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EARLY LOADING DOSE OF DUAL ANTIPLATELET TREATMENT IN ACUTE ISCHEMIC STROKE ASSOCIATED WITH TANDEM LESION

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ABSTRACT

Background and Purpose: Acute antiplatelet treatment in tandem lesions treated with intravenous thrombolysis (IVT), endovascular thrombectomy (EVT) and acute carotid stenting (CAS) is challenging as a careful balance between the risk for intracerebral hemorrhage (ICH) and stent thrombosis is needed. We aimed to investigate the effects of early (within 12 hours) loading dose of Aspirin and Clopidogrel (A+C) after IVT and EVT+CAS.

Methods: A retrospective analysis from a single center was performed. The primary outcome was the occurrence of ICH, secondary outcomes included rates of parenchymal hematoma, stent thrombosis, death, and independence at 90 days.

Results: The study included 78 patients all receiving IVT, EVT+CAS, and 500 mg Aspirin at stent placement. 7 patients did not receive any adjunctive Clopidogrel: 2 because of early stent thrombosis and 5 due to intracerebral hematoma. In the 71 patients receiving Clopidogrel, an early loading dose (300 mg within 12 hours from IVT) did not affect the rate of ICH (33.3% versus 52.1% [$p>0.05$]). The only significant predictor of ICH was the ASPECT score calculated on a CT scan obtained before Clopidogrel treatment (OR 0.57, 95% CI 0.40–0.83), and ASPECTS <8 identified patients at higher risk of ICH. The rate of stent occlusion was lower in patients treated with early A+C (0% vs 8.3%); other secondary outcomes did not differ.

Conclusions: Administering a loading dose of A+C within 12 hours after IVT, EVT and CAS in tandem lesions resulted safe in terms of hemorrhagic transformation and effective in preventing stent thrombosis.

Key messages

What is already known on this topic – Treatment of tandem lesions is challenging as evidence from RCT is lacking. Particularly troublesome is the use of antiplatelets after IVT+EVT plus acute CAS

What this study adds – Early (< 12 hours) dual antiplatelet loading dose within 12 hours from IVT+EVT plus emergent CAS is safe in terms of hemorrhagic transformation and effective in preventing stent thrombosis.

How this study might affect research, practice or policy – Early dual antiplatelet therapy may be routinely administered in patients undergoing IVT+EVT plus emergent CAS, improving the rate of stent patency and possibly the functional outcome of patients with acute ischemic stroke and tandem occlusion.

Key-words: Acute Ischemic Stroke; Tandem occlusion; Carotid artery stenting; Intravenous Thrombolysis; Dual antiplatelet therapy

INTRODUCTION

Tandem lesions, defined as simultaneous cervical common or internal carotid artery severe stenosis or occlusion associated with ipsilateral intracranial carotid or middle cerebral artery occlusion, account for approximately 15% of anterior circulation ischemic strokes [**Poppe et al, 2020**].

The atherosclerotic disease is the main pathophysiological process underlying the occurrence of tandem lesions and it is more prevalent in man, in Caucasian people and is typically associated with increasing age. Other possible causes of the tandem lesion are less frequent and are identifiable in dissections, cardioembolic dissemination, or very infrequent diseases, such as the carotid web. **[Rockman et al. 2013; Di Donna et al., 2023]**

Ischemic strokes associated with tandem lesions are burdened by very poor prognosis and a worse outcome than intracranial occlusion alone, with a combined mortality and severe disability rate of approximately 80% [**Rubiera et al, 2006**]. Furthermore, tandem lesions are considered an independent predictor of poor long-term functional outcomes, due to the extension of the ischemic area and the tendency to complicate with hemorrhagic infarction [**Goyal et al, 2016]**.

The bridging therapy of intravenous thrombolysis (IVT) and mechanical thrombectomy (MT), when indicated, is a cornerstone of intracranial large vessel occlusion (LVO), since 1995 when the first published study demonstrated the efficacy of intravenous thrombolysis over aspirin

(NINDS study) and 2015 when the “big five” study on mechanical thrombectomy in large vessel occlusion demonstrated the dramatic effectiveness of clot removal through the endovascular approach on functional outcome. **[NINDS study, 1995; Goyal et al, 2016; Berkhemer et al, 2015; Goyal et al, 2015; Saver et al, 2015; Campbell et al, 2015; Jovin et al, 2015].**

Nevertheless, high-quality evidence in the management of patients with acute ischemic strokes and tandem lesions is scarce, as this population is underrepresented in existing trials **[Goyal et al, 2016],** and specific randomized trials are lacking. Therefore, the optimal management of such patients remains uncertain, with several questions still unanswered. Among the main questions unanswered or partially addressed in the management of tandem occlusion, there are the usefulness of bridging intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) versus mechanical thrombectomy alone, due to low recanalization rate and an increased risk of ICH associated with IVT-alone approach, considered to be less effective in this cohort of patients due to high thrombus length; the angioplasty alone versus acute carotid artery stenting in the context of emergency treatment of the extracranial occlusion, and the anterograde (extracranial, neck first) versus retrograde (intracranial, head first) approach during mechanical thrombectomy. **[Di Donna et al, 2023]**

Another major concern in the management of tandem lesions not yet addressed in the acute stroke care setting is the antiplatelet regimen in patients receiving intravenous thrombolysis (IVT), mechanical thrombectomy (MT), and acute carotid stenting (CAS), as we need to

balance the risks for hemorrhage and stent thrombosis. We have conflicting evidence coming from medical literature; on one hand, national and international guidelines suggest not starting antiplatelet therapy until 24 hours after IVT **[Berge, 2021]**; on the other hand, the risk of stent thrombosis reaches its peak in the first 24 hours after the stent placement **[Pop et al, 2019].**

The first statement comes from results observed in the ARTIS (Antiplatelet therapy in combination with Rt-PA Thrombolysis in Ischemic Stroke) trial, where in the face of an equal chance of good outcome in the aspirin + IVT group versus IVT group alone, the relative risk for symptomatic ICH (as defined in the ECASS-3 trial) were more than doubled (RR 2.78 95% CI: 1.01-7.63) **[Zinstok et al, 2012; de los Rios La Rosa et al; 2012].**

However, the grade of the guidelines recommendation, based only on one large trial and others very small randomized trials, is low.

As stated before, on the other hand, we have a high risk of stent thrombosis during the first 24 hours. The overall risk of stent thrombosis in the population receiving acute stent placement is around 20%; recent evidence observed that nearly 90% of stent thrombosis occurs in the first 24 hours of its placement. Moreover, the stent thrombosis is strictly related to patients' long-term outcome: only 7% of patients with stent thrombosis showed functional independence at 3-month evaluation meanwhile a good functional outcome was reached in 55% of patients with no evidence of stent thrombosis. **[Pop et al, 2019]**

Considering these observations appears to be crucial to ensure stent patency in patients receiving acute carotid artery stenting. An option could be not to treat extracranial stenosis or occlusion with acute stenting but only with angioplasty-alone approach; nevertheless, a very recent metanalysis on fifteen published studies showed a net benefit from eCAS over no-stenting approach with a significantly higher good functional outcome (OR 1.52, 95% CI 1.19-1.95), an higher rate of successful recanalization in stenting group, a lower risk of carotid restenosis with relative safety from early administration of anti-thrombotic drugs. **[Diana et al. 2023]**

Here come pharmacokinetic and pharmacodynamic evaluations on interaction and possible negative effects of co-administration of Rt-PA and antithrombotic drugs, in particular clopidogrel. The recombinant tissue-type plasminogen activator (Rt-PA) is obtained from the DNA of the endogenous tissue plasminogen activator of human melanoma cells. It has 527 amino acids with a serine-protease domain and its function is to activate free plasminogen in fibrin, to dissolve blood clots. It has a half-life of a few minutes with liver-clearance or inactivation by Plasminogen Activator inhibitor – 1 (PAI-1). Nevertheless, the bond between active plasmin, alteplase, and fibrin protects alteplase from inhibitors and prolongs its plasmatic half-life**. [Chester et al, 2019]**

An initial study on the safety and the efficacy of alteplase administration in acute ischemic stroke showed a maximum risk of intracerebral hemorrhage in the first 12 hours after alteplase administration, which is more pronounced at higher dosages than those approved for acute ischemic

stroke (100 and/or 150 mg versus 90 mg), with a progressive risk reduction as hour passing. **[Gore et al, 1991]**

TABLE 3. Time of Onset of Intracerebral Hemorrhage and Cerebral Infarction

	Intracerebral hemorrhage					
	150 mg rt-PA (*N*=12)		100 mg rt-PA (*N*=11)		Total (*N*=23)	
Time of onset (hr)	*n*	%	*n*	%	*n*	%
≤12	7	58.3	8	72.7	15	65.2
>12 and ≤24	3	25.0	1	9.1	4	17.4
>24 and ≤48	1	8.3	1	9.1	2	8.7
>48	1	8.3	1	9.1	2	8.7

rt-PA, recombinant tissue-type plasminogen activator.

