MECHANICAL THROMBECTOMY FOR ACUTE ISCHEMIC STROKE DUE TO LARGE VESSEL OCCLUSION: A TWO-YEAR EXPERIENCE IN GREEK CENTERS OF SITS REGISTRY

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Abstract

Introduction: Mechanical Thrombectomy (MT) is the current standard of care for the treatment of acute ischemic stroke (AIS) due to large vessel occlusion (LVO). Safety and efficacy of MT has not been systematically studied in Greece.

Aim: We evaluated the safety and efficacy of MT in AIS patients due to LVO using data from Greek centers participating in The Safe Implementation of Treatments in Stroke (SITS) registry and compared different endpoints to patients from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration cohort.

Methods: We prospectively evaluated consecutive AIS patients with LVO who were treated with MT in 5 Greek hospitals during a two year-period. Safety endpoints included the prevalence of peri-procedural complications, symptomatic intracranial hemorrhage (sICH) and mortality. The rates of complete reperfusion (TICI IIb/III), neurological improvement at 24 hours (defined as a NIHSS reduction by 8 points at 24 hours in comparison to admission NIHSS-score) and 7 days post-stroke, three-month functional independence (modified Rankin score 0-2) were used as efficacy endpoints. Patient demographics, safety and efficacy endpoints were compared to the HERMES cohort.

Results: A total of 30 patients with AIS due to LVO (mean age 55 years, 67% men, median NIHSS-score 18 points, IQR: 13-22) were treated with MT (median onset to groin puncture time: 270 min) in 5 tertiary centers. The rates complete reperfusion (78%) and early neurological improvement at 24 hours (47%) were comparable to those of HERMES cohort (71% & 50% respectively). Three-month mortality was 23% in the Greek cohort and 15% in the HERMES cohort, whereas sICH occurred in 6.6% of our patients (4.4% in HERMES cohort). The rates of three-month functional independence were 43% and 46% in the Greek and HERMES cohort.

Conclusions: The present report confirms safety and efficacy of MT in AIS patients due to LVO in Greece. Further implementation of MT in the clinical practice of Greek stroke centers with specialized Neurology, Anesthesiology and Interventional Radiology Departments is required.

Key words: Ischemic stroke, mechanical thrombectomy, Greece

ΜΗΧΑΝΙΚΗ ΘΡΟΜΒΕΚΤΟΜΗ ΣΤΟ ΟΞΥ ΙΣΧΑΙΜΙΚΟ ΑΕΕ ΛΟΓΩ ΑΠΟΦΡΑΞΗΣ ΜΕΓΑΛΟΥ ΕΝΔΟΚΡΑΝΙΟΥ ΑΓΓΕΙΟΥ: ΔΙΕΤΗΣ ΕΜΠΕΙΡΙΑ ΤΩΝ ΕΛΛΗΝΙΚΩΝ ΚΕΝΤΡΩΝ ΤΟΥ SITS REGISTRY

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Περίληψη

Εισαγωγή: Μηχανική Θρομβεκτομή (ΜΘ) αποτελεί μια πρόσφατα εγκεκριμένη θεραπεία αντιμετώπισης ασθενών με οξύ ισχαιμικό αγγειακό εγκεφαλικό επεισόδιο (ΙΑΕΕ) σε έδαφος οξείας απόφραξης μεγάλου ενδοκράνιου αγγείου (ΟΑΜΕΑ). Η ασφάλεια και αποτελεσματικότητα της ΜΘ στην Ελλάδα δεν έχει μελετηθεί σε συστηματική βάση.

Σκοπός: Συγκεντρώσαμε δεδομένα ασφάλειας και αποτελεσματικότητας της ΜΘ από ασθενείς που νοσηλεύθηκαν σε ελληνικά κέντρα που συμμετέχουν στο αρχείο καταγραφής ασθενών The Safe Implementation of Treatments in Stroke (SITS). Συγκρίναμε τα αποτελέσματα με τα δημοσιευμένα δεδομένα της κοόρτης του Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration.

Μέθοδοι: Αξιολογήθηκαν διαδοχικοί ασθενείς με οξύ ΙΑΕΕ σε έδαφος ΟΑΜΕΑ που αντιμετωπίσθηκαν με ΜΘ κατά τα τελευταία δύο έτη σε 5 Ελληνικά κέντρα που συμμετείχαν στο αρχείο καταγραφής ασθενών SITS. Η ασφάλεια της ΜΘ εκτιμήθηκε με βάση τον επιπολασμό των περι-επεμβατικών επιπλοκών, τη συχνότητα της συμπτωματικής ενδοκράνιας αιμορραγίας (ΣΕΑ) και την ενδονοσοκομειακή θνησιμότητα. Η αποτελεσματικότητα της ΜΘ εκτιμήθηκε με βάση την πιθανότητα πλήρους επαναιμάτωσης, βελτίωσης της νευρολογικής βαρύτητας του ΙΑΕΕ σε 24 ώρες (ελάττωση του NIHSS-score κατά 8 ή περισσότερους βαθμούς) και 7 ημέρες σε σχέση με την εισαγωγή και της λειτουργικής ανεξαρτησίας στους 3 μήνες (σκορ 0-2 στην τροποποιημένη κλίμακα αξιολόγησης της αναπηρίας κατά Rankin). Τα δημογραφικά χαρακτηριστικά καθώς και τα καταληκτικά σημεία ασφάλειας και αποτελεσματικότητας συγκρίθηκαν με τα αντίστοιχα της ομάδας μελέτης HERMES.

