use in this setting cannot be routinely recommended.40

Cangrelor, an intravenous antiplatelet agent characterized by rapid onset and offset of action, has been used in some centers, but data are currently insufficient to recommend its routine use.41

Is There a Role for Embolic Protection Devices?

For embolic protection devices **using either distal filters or proximal flow reversal**, data pertain almost exclusively to patients undergoing nonacute carotid stent placement for primary or secondary stroke prevention.

The benefit of embolic protection devices during stent placement remains debated, and in the absence of high-quality comparative studies, their use is not universally endorsed.

Given the urgency of EVT for stroke and potential patient instability, embolic protection devices are rarely used in this setting

Conclusion

- Strokes caused by a TL represent up to one-fifth of all strokes treated with EVT.

- Overall, **stenting** of the cervical ICA in the acute setting of stroke seems **not to reduce the positive treatment effect**

Conclusion

- '**Non-aggressive' anti-platelet regime (ASA)** seems to be a reasonable trade-off between risk of sICH and stent occlusion

- Decision to stent should be based on **individual patient selection** (e. g. lesion etiology/morphology, residual adherent thrombus, hemodynamic impairment, NIHSS/infarct size, diabetes) and stents/technique used (as non-thrombogenic as possible)

- In this context, only the results of randomized-controlled trials like TITAN (NCT03978988) and EASI-TOC62 will help determine the benefit of acute stent placement, or absence thereof, in patients with TLs.