Fig. 1 (from Gore et al, 1991). Time of onset of intracerebral hemorrhage and Cerebral infarction after administration of 150 or 100 mg of intravenous rt.PA.

These data were confirmed in the NINDS Trial, the first trial to test the efficacy and safety of rt-PA in acute ischemic stroke, with a rate of 70% of total ICH observed within 16 hours from drug administration. **[NINDS study subgroup, 1997].**

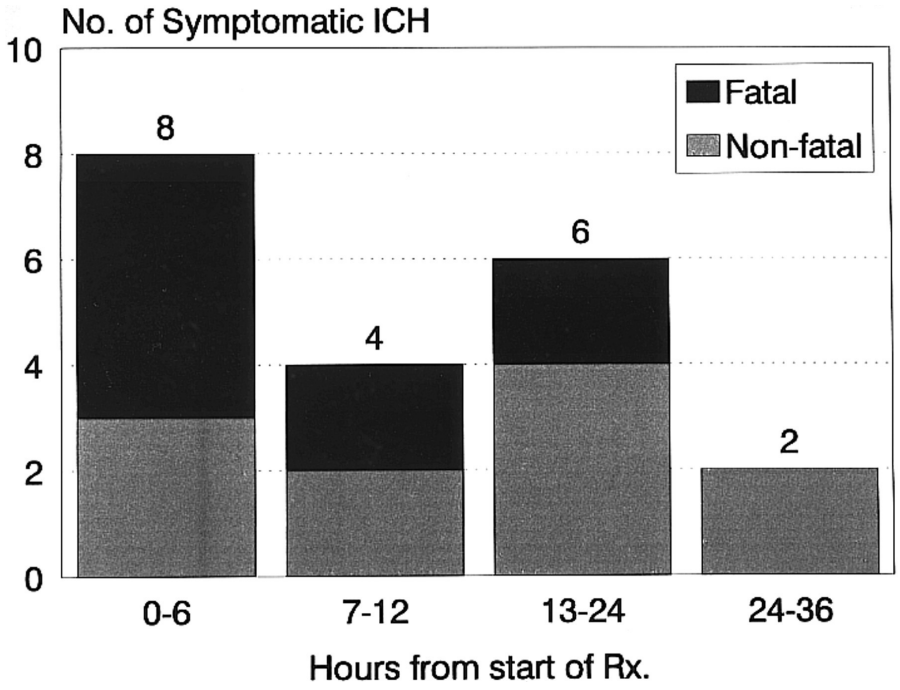


Fig. 2 (from NINDS substudy, 1997). Number of symptomatic ICH from the starting of therapy with intravenous rt-PA.

Clopidogrel is an inactive pro-drug that receives liver activation through a series of cytochrome P450 enzymes, in particular CYP2C19. It is an irreversible P2Y12 receptor antagonist and it finds its clinical indication in the reduction of atherosclerotic events in patients with myocardial infarction, peripheral arterial disease (including carotid atherosclerosis), and ischemic stroke. Usually, the daily dosage of clopidogrel is 75 mg; however when necessary, and in particular in percutaneous coronary intervention in the emergency setting, clopidogrel is administered through a loading dose (300 mg in a single administration) followed by 75 mg

daily. It is crucial, to ensure stent patency both in coronary stenting and in carotid artery stenting, to administer adjunctive clopidogrel to aspirin. Several studies tried to assess the delay in the antiplatelet effect of clopidogrel administration after loading dose: it has been shown that the effect begins after two hours and reaches its peak in a range between 5-6 hours from the clopidogrel loading dose. **[Heftl et al. 2000]**

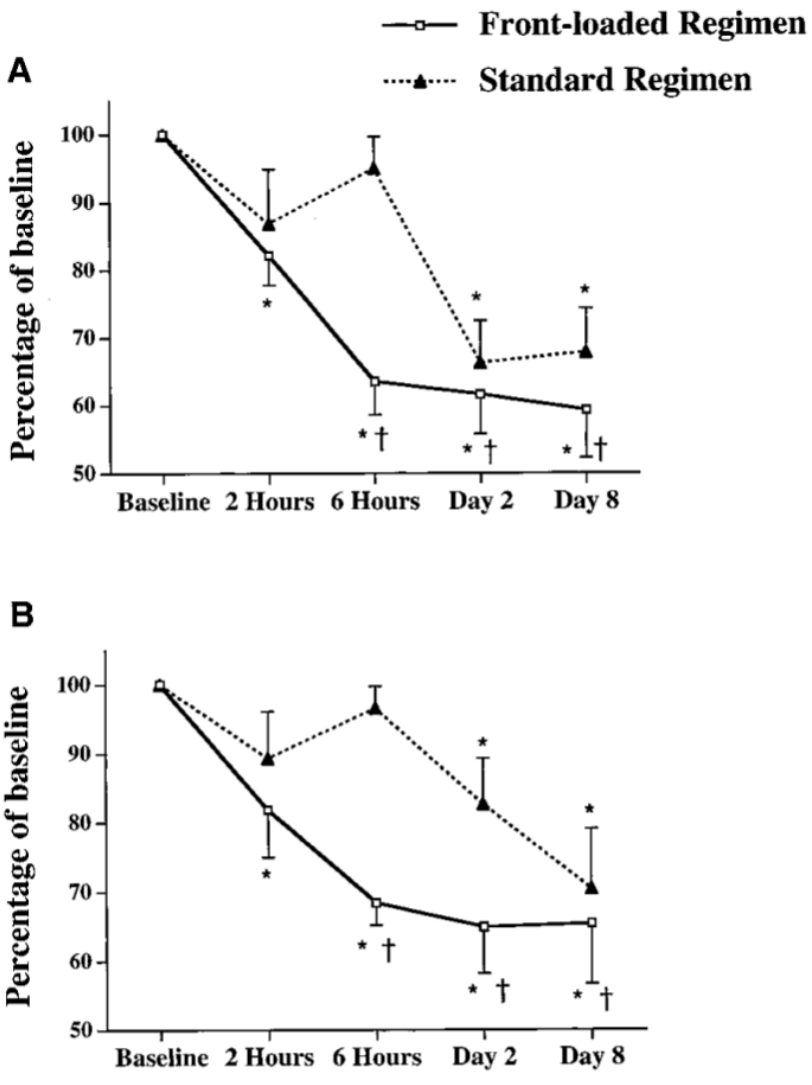


Fig. 3 (from hefti et al, 2000). Effects of clopidogrel treatment on platelet aggregation.

Nevertheless, in the set of ischemic strokes due to tandem occlusion, still exist uncertainties about the single versus dual antiplatelet treatment, the optimal timing, and the dose. Intraprocedural loading dose of dual antiplatelet treatment may preserve stent patency at the cost of a potential increase in ICH; whereas, late antiplatelet treatment may cause stent thrombosis precluding neurological improvement.

Under these premises, the aim of this study, from a single high-volume stroke center, is to investigate the safety of a stepwise, early (after 6 hours but within 12 hours from IVT) loading dose of Clopidogrel in acute ischemic stroke patients harboring a tandem lesion, treated with IVT + endovascular thrombectomy (EVT) and CAS, with intravenous bolus of 500 mg aspirin at the moment of stent release.

METHODS

The study was designed as a retrospective cohort study, which included patients with acute ischemic stroke treated with acute reperfusion strategies at AORN Cardarelli, Naples, Italy, from 1st January 2019 to 31th December 2022. Ethical approval was not sought for the present retrospective study because every patient was treated according to the current standard of care. This study was completed by the Helsinki Declaration as revised in 2013.

Baseline characteristics, procedural information, post-procedural complications, and functional outcomes after 3 months were recorded.

Study inclusion criteria included: acute ischemic stroke associated with tandem lesion, treated with IVT and bridging EVT plus CAS, receiving intraprocedural 500 mg Aspirin with postprocedural adjunctive Clopidogrel.

