Endovascular Thrombectomy for Acute Ischemic Stroke beyond 6 Hours from Onset: A Real-World Experience

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andomized controlled trials (RCTs) on acute ischemic stroke (AIS) due to large vessel occlusion

(LVO) established the superiority of endovascular

thrombectomy (EVT) in addition to the best medical management, including intravenous thrombolysis, over best

medical management alone within 6 hours from symptom onset.1–6 Some of these trials enrolled patients up to

85 or 12 hours2 from symptom onset. The HERMES collaboration individual patient data meta-analyses7,8 of the

first 5 RCTs1–5 showed that the probability of functional

independence (modified Rankin Scale [mRS], 0–2) at 3

months was 46.1%,7 and that although the magnitude

of benefit declines as time from symptom onset to groin

puncture increases, the treatment benefit also remains

beyond 6 hours after stroke onset, but it becomes nonsignificant after 7.3 hours.8

More recent trials demonstrated that the time window

for endovascular treatment can be extended up to 169

or 24 hours10 from the last time the patient was known

to be well, when the selection is based on neuroimaging evaluation showing a salvageable penumbra9 or a

mismatch between clinical deficit and infarct size.10 As a

result, current guidelines11,12 recommend thrombectomy

in the 6- to 24-hour time window for patients meeting

the DAWN10 and DEFUSE-3 trial9 criteria. The DAWN

and DEFUSE-3 trials9,10 focused on patients who suffered mainly from unwitnessed or wake-up stroke. Only

10% of treated patients and 14% of control patients

in the DAWN study10 and 34% and 39% of patients

and controls, respectively, in the DEFUSE-3 trial9 were

treated beyond 6 hours after witnessed stroke onset.

The aim of this study is to evaluate the outcome and

safety of EVT in patients with anterior circulation AIS

due to a proximal intracranial artery occlusion who were

treated beyond 6 hours from known symptom onset in a

large real-world cohort of patients included in the Italian

Registry of Endovascular Thrombectomy.

METHODS

The source of data is the Italian Registry of Endovascular Stroke

Treatments, a multicenter, prospective, observational internetbased registry which includes patients treated with thrombectomy since 2011. The purposes, organization, and structure

of the Registry were previously described in more detail.13,14

This registry was implemented to collect baseline and outcome

information for all treated patients and to share experiences

and operational protocols, with the aim to improve and standardize quality of care delivered throughout the national territory. Centers included in the registry were required to accept

the rules of the registry, including consecutive registration of all

patients with stroke receiving endovascular procedures, participation in regular meetings, and incorporation of the proposed

operational protocols in their routine local practice. The data

that support the findings of this study are available from the corresponding author upon reasonable request. Ethical approval

from the ethics committees of the participating centers and

patient informed consent were obtained. According to national

guidelines,15 patients admitted within 6 hours of stroke onset

were considered eligible for endovascular treatment if the following inclusion criteria were fulfilled: LVO documented on

CT angiography (CTA), a baseline CT Alberta Stroke Program

Early CT Score (ASPECTS) ≥6, and a prestroke mRS score ≤2. However, in selected patients, endovascular procedure was conducted beyond 6 hours after stroke onset. The decision to treat beyond the standard therapeutic window was individualized on the basis of findings obtained from admission brain noncontrast CT scans, CTA of cervical vessels, head single-phase CTA or preferably, multi-phase CTA of intracranial vessels and CT perfusion (CTP). The extension of early ischemic changes was evaluated on noncontrast CT by using ASPECTS. Collateral supply was graded on a 4-point scale for single-phase CTA,16 in which collaterals were categorized as poor (scores, 0–1) and good (scores, 2–3), and on a 6-point scale for multi-phase CTA, in which collaterals were classified as poor (grade, 0–3) and good (scores, 4–5).17 Cerebral blood flow, cerebral blood volume, and mean-transit-time CTP maps were generated for each patient. CTP was evaluated according to the classical CTP mismatch model18: (1) mean-transit-time lesion indicating total hypoperfusion; (2) cerebral blood volume lesion referring to infarct core; and (3) mean-transit-time-cerebral blood volume representing ischemic penumbra. CTP mismatch was defined as the difference between total hypoperfusion and infarct core size and was evaluated by visual inspection. For each modality, patients were judged to be candidates for EVT based on the following criteria: (1) noncontrast CT ASPECTS ≥6; (2) good collateral circulation (single-phase CTA collateral score of 2–3 or multi-phase CTA collateral score of 4–5); (3) CTP mismatch with an infarct core size ≤50% of total hypoperfusion extent or involving less than one-third of the MCA territory extent according to Turk et al19 and to mismatch ratio model. Patients