Αποτελέσματα: Συνολικά αντιμετωπίστηκαν με ΜΘ 30 ασθενείς με ΙΑΕΕ σε έδαφος ΟΑΜΕΑ σε 5 κέντρα (μέση ηλικία 55 έτη, 67% άνδρες, διάμεση τιμή του NIHSS-score κατά την εισαγωγή: 18 βαθμοί). Η διάμεση τιμή του χρόνου που μεσολάβησε από την έναρξη των συμπτωμάτων μέχρι την έναρξη της ΜΘ ήταν 270 λεπτά. Τα ποσοστά πλήρους επαναιμάτωσης (78%) και πρώιμη νευρολογικής βελτίωσης στις 24 ώρες (47%) ήταν παρόμοια με τα αντίστοιχα της ομάδας μελέτης HERMES (71% & 50% αντίστοιχα). Η θνητότητα στους τρεις μήνες ήταν 23.3% στους Έλληνες ασθενείς και 15.3% στους ασθενείς της HERMES ενώ τα ποσοστά ΣΕΑ ήταν αντίστοιχα (6.6% στην Ελληνική μελέτη και 4.4% στη μελέτη HERMES). Το 43% των Ελλήνων ασθενών ήταν λειτουργικώς ανεξάρτητοι 3 μήνες μετά το ΙΑΕΕ, ποσοστό αντίστοιχο του 46% που καταγράφηκε στην ομάδα ασθενών της μελέτης HERMES.

Συμπέρασμα: Τα παρόντα πιλοτικά δεδομένα επιβεβαιώνουν την ασφάλεια και αποτελεσματικότητα της ΜΘ σε ασθενείς με οξύ ΙΑΕΕ σε έδαφος ΟΑΜΕΑ στη χώρα μας. Η καθιέρωση της ΜΘ στην κλινική πρακτική αντιμετώπισης των ΑΕΕ στον Ελλαδικό χώρο σε εξειδικευμένα κέντρα με κατάλληλα εκπαιδευμένα τμήματα Νευρολογίας, Επεμβατικής Ακτινολογίας και Αναισθησιολογίας κρίνεται αναγκαία.

Λέξεις ευρετηρίου: Ισχαιμικό ΑΕΕ, μηχανική θρομβεκτομή, Ελλάδα

Introduction

Stroke is a major cause of death and disability with an increasing impact on societies due to the aging of the general population [1,2]. Ischemic stroke accounts approximately for 80% of all strokes and can be successfully treated in the acute phase using reperfusion therapies. Two such therapies are approved for the treatment of acute ischemic stroke (AIS): intravenous thrombolysis (IVT) and mechanical thrombectomy (MT). The efficacy of IVT using recombinant tissue plasminogen activator (tPA) for improving Favorable Functional Outcome (FFO) at three months has been established since 1995 with a number needed to treat (NNT) of 8 [3]. However, treatment effect rapidly fades with time and only half as many AIS patients will gain benefit in the 3-4.5hrs time window [4]. Symptomatic intracranial hemorrhage (sICH) is the major adverse event of tPA, with a number needed to harm (NNH) of approximately 30 and 38 for the 0-3 hrs and 3-4.5 hrs time windows respectively [5]. Besides safety concerns, there are efficacy issues with IVT. Recanalization of occluded arteries in large vessel occlusions (LVO) is associated with increased FFO and decreased mortality rates [6,7], but IVT results in recanalization in less than one third and one sixth of patients with proximal middle cerebral artery (MCA) and terminal internal carotid artery (TICA) occlusions respectively [8]. In a minority of patients (15%-34%) of achieved recanalizations, reocclusion and subsequent neurological deterioration may follow [6].

Endovascular reperfusion therapies (ERT) appear to have complementary advantages to IVT such as wider time windows of treatment and higher recanalization rates for LVO patients. A wide variety of ERT have been studied in AIS: intra-arterial thrombolysis, MT using coil retrievers, thromboaspiration and MT using stent retrievers [9]. Despite initial doubts on MT efficacy [10], MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) was the first randomized-controlled clinical trial (RCT) providing clear evidence in favor of endovascular therapy versus standard treatment for AIS due to LVO [11]. A total of 4 RCTs evaluating the efficacy of ERT were prematurely halted afterwards in view of the positive findings of MR CLEAN trial: Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) [12], Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND-IA) [13], Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) [14] and Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) [15]. The results of these prematurely terminated RCTs were consistent with the findings of MR CLEAN trial and showed that MT increased the odds of FFO for AIS patients in comparison to standard therapy. These five RCTs [11-15] established MT as a safe and highly effective treatment for AIS patients with LVO in the anterior circulation. For every six ELVO patients treated with MT three more will achieve complete recanalization at 24 h following symptom onset and one more will be functionally independent at 3 months in comparison to best medical treatment [16].

MT has never been systematically studied in Greece. The Safe Implementation of Treatments in Stroke (SITS) registry is a leading international stroke registry founded in 1996 as an initiative by participants in the European-Australian randomised stroke thrombolysis studies [17]. It includes over 180,000 patient files from stroke units offering reperfusion therapies to ischemic stroke patients from over 70 countries worldwide. A total of 18 Greek centers participate in the SITS registry, offering IVT to AIS patients. Among these centers, 5 also offer endovascular treatment. We sought to prospectively evaluate the safety and efficacy of endovascular treatment in AIS patients due to LVO in Greece using data collected in SITS Registry.

Methods

We prospectively evaluated AIS patients with LVO who were treated with MT in Centers participating in SITS Registry in Greece over a two-year period (January 2015-December 2016). The participating centers were Metropolitan Hospital in Piraeus, Attikon University Hospital in Athens, Rio University Hospital in Patras, Alexandroupolis University Hospital and AHEPA hospital in Thessaloniki.

Demographics and risk factors were prospectively recorded as previously described in SITS Registry [18]. Stroke severity was assessed using serial measurements of NIHSS (National Institute of Health Stroke Scale) score [18]. Safety endpoints included the prevalence of peri-procedural complications, symptomatic intracranial hemorrhage (sICH) and mortality [11-15]. SICH was defined using standard SITS registry definitions [19]. The rates of complete reperfusion, neurological improvement at 24 hours and 7 days post-stroke, three-month functional independence were used as efficacy endpoints. Reperfusion following MT was evaluated using Thrombolysis in Cerebral Infarction (TICI) grades [11-15]. Complete reperfusion was defined as TICI grades of IIb or III [11-15]. Early neurological improvement at 24 hours or 7 days was defined as a reduction in NIHSS-score of 8 points or greater [19]. Functional status at three months was evaluated using modified Rankin Scale (mRS). Patients with mRS-scores of 0-2 were considered as functionally independent [11-15].