Baseline features, recorded in our local registry, were: age, gender, pre-stroke disability measured at modified Rankin Scale (mRS; supplementary material) history of hypertension, diabetes, atrial fibrillation, dyslipidemia, smoking, previous stroke or transient ischemic attack; time of symptoms onset, hospital arrival, door-to-needle, door-to-groin and groin-to-recanalization time. Stroke severity was assessed by the National Institute of Health Stroke Scale (NIHSS, supplementary material), and the degree of disability was rated by mRS. Early signs of infarction at baseline imaging were assessed using the Alberta Stroke Program Early Computed Tomography (ASPECT) Score (supplementary material). The site of

occlusion was determined by a computed tomography angiography (CTA) and confirmed by a subsequent digital subtraction angiography. Concomitant treatment strategies including type of anesthesia, balloon angioplasty and CAS, procedural technique (intracranial- or extracranial-first approach), periprocedural adjunctive medications (Aspirin and/or Clopidogrel), and relative timing and dosing were also collected.

The main outcome of this study was the occurrence of intracerebral hemorrhage (defined as any kind and/or extension of hemorrhagic transformation of ischemic lesion, from hemorrhagic infarction HI1 to parenchymal hematoma PH2); as secondary outcome measures, we considered the rate of parenchymal hematoma (PH1 and PH2, defining PH1 as a clot not exceeding 30% of the infarcted area with some mild space-occupying effect and PH2 as dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect), the rate of stent thrombosis, mortality, and functional independence, at 90 days, defined by a mRS score 0-2.

Tandem lesions were diagnosed in patients with relevant extracranial carotid artery pathology (occlusion or stenosis >70% according to NASCET [North American Symptomatic Carotid Endarterectomy Trial] criteria) due to atheromatous plaque or dissection, and concomitant ipsilateral intracranial carotid or middle cerebral artery (M1 or M2 segment) occlusion. **[NASCET trial, 1991]**

The decision to perform IVT and EVT was based on current guidelines. Reperfusion success was defined as mTICI2b-3, measured by the modified Thrombolysis in Cerebral Infarction (mTICI) score. The decision to

perform acute stenting and the related antiplatelet treatment was based on the interdisciplinary consensus agreement between the stroke neurologist and the interventional neuroradiologist. All patients receiving CAS were given 500 mg intravenous Aspirin at stent placement, and then 100 mg daily. Lacking high-quality evidence, the timing and dosing of adjunctive Clopidogrel was left to the judgment of the treating physician and is the variable under evaluation.

Before any Clopidogrel treatment, the blood-brain-barrier damage was evaluated by a non-contrast CT scan, and a modified ASPECT score was assigned, based on cerebral areas of hyper-density, and calculated according to the ASPECT scoring method (pre-Clopidogrel ASPECTS). Moreover, stent patency was also assessed before Clopidogrel treatment by carotid ultrasound and was then repeated on day 1 and discharge or if clinically indicated.

Radiological hemorrhagic complications were classified into four subtypes, Hemorrhagic infarction type 1 and 2, and Parenchymal Hematoma type 1 and 2, according to the European Cooperative Acute Stroke Study (ECASS II) **[Hacke et al. 1998].**

Two experienced neuroradiologists, blinded for treatment allocation, reviewed CT images, assigned ASPECT scores, and classified hemorrhagic transformation. In case of disagreement, a conclusive opinion was obtained from the Head of Neuroradiology, equally blinded for treatment assignment.

STATISTICAL ANALYSIS

The study data were analyzed using STATA 13 (SPSS Inc., Chicago, IL).

Patients were divided into two groups: those receiving 300 mg Clopidogrel loading dose within 12 hours and after at least six hours from IVT, followed by 75 mg daily, and those who did not. The latter group included patients who received either 300 mg of Clopidogrel after 12 hours from IVT, or patients who were started on Clopidogrel 75 mg without any loading dose.

Descriptive statistics were used for primary data processing: continuous variables were described by mean and standard deviation (if normally distributed) or by median and interquartile range (if not normally distributed); categorical variables were presented as percentages. To test the normality of the data distribution, we used the Kolmogorov-Smirnov test. The significance of differences in the study groups was tested by Mann-Whitney for continuous variables and by contingency tables for categorical variables. To verify the effect of Clopidogrel on primary outcome, we first performed a chi-square test to compare the rate of hemorrhagic complications in each subgroup, and then the differences in the rate of secondary outcomes (namely, rate of parenchymal hematoma type 2, mortality, functional independence and rate of stent thrombosis). Afterward, we investigated the impact of all variables on the primary outcome by multivariable logistic regression. To examine the simultaneous influence of predictors on outcome, a multinomial logistic regression was used, after checking that its assumptions were met:

linearity, absence of outliers, independence of variables, and absence of collinearity. The final model was obtained by stepwise forward regression procedure. Quality of the final model was examined with the Likelihood ratio test, and with the Pearson Chi-square test. The results of all used statistical tests were considered significant if the probability of the null hypothesis was less than 0.05.

Furthermore, we performed an ROC analysis to identify a cut-off in the ASPECT score, able to predict a higher risk for intracerebral hemorrhage. Finally, we further divided our cohort according to timing (considered as a continuous variable) and dosage (treated as a binary variable, 75 vs 300 mg) of the first administration of clopidogrel; then we repeated the univariate and the multivariate logistic regression and we performed an analysis of variance (ANOVA) to evaluate the effect and the possible mutual interactions of pre-clopidogrel load ASPECT score and these two variables on safety outcome.

RESULTS

From 1st January 2019 and 31st December 2022 1240 acute ischemic stroke patients were treated at AORN "A. Cardarelli", with intravenous thrombolysis and/or mechanical thrombectomy. 78/1240 (6.3%) patients met the inclusion criteria for the study. Clinical, demographic, radiological, and procedures features are reported in Table 1.

Stroke etiology was carotid artery dissection in 8/78 (10.2%) patients, and large artery atherosclerosis in 70/78 (89.8%). Baseline characteristics are presented in Table 1.

73/78 (93.5%) patients received IVT and intracranial EVT, whereas in 5/78 (6.5%) patients intracranial clot lysis was evident at the first angiographic run so there was no necessity to perform mechanical thrombectomy but only acute carotid artery stent placement to ensure patency of the vessel.

7 out of 78 (8.9%) patients did not receive any Clopidogrel dose: in 5/7 a cerebral hematoma was already evident at the CT scan performed before Clopidogrel treatment; in 2/7 stent occlusion was showed at the extracranial carotid evaluation before Clopidogrel start, performed 20 and 22 hours after IVT.

30/71 (42.2%) patients received 300 mg Clopidogrel after 6 hours but within 12 hours from IVT starting; of the remaining 41 patients, 19/71 (26.7%) received 300 mg Clopidogrel after 12 hours from IVT, and 22/71 (30.9%) patients received Clopidogrel 75 mg once daily; so 48/78 patients

(57.8%) did not receive a clopidogrel load in the early time window.

For the primary outcome measure, we did not find any significant difference in the rate of intracerebral hemorrhage between patients who received a loading dose of Clopidogrel within 12 hours from IVT and those who did not (33.3% versus 52.1%; P=0.06) (Table 2), confirmed at the ordinal logistic regression (p-value for the model: 0.10; (Table 3).

Patients treated with clopidogrel load within 12 hours showed in 9 cases out of 30 (30%) only hemorrhagic infarction type HI-1 or 2 and in 1 case out of 30 (3.3%) a parenchymal hematoma type PH-2; whereas patients not receiving the clopidogrel load in early time window showed in 14 cases out of 48 (29.1%) hemorrhagic infarction type HI-1 or 2 and in 11 cases out of 48 (22.9%) a parenchymal hematoma type PH-1 or PH-2 (table 4)

For secondary outcome measures: no significant difference was found in the rate of mortality (20% versus 14.6%; P=0.53), functional recovery (mRS 0-2: 66.7% versus 53.1%; p=0.24; fig. 4), and rate of intrastent thrombosis (table 2).