with noncontrast CT ASPECTS <6, with poor collaterals, without CTP mismatch or with CTP mismatch but an infarct core

size >50% of total hypoperfusion extent or involving more than

one-third of the MCA territory extent, with an inability to complete multimodal CT protocol at baseline or with poor CT quality

were excluded. The same inclusion and exclusion criteria were

also used for the selection of patients treated with endovascular therapy within 6 hours of stroke onset. We extracted data for

patients with LVO (occlusion of the internal carotid artery, and

middle cerebral artery M1 or M2), treated within and beyond 6

hours of stroke onset between 2011 and 2017. Patients with

an occlusion of middle cerebral artery M3, anterior cerebral

artery, or the posterior circulation were excluded. To include

only cases definitely treated beyond 6 hours, patients with

unknown onset of stroke (due to patients being unconscious,

disoriented or aphasic, when a witness was not available, or

when the patient awoke with stroke symptoms) were excluded

from this analysis. For each patient, demographics, stroke risk

factors, prestroke mRS, stroke severity (National Institutes of

Health Stroke Scale [NIHSS] at admission), baseline neuroimaging, and data on endovascular treatment were collected.

Clinical follow-up was assessed by mRS at 3 months. The primary outcome measure was the score on mRS at 90 days,

as assessed by a local trained neurologist through in-person

visit, or through a phone standardized interview when a face-toface assessment was not possible. We examined the following

dichotomizations of the mRS score: 0 to 1 versus 2 to 6, 0 to 2

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versus 3 to 6, and 0 to 3 versus 4 to 6. For efficacy measures, arterial recanalization was rated according to the Thrombolysis in Cerebral Infarction (TICI) score.20 Successful recanalization was defined as TICI score 2b or 3, while TICI 3 defined as complete recanalization. Symptomatic intracranial hemorrhage (sICH) was defined as any intracranial hemorrhage associated with a 4 point increase in the 24 hours NIHSS score, according to the ECASS II definition.21 SICH, procedural adverse events (subarachnoid hemorrhage and vessel dissection), and death rate were considered safety measures.

Statistical Analysis

Data were presented as absolute numbers, percentages, mean±SD if normally distributed or median and interquartile ranges, as appropriate. Dichotomous variables were compared using the $\chi 2$ test, while continuous variables were compared by Student t test or Mann-Whitney U test as appropriate on the basis of data distribution. A multivariable logistic regression analysis to adjust for sex, age, history of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking status (current or former), NIHSS score at entry, site of occlusion, and ASPECTS score, was also run to compare outcome and safety measures between subgroups of patients treated at different times. The functional outcome was further evaluated with ordinal logistic regression, taking the whole range of mRS into account as a dependent variable adjusted for the above variables. The adjusted common odds ratio (OR) and corresponding 95% CI for a shift in the direction of a better outcome on

the modified Rankin scale was, therefore, calculated. A $P<0.05$ was considered significant for all tests.