Patient demographics, safety and efficacy endpoints of our cohort were compared to the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke

Table 1. Baseline clinical and imaging characteristics in Greek SITS (Safe Implementation of Thrombolysis in Stroke) registry centers and HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration cohort.

Variable	Greek cohort of SITS registry centers (n=30)*	HERMES collaboration cohort (n=634)
Baseline clinical characteristics		
Median age (years)	55 (45-69)	68 (57-77)
Males (%)	20 (66.7%)	52%
Hypertension (%)	16 (53.3%)	56%
Diabetes mellitus (%)	2 (6.7%)	13%
Atrial fibrillation (%)	8 (26.7%)	33%
Heart Failure (%)	6 (20.0%)	N/A
Hyperlipidemia (%)	8 (26.7%)	N/A
Smoking (%)	14 (46.7%)	31%
Prior stroke (%)	4 (13.3%)	N/A
Baseline NIHSS score (median, IQR)	18 (13-22)	17 (14-20)
SBP at baseline (median, IQR)	142 (130-160)	N/A
DBP at baseline (median, IQR)	80 (70-90)	N/A
Baseline blood glucose at baseline (mg/dl)	N/A	119 (106-140)
Baseline imaging characteristics		
ASPECTS score on baseline CT (median, IQR)	8 (7-10)	9 (7-10)
Intracranial occlusion location		
Internal carotid artery	3 (10.0%)	21%
M1 segment MCA	13 (43.3%)	69%
M2 segment MCA	5 (16.8%)	8%
Tandem occlusion (ICA+MCA)	4(13.3%)	N/A
Other	5 (16.7%)	2%
BA	4 (13.3%)	N/A
PCA	1 (3.3%)	N/A
VA	0 (0%)	N/A

* 2 patients with inhospital strokes and 1 patients with intraprocedural complication
MCA: middle cerebral artery; ICA: internal carotid artery; BA: basilar artery; PCA: posterior cerebral artery; VA: vertebral artery; IQR: interquartile range; N/A: not available

Trials (HERMES) collaboration cohort [19]. The HERMES collaboration pooled data from 634 patients included in the aforementioned five MT RCTs: MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA.

We presented continuous parametric data by using their mean values together with their corresponding standard deviations (SDs). We used median values with their corresponding interquartile ranges (IQR) for the presentation of non-parametric data and percentages for all dichotomous variables. Statistical comparisons between different subgroups were performed using the Pearson's x2 test, unpaired t-test, Mann–Whitney U test and Kruskal-Wallis test adjusted for ties, where appropriate. Serial NIHSS-score measurements at 24 hours and 7 days were compared with admission NIHSS-score using Wilcoxon signed rank-test. The adjusted Wald method, which provides the best coverage for binomial confidence intervals (CI) when samples are < 150 [18], was used for the computation of 95%CIs. All statistical analyses were performed with the use of the Stata Statistical Software Release 13 for Windows (College Station, TX, StataCorp LP).

Table 2. Interventional characteristics in Greek cohort of SITS (Safe Implementation of Thrombolysis in Stroke) registry centers and HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration cohort.

Interventional characteristics	Greek cohort of SITS registry centers (n=30)*	HERMES collaboration cohort (n=634)
IA treatment (%)	1 (3.3%)	N/A
IVT pretreatment (%)	10 (33.3%)	83%
Concomitant stenting (%)	3 (10.0%)	N/A
Catheters used (%)	Solitaire (68.9%), penumbra (27.6%), trevo (3.5%)	N/A
Onset to door time (min, median, IQR)	120 (56-255)*	N/A
Onset to imaging time (min, median, IQR)	125 (62-270)*	N/A
Onset to groin puncture (min, median, IQR)	270 (210-395)*	N/A
Onset to reperfusion (min, median, IQR)	332 (265-453)*	285 (210-362)

*2 patients with inhospital strokes and 1 patients with intraprocedural complication
IQR: interquartile range; N/A: not available

Results

Baseline Clinical Characteristics

A total of 30 patients with AIS due to LVO (mean age 55 years, 67% men, median NIHSS-score 18 points, IQR: 13-22) were treated with MT (median onset to groin puncture time: 270 min) in 5 tertiary centers during the study period. The most common location of occlusion was proximal (M1) MCA (43%). The baseline characteristics of our patients are presented in parallel with respective data from the HERMES cohort in Table 1. The patients in the Greek cohort had similar stroke severity at hospital admission in comparison to HERMES data (median admission NIHSS-score 18 vs. 17 points). Baseline