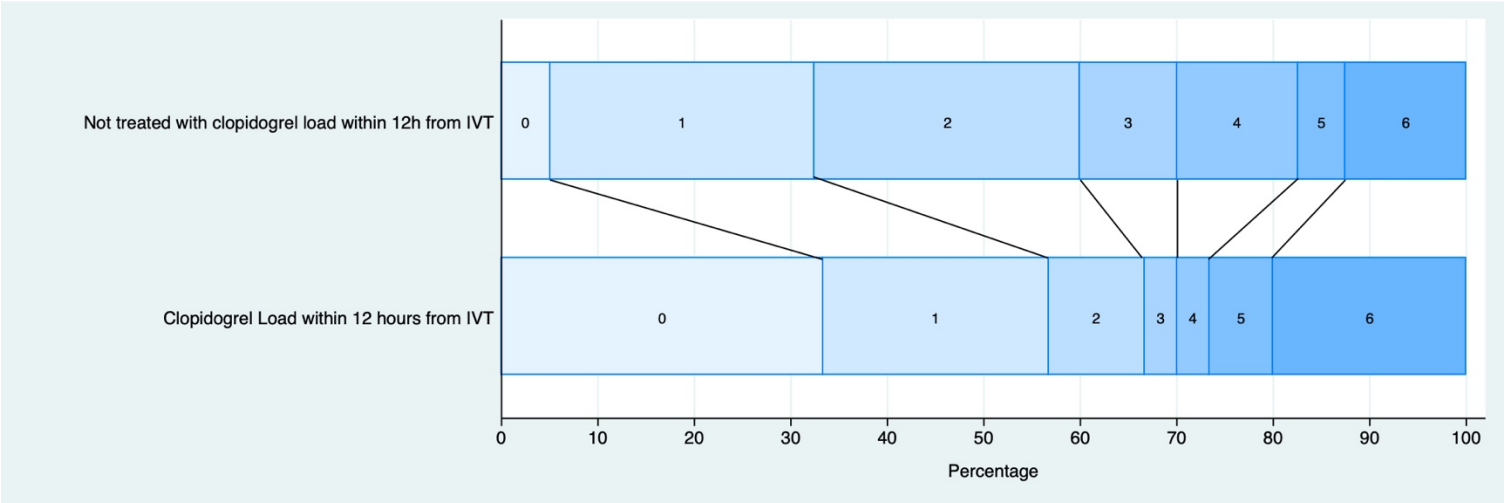


Fig. 4 Functional outcome at 90-days in the group of patients receiving clopidogrel load within 12 hours from IVT versus patients not treated with clopidogrel load within 12 hours from IVT.

Stent occlusion was globally rare, occurring in 4/78 (5.1%) patients on day 1. In two patients, stent occlusion occurred before any Clopidogrel treatment. Notably, in these patients, brain CT and carotid ultrasound evaluation for Clopidogrel treatment were performed beyond 12 hours after IVT (namely at 20 and 22 hours from IVT). Moreover, we observed stent occlusion in 1 patient receiving Clopidogrel 75 mg daily without any loading dose and in 1 patient receiving clopidogrel loading dose after 19 hours. No subsequent stent thromboses were observed between day 1 and discharge. Dichotomizing for Clopidogrel loading dose within 12 hours from IVT, 0% versus 8.3 % presented acute stent occlusion ($p>0.05$).

Then we performed univariate logistic regression, where we observed statistical significance for thrombolysis in conventional therapeutic windows, presence of hypertension, and ASPECT value. Afterward, by performing multivariate analysis with variable significance at univariate and adjusting for demographic and clinical covariates (age, sex, timing of clopidogrel treatment, presence of diabetes), the only significant predictor for intracerebral hematoma was lower pre-Clopidogrel ASPECTS (OR 0.57, 95% CI 0.40 – 0.83, $p<0.001$).

The ROC analysis performed to assess the best ASPECT value associated with the risk of intracerebral hemorrhage showed an AUC of 0.75 (SE 0.05, CI 0.65-0.86), with ASPECT score ≤ 8 showing the highest sensitivity (78%) and specificity (68%) in predicting the risk of ICH (Fig.5).

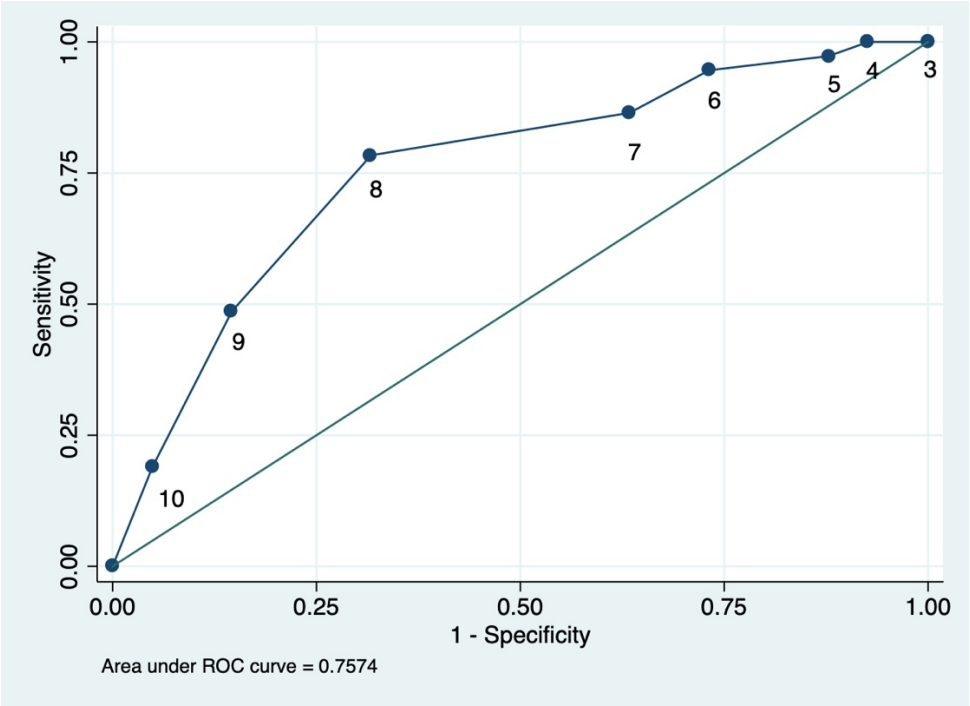


Fig. 5 ROC Analysis according to pre-Clopidogrel ASPECT Score

Subsequently, to further confirm and generalize our data, we divided our cohort according to timing and dosage of the first administration of clopidogrel, Globally, 52 patients received clopidogrel load, 30 within 12 hours from IVT starting and 22 after more than 12 hours; 19 patients received only 75 mg of clopidogrel, all after more than 12 hours from IVT starting; 7 patients did not receive any clopidogrel dosage for reasons explained before in the text.

The rate of hemorrhagic complications was 10/30 (33.3%) in the group receiving clopidogrel load within 12 hours (9 as HI 1/2 and 1 as PH 1-2), 10/19 (52.6%) in patients receiving 75 mg of clopidogrel more than 12 hours from IVT starting (6 as H I1/2 and 4 as PH 1/2) and of 8/22 (36.4%) in patients receiving clopidogrel load after more than 12 hours from IVT starting (7 as HI 1-2 and 1 as PH 1-2). Rate of hemorrhagic complications according to timing and dosage of first clopidogrel administration are resumed in Table 4.

By repeating regression analysis using these two independent variables we observed no change in results (Fig. 6); the ANOVA performed to assess the interaction between the ASPECT score and timing and dosage of the first clopidogrel administration confirmed the independent role of ASPECT score ($p=0.01$) in determining a higher risk of hemorrhagic complications without any kind of interaction with clopidogrel administration.