RESULTS

Out of 3057 patients with AIS whose time at stroke onset was known, 327 (164 women and 163 men) treated beyond 6 hours after symptom onset were included in the analysis. Their mean age was 66.8±14.9 years. Good collaterals were identified by single-phase CTA in 209 and by multi-phase CTA in 118 patients. All patients had a CTP mismatch. Of these, infarct core size was considered ≤50% of total hypoperfusion extent in 174 and less than one-third the middle cerebral artery territory extent in 153 patients. Table 1 summarizes clinical and demographic data of included patients. The median NIHSS score at baseline was 16 (interquartile range, 12–20). The most frequent site of occlusion was the middle cerebral artery M1 (45%). The median onset-to-groin puncture time was 430 minutes (interquartile range, 390–570). Two hundred and one patients (61.5%) were treated between 361 and 480 minutes, 55 (16.8%) between 481 and 600 minutes, 22 patients (6.7%) between 601 and 720 minutes, and 49 patients (15%) beyond 12 hours (up to 24 hours) from symptoms onset. Functional independence (mRS, 0–2) at 90-day follow-up was achieved by 41.3% of cases (Table 2). The proportion of patients with stroke with complete recovery or minimal disability at 3 months (mRS, 0–1) was 26.9%, while 53.2% of patients survived with a disability range of 0 to 3. The 3-month case fatality rate was 17.1%. SICH

occurred in 22 patients (6.7%). A successful recanalization was achieved in 232 patients (70.9%), while TICI score of 3 was recorded in 167 subjects (51.1%).

Outcomes by final TICI score are reported in Table 3.

When focusing on patients with internal carotid artery and M1 occlusion (excluding those with M2 occlusion), the findings concerning outcomes were not significantly different, since the proportions of patients with 90-day mRS 0 to 1, 0 to 2, and 0 to 3 were 25.4% (72/284), 39.1% (111/284), and 50.4% (143/284), respectively.

Twenty-one patients (7.4%) had sICH, and the 3-month case fatality was 17.3% (49/284). Complete recanalization was achieved in 146 (51.4%) of patients, and TICI 2b/3 was recorded in 200 (70.4%).

We compared outcome data between patients who underwent EVT beyond 6 hours and patients with AIS treated within 6 hours of symptom onset extracted by the Italian Registry with the same selection criteria (Table 1). This population included 2730 patients (1352 men and 1378 women) with a mean age of 69.73±13.6 SD and a median NIHSS at baseline of 18 (interquartile range, 13–21).

Patients treated beyond 6 hours were significantly younger than patients treated earlier (P<0.001), had a lower baseline NIHSS score (P<0.01), and a lower

Table 1. Clinico-Demographic Characteristics, and Outcome of Patients Treated Within and Beyond 6 Hours

	Beyond 6 Hours	Within 6 Hours
Sex, men, n (%)	163 (49.8)	1352 (49.5)
Age, mean±SD	66.8±14.9*	69.73±13.7*

History, n/N (%)

Hypertension 186/319 (58.3) 1625/2585 (62.9)

Diabetes mellitus 51/317 (16.1) 408/2585 (15.8)

Dyslipidemia 67/317 (21.1) 641/2585 (24.8)

Atrial fibrillation 92/318 (28.9) 878/2584 (34.0)

TIA/stroke (last 3 mo) 12/327 (3.6) 117/2720 (4.3)

Smokers 67/317 (21.1) 636/2585 (24.6)

History of malignancy 16/320 (5.0) 155/2725 (5.7)

Baseline NIHSS (median, IQR) 16, 12–20† 18, 13–21†

ASPECTS (median, IQR) 8, 7–10‡ 9, 8–10‡

IV thrombolysis, n/N (%) 25/327 (27.6)§ 1774/2730 (65.0)§

Onset to groin puncture time

(median, IQR)

430 (390–570)* 220 (170–273)*

Site of occlusion n (%) Total number 327‡ Total number 2730‡

Middle cerebral artery,

proximal (M1)

147 (45.0) 1338 (49.0)

Middle cerebral artery, distal (M2) 43 (13.1) 421 (15.4)

Carotid T 52 (15.9) 446 (16.3)

Tandem occlusion 85 (26.0)† 525 (12.9)†

ASPECTS indicates Alberta Stroke Program Early CT Score; IQR, interquartile

range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke

Scale; and TIA, transient ischemic attack.

*P<0.001, †P<0.01, ‡P<0.05, §P<0.0001.

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median ASPECTS score. No significant differences were found regarding vascular risk factors and comorbidities. A tandem occlusion was more frequent in patients treated later (P<0.01).