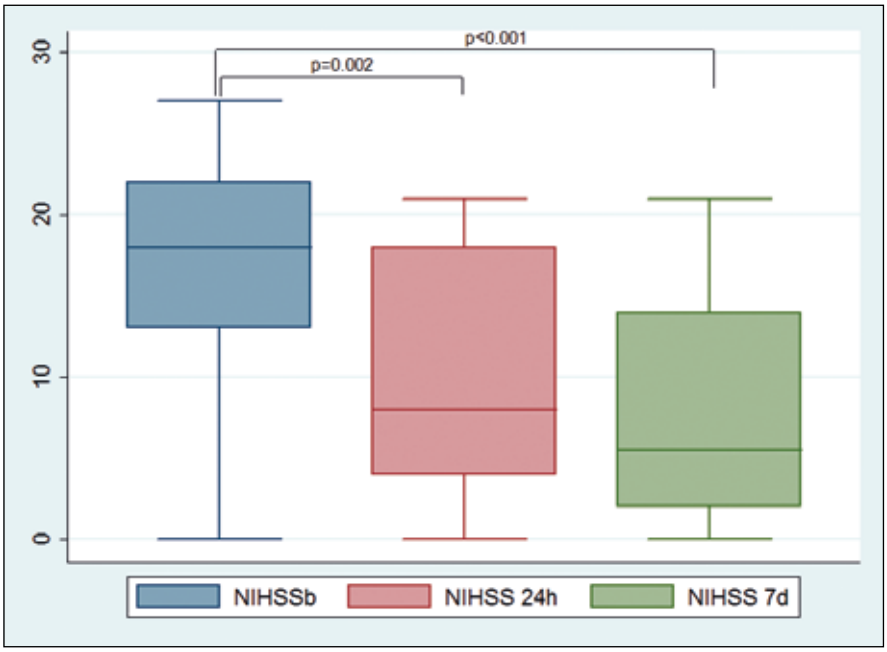

Figure 1. Box plots showing NIHSS-scores at baseline (NIHSSb), 24 hours and 7 days post stroke in AIS patients treated with MT. Median NIHSSb was 18, median NIHSS at 24 hours was 8 and median NIHSS 7 days post stroke was 5.5. The reduction in stroke severity was statistically significant at 24 hours (p=0.002) and 7 days (p<0.001) post stroke.

Table 3. Efficacy and safety outcomes in Greek cohort of SITS (Safe Implementation of Thrombolysis in Stroke) registry centers and HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration cohort.

Variable	Greek cohort of SITS registry centers (n=30)*	HERMES collaboration cohort (n=634)
Efficacy outcomes		
Complete reperfusion (%, 95%CI)	78.1% (62.3-90.9%)	71%
Median NIHSS score at 24h (IQR)	8 (4-18)	8 (3-16)
Median change in NIHSS score from baseline to 24h	-4 (-13 to -1)	-7 (-12 to -1)
Early neurological recovery at 24h (%, 95%CI)**	46.7% (29.5-64.2%)	50.2% (46.2-54.1%)
Median NIHSS score at 7d (IQR)	5.5 (2-14)	N/A
Median mRS score at 90 days (IQR)	3 (1-5)	N/A
mRS score 0–1 at 90 days (%, 95%CI)	26.7% (14.0-44.6%)	26.9%
mRS score 0–2 at 90 days (%, 95%CI)	43.4% (27.4-60.8%)	46.0%
Safety outcomes		
Dissection (%)	3.3% (0-18.1%)	N/A
Infract in new territory (%)	6.6% (0.8-22.4%)	N/A
Symptomatic intracranial hemorrhage (%, 95%CI)	6.6% (0.8-22.4%)	4.4%
Parenchymal hematoma type 2 (%, 95%CI)	10.0% (2.7-26.4%)	5.1%
Myocardial infarction (%)	6.6% (0.8-22.4%)	N/A
Mortality (%, 95%CI)	23.3% (11.5-41.2%)	15.3%

*2 patients with inhospital strokes and 1 patients with intraprocedural complication
** defined as a reduction in NIHSS score from baseline of at least 8 points or reaching 0–1
IQR: interquartile range; N/A: not available

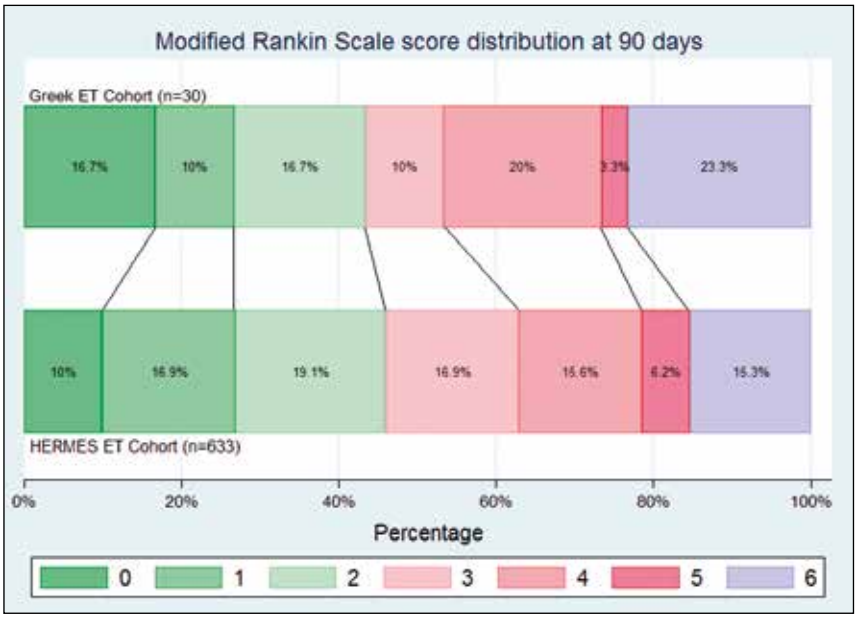

Figure 2. Grotta bars showing distribution of mRS-scores at 3 months in Greek and HERMES cohorts of AIS patients treated with MT.

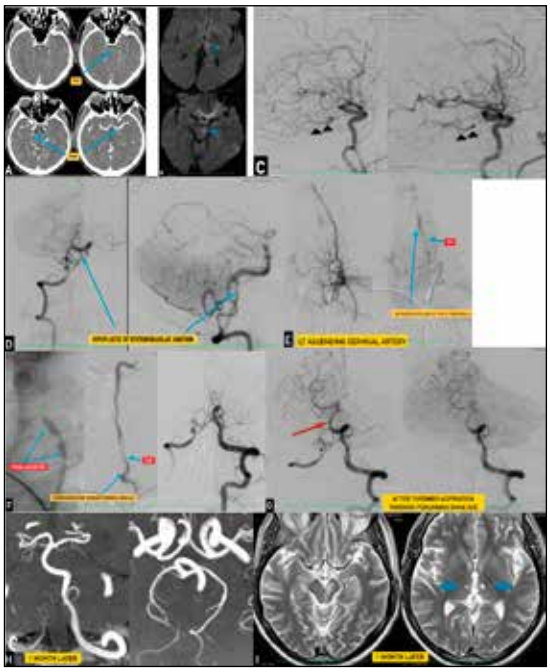

Figure 3. A 54-year-old man woke-up with dysarthria, diplopia and gradual deterioration of the level of consciousness. He reported transient symptoms of dizziness, rotational vertigo and sweating during the past 24 hours. On the same afternoon he was transferred to the emergency department where he presented with GCS=12/15, bilateral eyelid ptosis, left mydriasis, ophthalmoplegia of the vertical and horizontal conjugate eye movements, right VII nerve central paresis, dysarthria and mild paresis of the right upper and lower limbs (NIHSS-score:13 points).