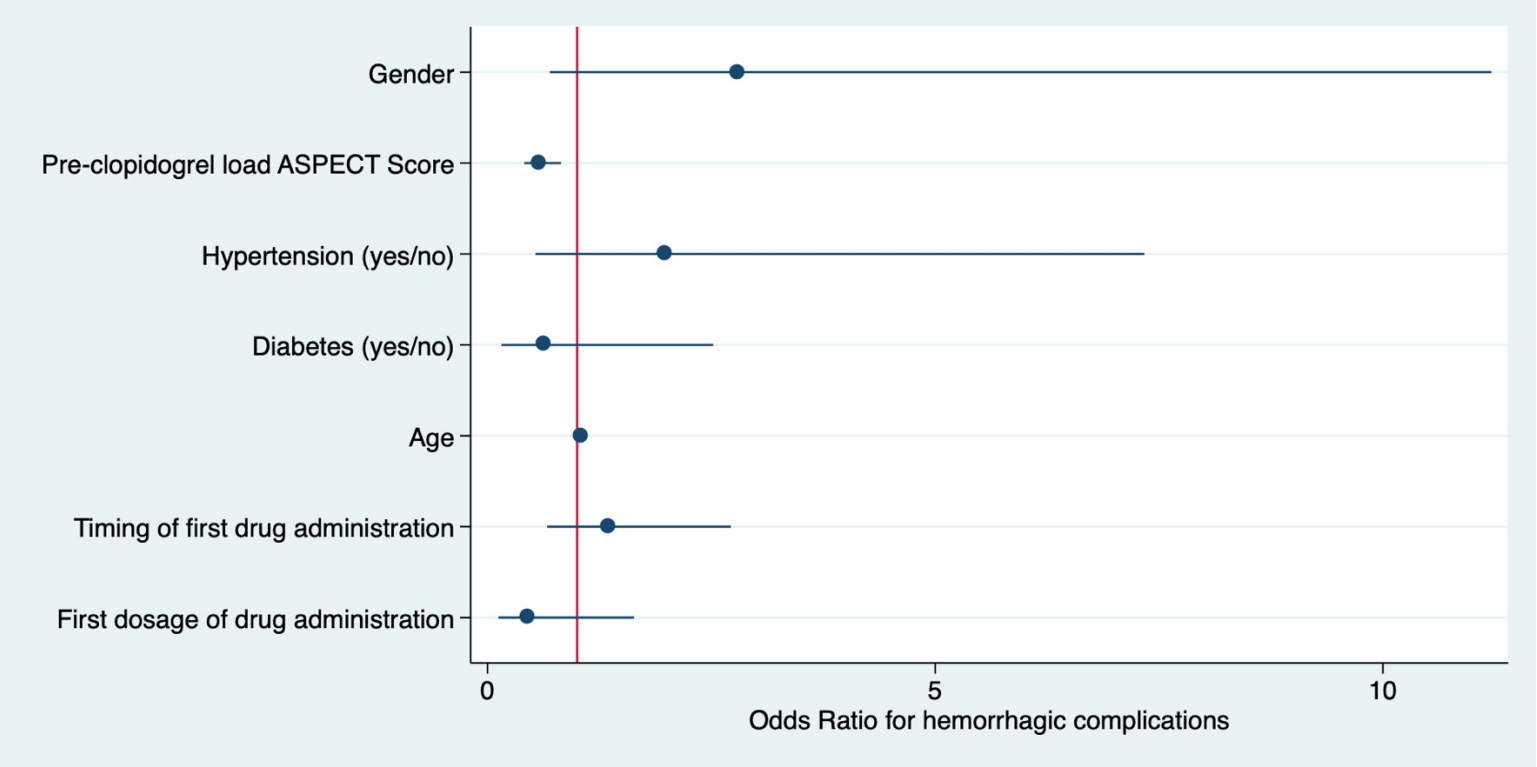


Fig. 6 Multivariate logistic regression analysis on presence/absence of hemorrhagic complications

DISCUSSION

Treatment of acute stroke associated with tandem lesions is still challenging. Despite high rates of death and dependency, treatment relies on low-quality evidence, as specific randomized controlled trials are lacking. Among the “big five” trials, which led to the introduction of mechanical thrombectomy as the standard of care in acute ischemic stroke due to large vessel occlusion, tandem lesions were very unrepresented or were even considered as exclusion criteria.

Uncertainties exist regarding 1) the usefulness of intravenous thrombolysis; 2) which lesion (intracranial or cervical) should be addressed first; 3) which treatment (stenting or balloon angioplasty only) should be pursued in the acute phase; 4) which antiplatelet regimen should be given in case of acute stenting.

Recent observational data suggest bridging IVT+EVT is associated with higher odds of complete recanalization and better functional outcome **[Anadani et al, 2022; Min et al, 2021]**, so it is not justifiable and would be unethical the avoidance of intravenous thrombolysis in the tandem lesion. In acute ischemic stroke patients due to tandem occlusion has been recently proposed to avoid intravenous thrombolysis to reduce hemorrhagic risk, in the hypothesis to perform acute carotid stenting with consequent administration of early high-dosage of antithrombotic drugs. Nevertheless in recent paper and metanalysis of comparison between bridging therapy and MT alone, the latter approach failed in showing statistical non-inferiority. **[Horvat et al. 2023]**

Moreover, in 10% of cases, the CT-angiography-diagnosed tandem occlusion turned out to be, during digital subtraction angiography, a carotid artery "pseudo-occlusion" in which the not-opaque, stagnant blood column in the proximal carotid internal artery, is due to intracranial carotid distal occlusion mimicking a complete occlusion of ICA as observed in tandem occlusion.

In addition, a small percentage (around 6% indeed) of patients shows an efficient recanalization with IVT alone; for all of these reasons, the avoidance of IVT in this class of patients could potentially be harmful and could reduce the chances for a complete functional recovery. **[Di Donna et al, 2023]**

Another point of debate is about the intracranial- or extracranial-first approach. At the moment of this draft, there is no clear consensus on the superiority of one of these two possible endovascular approaches. In the anterograde-neck first approach, the neuro-interventionalist firstly addresses extracranial occlusion; while in the retrograde - head first, intracranial occlusion is firstly addressed. The main advantage of the anterograde approach is to restore both blood flow and anterior circulation hemodynamics with an increased likelihood of distal recanalization, by improving accessibility, not-blinded navigation, of intracranial occlusion. Nevertheless, this approach lead to an increased time for intracranial recanalization with the increased risk of growth of final infarct volume. The retrograde approach provides a faster intracranial recanalization, potentially reducing final ischemic volume; nevertheless, it could be associated with distal embolization and a substantially blinded navigation,

having to reach the distal occlusion without having previously solved the extracranial occlusion. However, despite inconclusive evidence, in many centers the treatment of choice is to prioritize intracranial occlusion and distal revascularization, when technically possible, over the treatment of proximal extracranial carotid occlusion, to preserve brain integrity. **[Yang et al, 2019]**

The third point to be addressed regards the possible approaches to extracranial lesions, namely balloon angioplasty versus stenting placement. Recent evidence seems in favor of the stenting approach, however, we have no robust data to formalize high-grade recommendations. **[Farooqui et al, 2023; Diana et al, 2023; Zevallos et al, 2022]**

Principal evidence came from the TITAN registry, a retrospective, multicenter registry analysis in which acute stent placement was independently associated with good functional outcomes. Similar evidence came from the STRATIS registry (prospective, observational, and non-randomized) in which the stenting of extracranial lesions leads to a better outcome. In any case, to have a definitive and clear recommendation we must wait for the results coming from randomized controlled trial, the EASI-TOC trial (Endovascular Acute Stroke Intervention-Tandem Occlusion) and the TITAN trial (Intracranial Thrombectomy and Extracranial Carotid Stenting Versus Intracranial Thrombectomy Alone In Acute Anterior Circulation Strokes With TANdem Occlusion: the Randomized Controlled TITAN Trial). **[Anadani et al., 2019; Mueller-Kronast et al, 2017; Di Donna et al, 2023].**

As stated before, the available evidence seems in favor of the carotid artery stenting except in the case of extracranial carotid artery dissection. **[Marnat et al, 2020]**

This is one of the main concerns in the interpretation of data coming from trial or observational series on tandem lesions: according to definition, under the umbrella of "tandem occlusion" or "tandem lesion" reside many nosological entities (as atheromatic lesions, dissection, carotid webs or cardioembolic occlusions, etc.), that frequently differs in physio-pathological and therapeutical implications. Dissection is an acute, sudden occlusion without the possibility of developing collaterals over time; however is more frequent in young people with a very good circle of Willis. Conversely, the typical tandem lesion is due to an atheromatic lesion developing over time, occurring more often in elderly people with good-collateral circles but a poor long-term outcome This heterogeneity leads to conflicting results and contributes to creating uncertainty in therapeutic indications.

Anyway, the main unsolved issue that we tried to address in this manuscript is which periprocedural antiplatelet regimen, if any, should be reserved for patients receiving acute CAS, mainly those pretreated with IVT. As stated in the introduction we are in the awkward position to have to get by hemorrhagic risk of intracerebral infarction and risk of stent thrombosis. The hemorrhagic risk is based on guidelines indicating to withheld antithrombotic drugs until 24 hours after IVT, inspired by the ARTIS trial results **[Berge et al, 2021; Zinkstok et al, 2012],** which evaluated the effect of early adjunctive Aspirin in patients treated with IVT

and prematurely terminated because of an excess of symptomatic intracranial hemorrhage (SICH) and no evidence of benefit.