The comparison of outcomes in patients treated beyond and within 6 hours was reported in Table 2. The common adjusted OR for a shift toward a better outcome was 1.59 (1.27–2.02) in favor of patients treated earlier.

The multivariable logistic regression analysis showed that the probability of surviving with mRS 0 to 1 (OR, 0.52 [95% CI, 0.38–0.7]), mRS 0 to 2 (OR, 0.58 [95% CI, 0.43–0.77]), or mRS 0 to 3 (OR, 0.59 [95% CI, 0.44–0.78]) was significantly lower in patients treated beyond 6 hours. No differences were found regarding recanalization rates and safety outcomes.

We compared baseline characteristics and outcomes (Table 4) of patients treated between 6 and 12 hours and those treated beyond 12 hours. We found no significant differences between these 2 groups, except for a higher probability for survival with mRS 0 to 3 in the group of patients treated 6 to 12 hours after stroke onset.

DISCUSSION

In this study, we analyzed outcome and safety data for patients with AIS treated with EVT beyond 6 hours from witnessed symptom onset in a real-world setting. EVT eligibility was decided by a combination of collateral

score and CTP mismatch assessed by visual inspection.

A qualitative evaluation of CTP mismatch was used due

to the limited availability of automated software programs

for a threshold-based calculation of infarct core, ischemic penumbra volumes, and of mismatch ratio (target

mismatch) at the time of patient enrollment in Italy. We

adopted an integrated approach, including CTA collateral

score and CTP mismatch; this approach has recently

been demonstrated to be promising for the selection of

patient with AIS candidates for reperfusion therapies.22,23

Mortality and sICH of patients treated beyond and

within the conventional time window were not significantly different, suggesting that patient with AIS treated

Table 2. Outcome and Safety Data

Beyond 6 Hours

(n=327)

Within 6 Hours

(n=2730) AdjOR (95% CI)

Shift analysis 1.57 (1.25–1.98)

Outcomes, n (%)

mRS 0–1 88 (26.9) 908 (33.3) 0.52 (0.38–0.7)

mRS 0–2 135 (41.3) 1271 (46.6) 0.58 (0.43–0.77)

mRS 0–3 174 (53.2) 1617 (59.2) 0.59 (0.44–0.78)

Death 56 (17.1) 443 (16.2) 1.19 (0.8–1.7)

TICI 2b/3 232 (70.9) 1999 (73.2) 0.7 (0.6–1.01)

TICI 3 167 (51.1) 1505 (5.1) 0.78 (0.6–1.003)

sICH 22 (6.7) 189 (6.9) 0.97 (0.58–1.6)

Data on final recanalization were not available for 3 patients treated beyond 6

hours. AdjOR indicates odds ratio adjusted for age, sex, site of occlusion, baseline, stroke severity, atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, smoke; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; and TICI, Thrombolysis in Cerebral Infarction.

Table 3. Outcome and Safety Data of Patients Treated Beyond 6 Hours According to Final TICI Score

	TICI 0	TICI 1	TICI 2a	TICI 2b	TICI 3
No. of patients	27	22	43	65	167
Outcome n (%)					
Death	11 (40.7)	8 (36.4)	5 (11.6)	10 (15.4)	20 (12)
sICH	0	2 (9.1)	3 (7)	6 (9.2)	10 (6)
3-month mRS					
mRS 0–1	1 (3.7)	2 (9.1)	7 (16.3)	18 (27.7)	60 (35.9)
mRS 0–2	3 (11.1)	3 (13.6)	19 (44.2)	22 (33.8)	88 (52.7)
mRS 0–3	6 (22.2)	6 (27.3)	26 (6.5)	30 (46.2)	106 (63.5)

Data on final recanalization were not available for 3 patients. mRS indicates modified Rankin Scale; TICI, Thrombolysis in Cerebral Infarction; and sICH, symptomatic intracranial hemorrhage.