(A) Contrast enhanced CT at admission: Hyperdense clot in the mid-basilar artery (red arrow). Both posterior communicating arteries are functional (yellow arrows). IVT was not offered due to the time window between symptom onset and presentation at the Emergency Department (>4.5hrs from symptom onset).

(B) DWI MRI: Acute ischemic lesions in the midbrain and the left thalamus (blue arrows).

(C) Left and right CCA (lateral projection): Both posterior cerebral arteries and the basilar tip is opacified through the posterior communicating arteries (black arrowheads).

(D) Right vertebral artery (AP and lateral projections): The right vertebral from the PICA origin up to the vertebro-basilar junction is hypoplastic (blue long arrows). The lower basilar artery is dolichous, tortuous and is suboccluded at the level of AICA's (anterior inferior cerebellar artery) origin.

(E) Left thyro-cervical trunk (AP projection, early and late phase): The left vertebral artery is occluded at its origin from the subclavian artery. The anastomoses at C1-C2 between the ascending cervical artery and distal vertebral reconstitute the flow retrogradely into the left vertebral artery (long blue arrow). Multiple filling defects are opacified into the lower left vertebral trunk representing clots (short blue arrow).

(F) Angioplasty of the occlusion of the left vertebral artery origin with a balloon 5x20mm, through a Neuron MAX 6F guide catheter. After the dilatation of the occlusion point, a Penumbra 5MAX ACE distal access catheter (DAC) together with the Neuron MAX catheter were advanced into the vertebral artery with continuous aspiration from the DAC of all the thrombotic material from the vessel lumen. Finally, the vertebro-basilar junctions were opacified bilaterally.

(G) Left vertebral artery (AP injection): After thromboaspiration, recanalization of the dolichotic and tortuous basilar trunk (red arrow) and of the right posterior cerebral artery. The left P1-segment of the left posterior cerebral artery was not opened, but the patency of the left posterior communicating artery, together with the possibility of hypoplastic left P1 were the main reason we did not pursue further reperfusion of left P1 posterior cerebral artery.

(H) MRA at 48 hrs: Complete patency of both posterior cerebral arteries and basilar trunk. The patient experienced a swift neurological recovery (GCS: 15/15 and NIHSS-score: 4 points at 48hrs).

(I) T2WI MRI at 1 month: Ischemic infarct in the left cerebral peduncle and two small ischemic foci in both thalami. The patient's mRS-score at three months was 1.

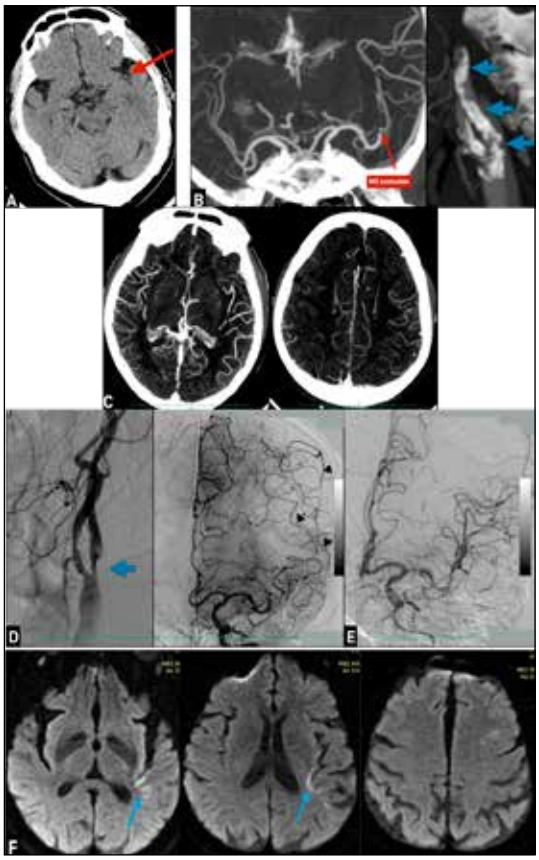

Figure 4. A 65-year-old man, with history of recent myocardial infarction and atrial fibrillation treated with apixaban (5mg bid), presented to the emergency department with sudden onset of right hemiparesis, and aphasia (NIHSS-score: 19 points).

(A) Brain non-contrast CT (NCCT) at admission: Hyperdense left MCA dot sign in the Sylvian fissure was identified (red arrow). IVT was not offered due to pretreatment with apixaban and recent myocardial infarction. ASPECTS score was 10/10.

(B) CTA: M2 occlusion on the left MCA (red arrow). Also heavily calcified atheromatous plaques in the left CCA bifurcation (blue arrows).

(C) Multiphase CTA: Good leptomeningeal collaterals up to the Sylvian fissure.

(D) Left CCA injection (Lateral cervical view and AP intracranial view): Eccentric calcified plaque in the left carotid artery bulb with 70% stenosis. (blue arrow). In the intracranial series, M2 occlusion of the left MCA artery with good opacification of the leptomeningeal collaterals up to the Sylvian fissure (black arrowheads).

(E) Left CCA injection (AP and lateral projections): TICI 3 recanalization, using triaxial approach with Neuron MAX 6F catheter, distal access catheter Penumbra 5MAX ACE and Solitaire stent-retriever 4x20mm. Mechanical thrombectomy was performed using distal aspiration from the DAC. No treatment of the carotid bulb lesion was undertaken at that time.

(F) DWI MRI 24h-post thrombectomy: Small infarction at the posterior part of the insula and the parietal lobe, with preservation of almost all the MCA territory. Early neurological recovery with a 16-point reduction in NIHSS-score (3 points) was documented at 3 days following stroke onset. The patient was scheduled for left internal carotid artery stenting after 2 weeks. The patient's mRS-score at three months was 1.