Moreover, the more recent MR CLEAN-MED showed that the administration of antiplatelet or anticoagulant medications during thrombectomy was associated with an increased risk of SICH **[Van der Stein et al, 2022].**

However, the risk-benefit ratio may differ according to stroke etiology, and 2019 AHA acute stroke guidelines state early Aspirin might be considered in the presence of concomitant high-risk **conditions [Power et al, 2019].**

From a pharmacological point of view, in the early large trials of thrombolysis for myocardial ischemia, intracerebral hemorrhage occurred within 12 hours after thrombolytic therapy in 65% of patients, within 12 to 24 hours in 17%, within 24 to 48 hours in 9%, and after 48 hours in 9% **[Gore et al, 1991]** and according to the NINDS trial, SICH typically occurred within 24 hours from IVT. Notably, two-thirds of total SICH and 80% of fatal SICH occurred within 12 hours; subsequently, the risk for severe hemorrhagic transformation is higher in the first few hours after treatment and then gradually tapers off **[NINDS study, 1997].**

On the other side of the coin resides the risk of stent thrombosis, equal to 20% and occurring in 90% of cases in the first 24 hours from stent placement: the unique effective strategy to maintain stent patency is to administer early antithrombotic drugs. **[Pop et al. 2019]**

Clopidogrel is a pro-drug that is absorbed in the intestine and activated in the liver. A 75 mg daily dose needs at least 4 days to induce platelet

inhibition, whereas a 300 mg-loading dose lowers the onset delay to approximately 6 hours **[Steinhubl et al, 2006]** so, theoretically, the administration of 300 mg Clopidogrel within 12 hours after IVT may be relatively safe, as significant platelet inhibition occurs at the tail end of the risk for SICH, becoming truly effective around 18 hours from IVT.

So, to synthesize all these premises, we decided to compare in terms of safety on hemorrhagic risk and effectiveness on the rate of stent thrombosis the administration of 300 mg-clopidogrel load in an early window (6-12 hours after thrombolysis) versus late administration (after 12 hours) of the clopidogrel load and/or direct administration of 75 mg daily clopidogrel without any load. As secondary outcomes, we set mortality and functional independence. As hemorrhagic transformation is the main concern in patients who need early antiplatelet treatment after IVT, all our patients underwent a brain CT scan before any Clopidogrel administration to calculate ASPECT score, to rule out early severe hemorrhagic transformation and to avoid futile treatments, given that the real hemorrhagic risk in patients with tandem lesions is related to the extension of the blood-brain barrier. Usually, the blood-brain barrier could be evaluated through the calculation of the ASPECT Score, which is a 10-point radiological-based score evaluating the integrity of the cerebral territories supplied by the middle cerebral artery. Typically, a lower ASPECT score is associated with extended blood-brain barrier damage, with poor functional outcomes and higher hemorrhagic risk in no longer recoverable ischemic areas. Referring to the literature, in patients undergoing EVT, post-treatment ASPECTS ≤ 7 may predict poor

prognosis, death, and hemorrhagic transformation, with positive predictive values of 75.7%, 21.4%, and 74.2%, respectively **[Chen et al, 2022].**

Indeed in our study, in 5/78 (6.4%) patients we found evidence of intracerebral hematoma, contraindicating aggressive dual antiplatelet treatment. The remaining patients showed various degrees of blood-brain-barrier damage, classified according to a modified ASPECT score with a median post-treatment ASPECTS of 8. Noteworthy, it did not differ in the two specified groups. To further limit futile treatments, we also assessed stent patency before Clopidogrel administration, finding two patients with carotid stents yet occluded. Interestingly, both events occurred approximately 20 hours after IVT, suggesting excessive delay in considering clopidogrel treatment. Moreover, a third patient developed stent occlusion in the group receiving 300 mg Clopidogrel after 12 hours from IVT, and a fourth patient while receiving 75 mg per day without any loading dose, confirming that an excessive delay in antithrombotic therapy on inappropriate dosing could lead to early stent thrombosis and a worse functional outcome. Among patients treated with clopidogrel load, only 9 patients out of 30 developed an intracerebral hematoma classified as "hemorrhagic infarction" of class 1 or 2, which means no clinical and negligible radiological significance. In only one case there was a development of parenchymal hematoma type 2 (so with clinical significance), in any case in a lower percentage, although without statistical significance, of what was observed in the group of patients not treated with an early loading dose of clopidogrel. On the results of our retrospective analysis, which did not show an excess of symptomatic

hemorrhagic transformation, we can affirm that a loading dose of 300 mg Clopidogrel, within 12 hours from IVT and 500 mg intraprocedural Aspirin, did not result in exceeding bleeding risks in patients treated with IVT + MT, emergent carotid stenting with 500 mg intravenous aspirin at stent release. As further observed in the multivariate logistic regression analysis, and then confirmed with ANOVA, both time and dosing of first administration of clopidogrel did not influence the presence of hemorrhagic infarction/parenchymal hematoma. Though not statistically significant, these data seem to suggest the possible optimal adjunctive Clopidogrel treatment strategy should be a loading dose given within 12 hours of IVT.

Albeit scarce and not very robust, scientific evidence suggests the same indication came from our results. A pooled analysis from the TITAN registry, assessing the impact of antiplatelet therapy during endovascular treatment for tandem occlusion, included 62 and 34 patients who had received dual and triple antiplatelet therapy, respectively. 56/96 (58.3%) had received prior IVT. In this cohort, significantly fewer patients with ASPECTS ≤ 7 received at least 2 antiplatelet drugs compared to those with ASPECTS > 7 (13% versus 32%; P 0.002). In the cohort of patients treated with EVT and CAS, the Authors found no increase of SICH in the dual antiplatelet group and an overall neutral effect of adjunctive dual antiplatelet regimen on functional outcome and mortality. The rate of stent thrombosis rate was 17.2% **[Zhu et al, 2020]**

Compared to the TITAN registry, in our study, both the median baseline and post-treatment ASPECT score was 8. However, 33/71 (46.4%) had a

post-treatment ASPECTS ≤ 7 (compared to 13% in the TITAN registry); 8 of them (24.2%) received 300 mg Clopidogrel within 12 hours from IVT. Interestingly, none of these 8 patients developed parenchymal hematoma.

The overall rate of death and functional independence in our cohort was 16.7% and 55.5%, respectively, similar to the TITAN registry (15.8% and 60.5%, respectively). The overall rate of stent thrombosis in our cohort was 5.1%, lower than what was reported in the TITAN registry. Notably, in our cohort, no patients developed stent thrombosis if the Clopidogrel loading dose was given within 12 hours from IVT.

Another interesting comparison to make is with another recent original research from Pop et colleagues, that treated patients with tandem lesions with a more aggressive antiplatelet treatment compared to ours. In this paper authors chose to treat each patient with dual antiplatelet treatment, starting at the moment of acute CAS (with a loading dose of aspirin administered in intravenous infusion and a loading dose of clopidogrel administered via nasogastric tube) with a rescue, intravenous continue infusion for 24 hours of tirofiban in case of evidence of stent shrinkage during digital subtraction angiography. This study showed that aggressive, intraoperative, dual antiplatelet treatment was associated with an increased rate of excellent recanalization, and reduced rates of carotid stent thrombosis at day 1, without an excess in bleeding risks. However, in the French study, only 54/161 (34.6%) patients had received prior IVT, and only 15 were in the aggressive dual antiplatelet group, limiting its conclusion in patients pretreated with IVT**. [Pop et al, 2023].**

In our study we present a more conservative approach, based on post-treatment ASPECTS, to minimize the risks for intracerebral hemorrhage, as all our patients had received IVT. We did not observe any case of stent thrombosis at day 1 in the subgroup of patients receiving intraoperative Aspirin plus 300 mg Clopidogrel within 12 hours from IVT and no excess bleeding risks. However, our tailored approach prevented Clopidogrel treatment in 5 patients who showed post-treatment ICH. Our findings are globally in line with the French study, but with a significantly less hemorrhagic transformation (16% in French study vs 3.3% of our cohort) and reinforce the suggestion of safety and efficacy of early dual antiplatelet treatment for tandem lesions. In particular, in patients receiving prior IVT, adjunctive Clopidogrel may be postponed for a few hours to enhance safety, according to post-treatment ASPECTS, without excessive risk of stent occlusion. However, later treatment (> 12 hours) or no loading dose seems to increase the rate of stent thrombosis and should therefore be avoided. Outcome comparisons between aggressively treated groups of the French study versus our registry are reported in Table 5.