Table 4. Demographic, Baseline Clinical Characteristics, Site of Occlusion, Interventional Workflow, and Outcome of Patients Treated Beyond 6 Hours, According to Onset to Groin Puncture Time

	6–12 Hours (n=278)	12–24 Hours (n=49)	AdjOR (95%CI)
Sex, men n (%)	135 (48.6)	28 (57.1)	

Age (mean±SD) 66.7 (15.2) 67.2 (13.1)

History, n/N %

Hypertension 159/273 (58.2) 27/46 (58.7)

Diabetes mellitus 47/270 (17.4) 4/47 (8.5)

Dyslipidemia 55/270 (20.4) 12/47 (25.4)

Atrial fibrillation 82/271 (30.2) 10/47 (21.2)

Smoker 56/270 (20.7) 11/47 (22.2)

Median (IQR)

baseline NIHSS

16 (12–20) 15.5 (10–22.75)

Site of occlusion, n (%)

M1 131 (47.1) 16 (32.7)

M2 37 (13.3) 6 (12.2)

Carotid T occlusion 43 (15.5) 9 (18.4)

Tandem occlusion 67 (24.1) 18 (36.7)

Median (IQR) time

to groin puncture

420

(386.5–494)*

953

(826–1130)*

Outcome, n (%)

mRS 0–1 78 (28.1) 10 (20.4) 2 (0.8–4.9)

mRS 0–2 118 (42.4) 17 (34.7) 2 (0.9–4.3)

mRS 0–3 154 (55.4) 20 (40.8) 2.6 (1.2–5.5)

Death 47 (16.9) 9 (18.4) 1.04 (0.4–2.7)

TICI 2b/3 198 (71.2) 34 (69.4) 0.9 (0.4–1.9)

TICI 3 144 (51.8) 23 (46.9) 1.1 (0.5–2.2)

sICH 17 (6.1) 5 (10.2) 0.5 (0.2–1.8)

AdjOR indicates adjusted odds ratio; mRS, modified Rankin Scale; sICH,

symptomatic intracranial hemorrhage; and TICI, Thrombolysis in Cerebral

Infarction.

*P<0.0001.

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later from onset, selected for EVT using the eligibility criteria described above, had safety profiles comparable to

patient with AIS treated earlier.

Patients who underwent EVT beyond 6 hours (within

24 hours) from symptom onset had a 27% probability

to survive with no or very mild disability and a 41.3%

probability of functional independence at 3 months after

stroke. These results are similar to those reported from a

meta-analysis on individual patients data8 from 5 RCT trials1–5 that identified 147 patients with stroke due to LVO

of the anterior circulation treated beyond 6 hours either

with mechanical thrombectomy (n=77) or with standard

medical care (n=70); the proportion of patients surviving with functional independence (mRS, 0–2) was 39%

for patients who underwent endovascular treatment and

24.4% in the control (best medical therapy) group. Our

findings were also consistent with data from previous

observational studies testing the possibility to extend the

time window for EVT beyond 6 hours by using advanced brain imaging, including CTP and magnetic resonance diffusion-weighed imaging (MR-DWI) and perfusionweighted imaging (MR-PWI).17,24–33 CTP, MR-DWI, and MR-PWI selection criteria were established by visual inspection in all but one23 of these articles. In one study, advanced imaging was adopted in 34% of patients.33 In these studies, the number of included patients ranged from 2125 to 2682; the site of occlusion involved anterior circulation25,26,28–33 and either anterior or posterior circulation;17,24,27,28 patients were treated beyond 8 hours,24,26,29,30 beyond 7 hours,17 beyond 6 hours from symptom onset, or, more frequently, from time last seen well25,27,28,31–33; the proportion of patients achieving a good functional outcome (90-day mRS, 0–2) ranged from 32%31 to 62%,33 and the case fatality rate ranged from 13% to 26.2% (Table 5). The utility of advanced imaging in the selection of late-presenting patients with AIS with LVO was further confirmed by a recent single-center study showing a good outcome in 36% of patients when those with baseline mRS >2 were excluded.34