CT imaging characteristics were similar with Alberta Stroke Program Early CT Score (ASPECTS) being 8 in our cohort (7-10) and 7 in the HERMES cohort (7-10). A total of 5 patients had LVO in the posterior circulation (16.6%) in our cohort, while posterior circulation occlusion were under-represented in HERMES (2%). Only one third of our patients were pretreated with IVT in contrast to HERMES (83% pretreatment rate with intravenous tPA).

Interventional Characteristics

The interventional characteristics of our study cohort are summarized in Table 2. MT was performed using Solitaire Stent retriever in 69% of cases, while

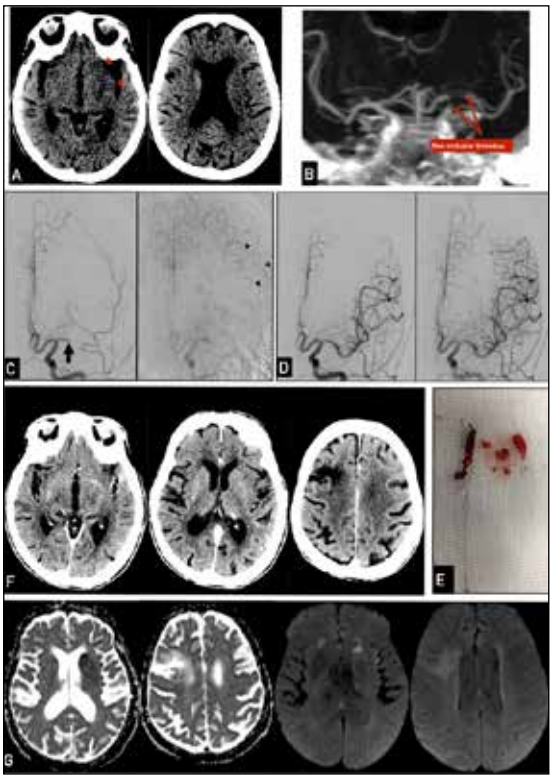

Figure 5. An 87-year-old female patient presented with acute (150 min) dysarthria and was admitted to the emergency department with mixed aphasia and mild right upper limb paresis (NIHSS-score=6). The patient had a history of ischemic stroke in the distribution of the frontal branch of right MCA (2 years ago), hypertension, atrial fibrillation treated initially with dabigatran and recent (7 days before) history of gastric hemorrhage following which she has been switched to low-dose apixaban (2.5mg bid).

(A) Brain NCCT at admission: slight hypodensity in the left insula (red arrowheads), ASPECTS 9/10. IVT was not offered (recent gastric bleeding, treatment with apixaban).

(B) CTA angiography: non-occlusive thrombus at the left ICA bifurcation (T-subocclusion) (red arrows). During the patient's transfer to the angiosuite, she deteriorated substantially with right hemiplegia and complete aphasia (NIHSS-score of 23).

(C) Left CCA injection (AP projection): Occlusion of the proximal M1 (black arrow) including the origin of the lenticulostriate perforators. Moderate leptomeningeal collaterals through anterior cerebral artery (black arrowheads).

(D) Left CCA injection post thrombectomy (AP and lateral projection): Recanalization TICI 3 was achieved with 1 pass, using biaxial approach with BGC (Celo 9F) and Solitaire stent-retriever 4x20mm.

(E) Parts of the thrombus retrieved.

(F) NCCT immediately post thrombectomy: Slight hyperdense opacification of the left insula due to luxury perfusion. The patient improved immediately after recanalization (NIHSS-score 6 points). At 24h the NIHSS-score was 1 point.

(G) DWI MRI at 1week: The only remaining ischemic lesion is at the anterior part of the lenticular nucleus. Please note the previous infarction in right MCA territory.

thromboaspiration with Penumbra device was used in 28% of the study population. Stenting of extracranial ICA was performed in three cases. The median onset to reperfusion time was longer in our cohort in comparison to HERMES dataset (332 vs. 285 min).

Efficacy outcomes

The efficacy outcomes of our cohort are shown in Table 3. The rates of complete reperfusion (78%) and early neurological improvement at 24 hours (47%) were comparable to those of HERMES cohort (71% & 50% respectively). The median NIHSS-score at 24 hours (8 points) and 7 days (5.5 points) were significantly lower (Figure 1) than median admission NIHSS-score (18 points). The rates of three-month functional independence were 43% and 46% in the Greek and HERMES cohort. The distribution of three-month mRS-scores in our and HERMES cohorts is