Delving deeper into the variable associated with increased bleeding risk, in our analysis the only significant predictor of parenchymal hemorrhage was pre-Clopidogrel ASPECT Score. Particularly, a score of 8 identified patients at higher risk of intracerebral hemorrhage with a sensitivity of 78% and a specificity of 68%. In the multivariate analysis, neither time nor dosing of clopidogrel administration influenced the appearance of blood in the context of ischemic lesions. Moreover, and very interestingly, a secondary analysis conducted with analysis of variance (ANOVA) on

hemorrhagic complications and evaluating the interaction of ASPECT score and timing and dosage of clopidogrel first administration did not show any influence of drug administration on safety outcome and any interaction with the grade of blood-brain barrier damage. Surprisingly, the only patients showing a parenchymal hematoma in the group receiving clopidogrel load within 12 hours from IVT had a pre-load ASPECT of 8, whereas patients with lower ASPECT scores did not show any complications.

Probably, the hemorrhagic infarctions could be influenced by variables not evaluated in our analysis, such as blood pressure control. An uncontrolled high blood pressure in the first 24 hours could increase the risk of hemorrhagic transformation and it is typically associated with poor functional outcomes. These data were not collected in our analysis so we are not able to conclude if there are other variables playing a role in the occurrence of hemorrhagic and/or thrombotic complications. It therefore becomes mandatory to carefully register every pressure fluctuation in the first 24 hours after IVT + EVT and CAS in tandem lesion patients to assess its real role. Anyway, for all these reasons, there is a need for a careful selection of patients candidates for dual antiplatelet treatment, to rule out severe blood-brain-barrier damage before aggressive treatments and to avoid futile or possibly harmful treatments

Notably, another very recent metanalysis conducted on tandem lesions and evaluating the safety and the efficacy of different anti-platelet regimens showed that high-intensity anti-thrombotic therapies, namely glycoprotein IIb/IIIa inhibitors with less robust evidence for dual antiplatelet therapy,

had a positive effect on good functional outcome over low-intensity antithrombotic therapies without any evidences on increased risk of sICH. Furthermore, as in our study, in this metanalysis, the only variable with a significant impact on functional recovery was the ASPECT score. **[Diana et al. 2023]**

Our study has limitations affecting the interpretation of the results: most importantly, the retrospective study design, from a single center, confers a reduced statistical power due to the overall cohort size and the relatively small number of cases.

However, some strengths are still present. Though retrospective, it included all cases of tandem lesions, prospectively collected in the local registry of acute reperfusion therapies, treated with IVT+EVT+CAS, and early dual antiplatelet treatment. Differently from several other case series, all patients in our study benefited from a standardized diagnostic approach, including brain CT (to enhance safety) and carotid ultrasound (to limit futility) before Clopidogrel treatment and at discharge, and the same dual antiplatelet medications. Notably, all patients included in our study had received prior IVT, so this analysis contributes to increased evidence in this population. Moreover, an imaging review for outcome assignment was performed by two experienced neuroradiologists who were blinded for treatment allocation, reducing potential detection bias.

Pending the results of specific ongoing randomized controlled trials, our study suggests that in patients with tandem lesions receiving intravenous thrombolysis and mechanical thrombectomy with acute carotid stenting, dual antiplatelet treatment with intraprocedural 500 mg Aspirin and

adjunctive 300 mg Clopidogrel loading dose, given within 12 hours from IVT, provided a post-treatment ASPECTS >8, is safe in terms of hemorrhagic transformation and effective in preventing stent thrombosis.

TABLES

Table 1: Patients' baseline characteristics

Variable	Total	Clopidogrel Load 6-12 h	Clopidogrel load > 12h or not received	P-value
Patients (%)	78	30/78 (29.5)	48/78 (61.5)	
Age (mean)	65.9±1	67.4±10.1	63.5±11.5	>0.05
Female (%)	17/78 (21.8)	9/30 (30)	8/48 (16.7)	>0.05
Hypertension (%)	53/78 (67.9)	19/30 (63.4)	34/48 (70.8)	>0.05
Diabetes (%)	15/78 (19.2)	6/30 (20)	9/48 (18.7)	>0.05
Atrial fibrillation (%)	6/78 (8)	2/30 (7.1)	4/48 (8.5)	>0.05
Dyslipidemia (%)	40/78 (51.2)	16/30 (56.6)	23/48 (47.9)	>0.05
Smoke (%)	37/78 (47.4)	13/30 (43.3)	24/48 (50)	>0.05
Previous stroke/TIA(%)	15/78 (19.2)	6/30 (20)	9/48 (18.7)	>0.05
CAD/CHF (%)	20/78 (25.6)	12/30 (40)	8/48 (16.6)	>0.05
Baseline mRS 0	54/78 (69.2)	36/48 (75)	18/30 (60)	>0.05
Baseline mRS 1	14/78 (18.2)	7/48 (14.5)	7/48 (23.3)	
Baseline mRS 2	10/78 (12.8)	5/48 (10.5)	5/48 (16.7)	
IVT beyond 4.5 hours (%)	26/71 (36.6)	7/23 (30.4)	5/12 (41.6)	>0.05

Baseline NIHSS [IQR]	15 (3-29)	17 (10-21)	15 (11-18)	>0.05
Baseline ASPECTS [IQR]	8 (7-9)	9 (7-9)	8 (7-9)	>0.05
IVT + MT + CAS (%)	73/78 (93.5)	28/30 (93.4)	45/48 (93.8)	>0.05
IVT + CAS (%)	5/78 (6.5)	2/30 (6.6)	3/48 (6.2)	>0.05
Door-to-needle time	59.2 ± 34.1	49.6 ± 24.1	64.8 ± 37.5	>0.05
General anesthesia (%)	40/66 (60.6)	11/21 (52.3)	8/10 (80)	>0.05
TICI ≥2b (%)	65/73 (89)	25/28 (89.2)	40/45 (88.8)	>0.05
Pre-Clopidogrel ASPECTS	8 (6-9)	8 (7-9)	7 (6-8)	>0.05

Group A: patients who received 300 mg Clopidogrel Loading dose within 12 hours from IVT (followed by 75 mg daily); Group B: who did not received 300 mg Clopidogrel Loading dose within 12 hours from IVT; CAD: Coronary Artery Disease; CHF: Chronic Heart Failure; IVT: Intravenous thrombolysis; NIHSS: National Institute of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; MT: Mechanical Thrombectomy; CAS: Carotid Artery Stenting TICI: Thrombolysis in Cerebral Infarction

Table 2: Primary and Secondary Outcomes (through chi-square)

Variable		Total	Clopidogrel Load 6-12 h	Clopidogrel load > 12h or not received	p-value
Intracerebral Hemorrhage (%)	None	43/78 [55.1% (44-66)]	20/30 [66.7% CI (47-81)]	23/48 [47.9% (33.9-62.2)]	0.06
	HI1-HI2	23/78 [29.5% (20-41)]	9/30 [30% (16-49)]	14/48 [29.1% (18-44)]	
	PH1-PH2	12/78 [15.4% 8.9-25)]	1/30 [3.3% (0.4-21)]	11/48 [22.9% (12.9-37.2]	
Functional Independence (%)		45/78 (58.4%)	20/30 (66.7%)	25/48 (53.1%)	0.24
Mortality (%)		13/78 (16.7%)	6/30 (20%)	7/48 (14.6%)	0.53
Stent Occlusion (%)		4/78 (5.1%)	0/30 (0%)	4/48 (8.3%)	0.10

Group A: patients who received 300 mg Clopidogrel Loading dose within 12 hours from IVT (followed by 75 mg daily); Group B: who did not

received 300 mg Clopidogrel Loading dose within 12 hours from IVT;

HI: Hemorrhagic Infarction; PH: Parenchymal Hematoma

Table 3. Univariate and multivariate analysis of factors associated with intracerebral hemorrhage

Risk factors	Crude OR (95%CI)	Adjusted OR (95%CI)	P value
IVT beyond 4.5 hours	5.19 (1.88 – 14.34)	3.36 (0.96 – 11.2)	0.06
Gender (male/female)	2.15 (0.69 - 6.76)	2.92 (0.66 – 13.2)	0.119
Pre-Clopidogrel ASPECTS	0.52 (0.37 – 0.75)	0.57 (0.40 – 0.83)	0.003
Hypertension (yes/no)	2.88 (1.03 – 8.03)	2.01 (0.55 – 7.3)	0.944
Diabetes mellitus (yes/no)	0.53 (0.16 – 1.79)	0.41 (0.05 – 3.46)	0.410
Age	1.01 (0.96 - 10.05)	1.03 (0.98 – 1.09)	0.206
Clopidogrel load within 12 hours from IVT	0.46 (0.17 – 1.18)	0.37 (0.11 – 1.27)	0.116