In our study, the comparison between patients treated within and beyond 6 hours after symptom onset demonstrated that the chance of good clinical outcome declined with longer onset to treatment intervals, without significantly affecting safety outcomes. Recent late windows trials9,10 showed a favorable outcome rate of 49% and 45%, respectively, similar to that reported by the HERMES Collaboration meta-analysis of early window trials.7 However, it should be acknowledged that the HERMES study incorporated early window patients

selected with CT and CTA without further advanced imaging, leading to the potential inclusion of a proportion of patients with a matched core and penumbra: this could have blunted the differences in outcome between patients treated in the early and late time windows. In fact, in RCTs enrolling patients in early time windows with advanced imaging (EXTEND IA and SWIFT PRIME),[1,3] the rates of good outcome were found to be 71% and 63%, respectively.[35] Therefore, these observations could explain the decrease in good outcomes over time reported in our study in which both early- and late-treated patients were selected with advanced imaging. Additionally, these findings seem to indicate that time remains a key variable in predicting clinical outcome on a population basis, but not at individual level, where it is just one of the many variables affecting outcome, reinforcing the

Table 5. Overview of Observational Studies on EVT Beyond 6 Hours

	No. of Patients	Age*	Baseline NIHSS†	mRS 0–2‡	Death‡	sICH
Natarajan et al[24]	30	72 (range 24–91)	12 (range, 5–22)	33.3	20	10
Abou-Chebl[25]	21	59.4 (17.2)	17.8 (5.5) mean (SD)	43	23.8 (30-day)	9.5
Jovin[26]	169	64 (16)	17 (range 10–29)	40	25	10
Jung[27]	128	61.1 (15.1)	15 (range 2–36)	35.2	26.2	3.7
Turk, 2013[17]	70	64.9	15.1	45.5	21.2	5.6
Abilleira et al[28]	154	65 (14.2)	17 (13–21)	35.7	23.4	8.4
Gratz[29]	22	67.1 (14.5)	16.5 (range 8–22)	36.4	18.2	9.1
Aghaebrahim et al[30]	128	64 (13.6)	14 (5.4) mean (SD)	50	22	5.5§
Tsurukiri et al[31]	31	74 (9)	17 (13–20)	32	13	10
Mokin et al[32]	248	66.1 (14.6)	16 (13–20)	46.2	21.6	11

69.9 (14) 16 (12–20)

Alsahli et al33 56 72 (60–82) 15 (8–20) 62 14 7

Present study 327 66.8 (14.9) 16 (12–20) 41.3 17.1 6.7

EVT indicates endovascular thrombectomy; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracranial

hemorrhage.

*Mean (SD) unless otherwise stated.

†Median (IQR) unless otherwise stated.

‡90-day unless otherwise stated.

§In this study, only data about hemorrhagic transformation PH type was reported.

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view that a selection of patients only based on time is no

longer justified.36

Taken together, the data obtained in the present study

suggest the possibility to extend the time window for

EVT beyond 6 hours after onset in the real world using

a combined approach based on the concomitant visual

assessment of CTA collateral extent and CTP mismatch

even in those centers not equipped with automated software programs able to calculate the different parameters

of target mismatch. Nevertheless, the lack of a control

group of untreated patients limits the strength of these

findings since it precludes an actual assessment of treatment effect, the comparison with previous RCTs and as a

consequence, the generalization of our results.

This study has other limitations, most of which are

inherent to its observational nature. First, despite central monitoring of data quality and completeness, it is

not possible to exclude reporting biases in a multicenter

prospective national registry with self-reported clinical

and outcome data. Second, the visual, qualitative interpretation of radiological findings could represent another

drawback of the current analysis, since it is now widely

accepted that threshold-based quantitative parameters

obtained with automated software programs represent

the best method for correctly identifying patients with

AIS who can benefit from EVT beyond 6 hours after

onset.9,10,12 However, our study showed a safety profile

similar to that reported in the setting of clinical trials.9,10

Although RCTs remain the gold standard in the assessment of intended effects of interventions, observational

studies can be useful for providing important information

under everyday circumstances.

ARTICLE INFORMATION

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