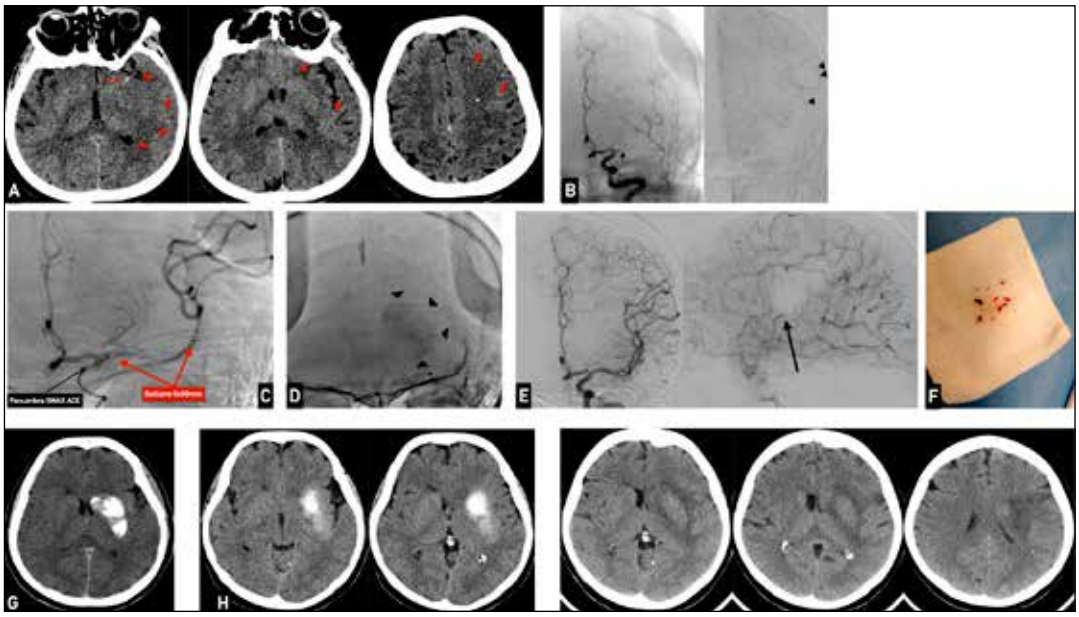

Figure 6. A 60-year-old female patient, with history of hypertension and congestive heart failure, woke-up at 9:30 am with right hemiparesis, right upper extremity and perioral numbness. At 12:15 she arrived at the ED (Emergency Department). Her clinical examination disclose a NIHSS-score of 22 points with right hemiplegia, complete aphasia and left gaze deviation.

(A) Brain NCCT at admission: hypodensity in the left lenticular nucleus, the insula and the left premotor area (red arrowheads) corresponding to an ASPECTS 7/10. Hyperdense MCA sign on the left (red arrow). IVT was not offered (wake-up stroke).

(B) Left CCA injection (AP projection): (Groin puncture at 14:20) Occlusion of the proximal M1 (black arrow) including the lenticulostriate perforators origin. Moderate leptomeningeal collaterals through anterior cerebral artery (black arrowheads).

(C) Tri-axial approach with BGC (Celo 9F), distal access catheter (Penumbra 5MAX ACE) (black arrow) and delivery of Solitaire stent-retriever 6x30mm (red arrows) across the occluding thrombus. Temporary by pass effect with re-opacification of the lenticulostriate perforators.

(D) During the retrieval of the Solitaire stent-retriever into the intermediate catheter that was advanced into the distal M1, contrast extravasation sign is opacified at the left basal ganglia area, due to luxury perfusion and blood-brain barrier disruption.

(E) Left CCA injection (AP and lateral projection): Recanalization TICI 2b was achieved (15:03) with 2 passes. On the lateral view: distal M3 occlusion of the posterior frontal branch of the MCA (black arrow) to the posterior frontal and anterior left parietal area, with retrograde filling from the leptomeningeal collaterals in the late venous phase.

(F) Small parts of the fragmented thrombus retrieved.

(G) Brain NCCT immediately post thrombectomy: Hyperdense opacification of the left basal ganglia due to contrast extravasation.

(H) Brain NCCT at 24h: parenchymal hematoma-type 2 (PH-2) at the head of the left caudate and the lenticular nuclei. The patient's experienced further neurological deterioration (NIHSS-score of 27 points) and the reperfusion hemorrhage was considered as symptomatic (symptomatic Intracranial Hemorrhage).

(I) Brain NCCT 1 week later: evolution of the hematoma and final infarction at the primary motor area. The patient's mRS-score at three months was 5.

shown in Figure 2. Characteristic examples of AIS patients from our cohort treated with MT are presented in Figure 3-5.

Safety outcomes

The safety outcomes of our cohort are shown in Table 3. One patient was complicated with a peri-procedural dissection (3.3%), while infarct in new arterial territory occurred in two patients (6.6%). Information on peri-procedural complications was not available in the HERMES cohort. However, the investigators of MR CLEAN trial have reported procedure-related vessel dissections and embolization into new territories outside the target downstream