OR: Odds Ratio; CI: Confidence Interval

IVT: Intravenous Thrombolysis

ASPECTS: Alberta Stroke Program Early CT Score

Table 4. Rate of radiological complications by timing and dosage of first clopidogrel administration

Radiological complications	Clopidogrel within 12h (n=30)		Clopidogrel after more than 12h (n=12)	
	75 mg (0)	**300 mg (30)**	**75 mg (19)**	**300 mg (22)**
None		20 (66.7%%)	9 (47.3%)	14 (63.6%)
H1-H2		9 (30%)	6 (31.6%)	7 (31.9%)
PH1-PH2		1 (3.3%)	4 (21%)	1 (4.5%)

Table 5. Comparison between primary and secondary outcome in the aggressive treated group from the French Study (Pop et al, 2023) versus early administration of clopidogrel load group from our cohort

Measure of Outcome	**French Study (DAPT + rescueIV tirofiban) n=61**	**Our study (IVT + MT + eCAS + DAPT) n=30**
Stent thrombosis at day 1	2 (3.5%)	0 (0% - 5.1% in overall cohort)
mTICI 2b-3	58 (95.1%)	25 (89.2%)
mRS 0-2 at 90 days	34 (57.6%)	20 (66.7%)
Mortality at 90 days	9 (15.3%)	6 (20%)
Any ICH	21 (25%)	10 (33.3%)
Parenchimal hematoma	10 (16.7%)	1 (3.3%)
Prior use of IV thrombolysis	15 (24.6%)	30 (100%)

SUPPLEMENTARY MATERIAL

mRS: Modified Rankin Scale (adapted from Shinohara et al. Cerebrovascular disease; doi: 10.1159/000091226)

mRS grade		Notes
0	No symptoms at all	No subjective symptoms and objective signs
1	No significant disability despite symptoms; able to carry out all usual duties and activities	Despite subjective symptoms or objective signs, there has been no change in the person's ability to work and activities of daily living compared to before the stroke
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance	Despite some limitations in the person's ability to carry out his/her usual duties and activities compared to before the stroke, he/she can lead an independent life
3	Moderate disability; requiring some help, but able to walk without assistance	Assistance[a] is essential for using public transport to get around, but is not essential for walking[b], eating, maintaining routine daily hygiene, using the toilet, etc.
4	Moderately severe disability; unable to walk without assistance, and unable to attend to own bodily needs without assistance	Assistance[a] is essential for walking[b], eating, maintaining routine daily hygiene, using the toilet, etc., but constant care is not required
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention	Assistance is necessary at all times

[a] Assistance includes physical assistance, verbal instruction, or supervision by another person.
[b] Ability to walk on a flat surface is mainly checked. In addition, assistance does not include the use of any aid (e.g. stick/cane, or walking frame/walker).

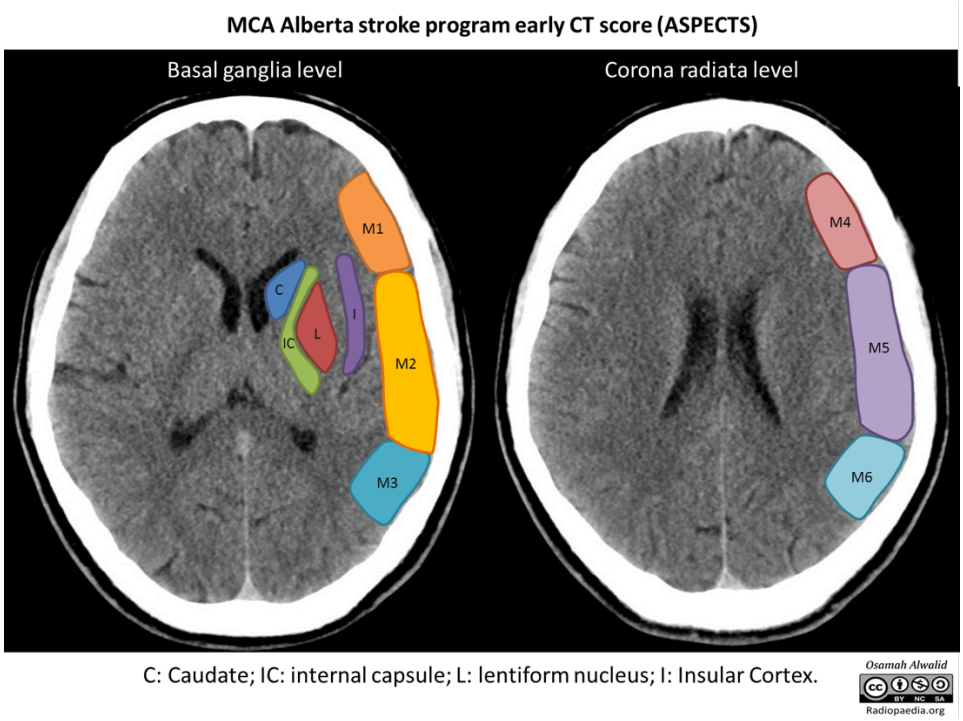
NIHSS: National Institutes of Health Stroke Scale (adapted from https://pbrainmd.wordpress.com/2015/05/04/nih-stroke-scale-nihss/)

National Institutes of Health Stroke Scale

Score = 0 No stroke
Score = 1-4 Minor stroke
Score = 5-15 Moderate stroke
Score = 15-20 Moderate to severe stroke
Score = 21-42 Severe stroke

National Institutes of Health Stroke Scale score	
1a. Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b. Level of consciousness questions: What is the month? What is your age?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly
1c. Level of consciousness commands: Open and close your eyes. Grip and release your hand.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2. Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4. Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5. Motor arm 5a. Left arm 5b. Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement
6. Motor leg 6a. Left leg 6b. Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7. Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8. Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe to total sensory loss
9. Best language	0 = No aphasia; normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia
10. Dysarthria	0 = Normal 1 = Mild to moderate dysarthria 2 = Severe dysarthria
11. Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Total score = 0–42.	

ASPECT SCORE: Case courtesy of Osamah A. A. Alwalid, Radiopaedia.org, rID: 72706



Segmental estimation of the middle cerebral artery (MCA) is made, and 1 point is deducted from the initial score of 10 for every region involved:

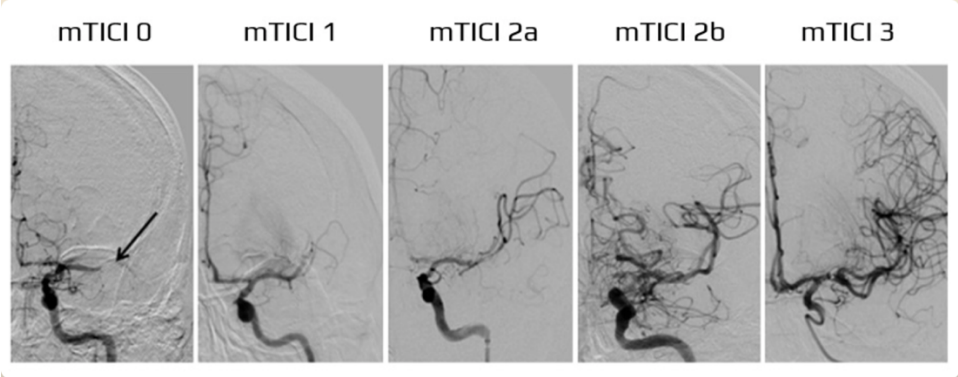
- Caudate, putamen, internal capsule, insular cortex
- M1: "anterior MCA cortex," corresponding to the frontal operculum
- M2: "MCA cortex lateral to insular ribbon" corresponding to the anterior temporal lobe
- M3: "posterior MCA cortex" corresponding to the posterior temporal lobe
- M4: "anterior MCA territory immediately superior to M1"
- M5: "lateral MCA territory immediately superior to M2"

- M6: "posterior MCA territory immediately superior to M3"

mTICI Scores (Sacks et al, Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke, International Journal of Stroke, 2018 doi: 10.1177/1747493018778713)

Score	Description
0	No perfusion, complete obstruction; no flow past occlusion of "major" vessel
1	Perfusion past initial obstruction but limited distal branch filling with little/slow distal perfusion
2a	Partial perfusion: < 50% of "major" vascular territory perfused (eg, filling and complete perfusion through one M2 division)
2b	Partial perfusion: ≥ 50% of major vascular territory is filled, but there is not complete and normal perfusion of entire territory
3	Complete or full perfusion with filling of all distal branches

mTICI: modified thrombolysis in cerebral infarction.



(https://www.stroke-manual.com/angiographic-grading-of-cerebral-revascularization/)

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