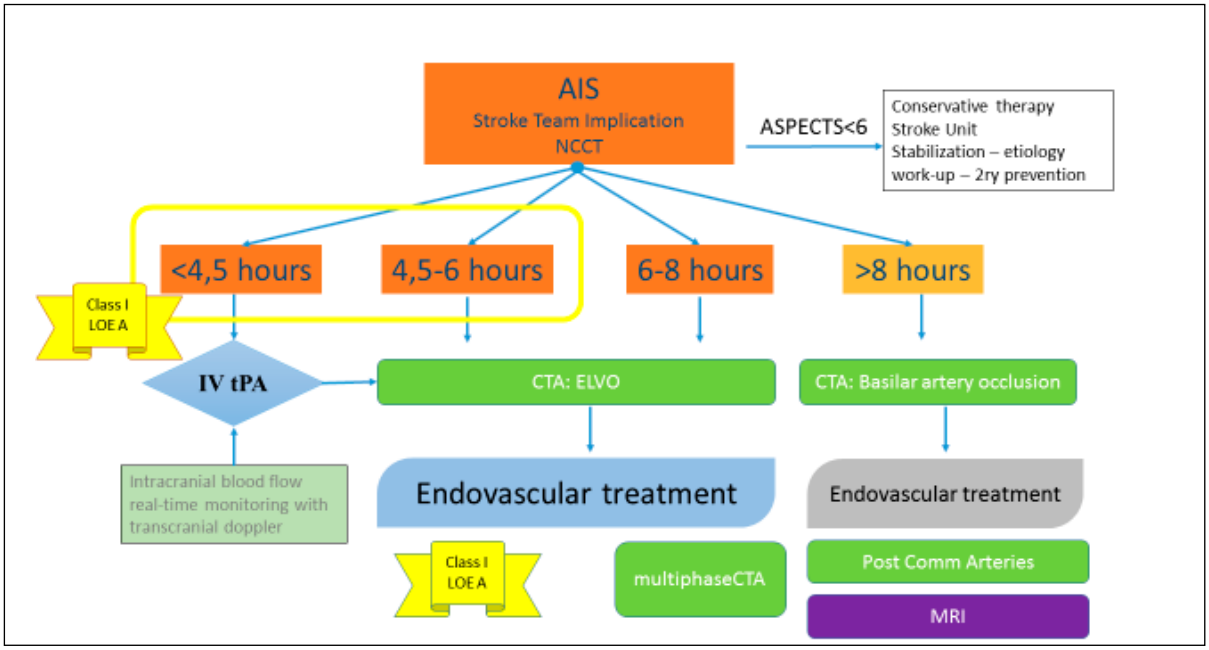

Figure 7. Protocol of systemic and endovascular reperfusion therapies for AIS patients included in our cohort. In anterior circulation LVO there is high level of evidence for clinical benefit with MT up to 6 hours after symptom onset with possible benefit up to 8 hours after symptom onset (REVASCAT trial [15]). CTA has been the non-invasive imaging technique for evaluating LVO in all participating centers. Some centers used transcranial Doppler for monitoring intracranial blood flow during IVT. One center used multiphase CTA as described in the ESCAPE trial [12] in order to assess collateral vessels. Posterior circulation ELVO has not been evaluated in the recent randomized controlled trials but is an indication for MT based on expert opinion. For posterior circulation stroke, some centers evaluated patency of posterior communicating arteries as a measure of collaterality [24]. Pre-treatment MRI has only been used in patients with diagnostic challenges (eg in a patient that had concomitant left M1 occlusion and unknown brain metastasis in the arterial territory of left M1).
LOE: Level of evidence. Post Comm Arteries: posterior communicating arteries.

territory of the occluded vessel in 1.7% and 8.6% of treated patients [11]. Three-month mortality was 23% in the Greek cohort and 15% in the HERMES cohort, whereas sICH occurred in 6.6% (n=2) of our patients (4.4% in HERMES cohort). An example of sICH complicating MT is shown in Figure 6. Two patients from our cohort suffered from acute myocardial infarction (6.6%). There are no published data on post-MT acute myocardial infarction neither in the HERMES cohort nor in most trials included in the HERMES analysis; in the REVASCAT trial one patient suffered from acute myocardial infarction in the MT treatment arm, corresponding to 1% prevalence [15].

Discussion

The implementation of MT in AIS has revolutionized stroke treatment and treatment protocols have been rapidly adapted to offer this highly effective treatment modality in the most severe patients with AIS those with LVO. The present pilot study provides reassuring information regarding the safety and efficacy of MT for acute LVO in selected Greek tertiary stroke centers participating in SITS registry. We also provide our protocol for acute systemic and endovascular reperfusion therapies (Figure 7) that may be shared by others centers in our country that are currently organizing their endovascular stroke services.

Reperfusion therapies in AIS are largely underused in Greece. With a population of 11 million inhabitants, there have been only 30 cases treated with MT in the Greek centers that contribute to the SITS registry over a two-year period. Although we have no data from other centers that offer endovascular reperfusion therapies but do not participate in the SITS registry, it is highly unlikely that adding these cases would significantly affect rates of endovascular treatment for AIS patients in Greece. MT is the current standard of care that should be offered to all patients with AIS due to LVO given its safety and substantial efficacy [20,21]. MT has recently received a Class I/Level A recommendation for AIS treatment by American and European recommendations [22,23]. Consequently, measures to enhance public awareness regarding this novel therapy are urgently needed in order to reduce post-stroke disability. Further implementation of MT in clinical practice in

centers with specialized Neurology, Anesthesiology and Interventional Radiology departments is also required. Close and inter-disciplinary collaboration between different medical specialties with interest in cerebrovascular diseases is a prerequisite to make this novel treatment readily available for the majority of stroke patients in our country.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.
2. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2014;383:245-54.
3. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. Arch Neurol 2004;61:1066-70.
4. Saver JL. The 2012 Feinberg Lecture: treatment swift and treatment sure. Stroke 2013;44:270-7.
5. Jauch EC, Saver JL, Adams HP Jr, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.
6. Tsivgoulis G, Apostolidou N, Giannopoulos S, Sharma VK. Hemodynamic causes of deterioration in acute ischemic stroke. Perspectives in Medicine 2012; 1: 177-184.
7. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007;38:967-73.
8. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke 2011;42:1775-7.
9. Hennerici MG, Kern R, Szabo K. Non-pharmacological strategies for the treatment of acute ischaemic stroke. Lancet Neurol 2013;12:572-84.
10. Broderick JP. Devices and clinical trials: overview and equipoise. Stroke 2013;44:S3-6.
11. Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11-20.
12. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019-30.
13. Campbell BC, Mitchell PJ, Kleinig TJ, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009-18
14. Saver JL, Goyal M, Bonafe A, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285-95.
15. Jovin TG, Chamorro A, Cobo E, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296-306.
16. Tsivgoulis G, Safouris A, Krogias C,et al. Endovascular reperfusion therapies for acute ischemic stroke: dissecting the evidence. Expert Rev Neurother 2016;16:527–34.
17. http://www.sitsinternational.org/. Accessed at 9/4/2017.
18. Tsivgoulis G, Roussopoulou A, Tavernarakis A, et al. The effectiveness and safety of intravenous thrombolysis for acute ischemic stroke: the experience in Greece. Nevrologia 2015;5:6-13
19. Goyal M, Menon BK, van Zwam WH,et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723–31.
20. Campbell B., Donnan G., Lees K., et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol 2015;14: 846–854.
21. Tsivgoulis G, Safouris A, Katsanos AH, Arthur AS, Alexandrov AV. Mechanical thrombectomy for emergent large vessel occlusion: a critical appraisal of recent randomized controlled clinical trials. Brain Behav. 2016;6:e00418.
22. Fiehler J., Cognard C., Gallitelli M., et al. European recommendations on organisation of interventional care in acute stroke (Eroicas). Int J Stroke 2016;11: 701–716.
23. Powers W., Derdeyn C., Biller J., et al. 2015 American Heart Association/American Stroke Association Focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46: 3020–3035.
24. Goyal N, Tsivgoulis G, Nickele C et al. Posterior circulation CT angiography collaterals predict outcome of endovascular acute ischemic stroke therapy for basilar artery occlusion. J Neurointerv Surg. 2016;8:783-6.