Universitat Autònoma de Barcelona

STENTRIEVER THROMBECTOMY FOR STROKE WITHIN AND BEYOND THE TIME WINDOW

Aitziber Aleu Bonaut

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Doctoranda:

Aitziber Aleu Bonaut

Dr. Antoni Dávalos Errando Dr. Marc Ribo Jacobi Dr. Antonio Escartin Siquier

A Dani.
A Alai.
A mi familia.
A pohuvipre.

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también, aunque no hayas podido venir. Gracias también al avi y la avia, por darme a Miguel. Gracias a la Kuki y a Joaquim, por el sofá, por las veladas y por las "Aleuadas".

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Eduardo Martinez Vila fue profesor de "Historia de la medicina" en primero de carrera. Luego vendrían las practicas de neurología, encontrarnos cuando yo era residente, más tarde como adjunto en los congresos, los años en el extranjero, … ¡Han pasado 24 años! Solo puedo decir que desde entonces, hasta ahora, Eduardo ha seguido mi carrera de cerca y he tenido su apoyo incondicional siempre. No podías faltar aquí. Gracias Eduardo. Recuerdo especialmente de los años de carrera a Berta y Mari, a Mikel Gorostidi y a los chicos del piso, y cómo no mencionar, a Carolina y a David, con los que permanece una gran amistad.

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Abbreviations

ACA: Anterior cerebral artery

ACILVO: Anterior circulation large vessel occlusion

AHA/ASA : American Heart Association/American Stroke Association

ANOVA: Analysis of variances

ASPECTS : Alberta Stroke Program Early CT Score

AUC: Area under the curve

BP: Blood pressure

CAD: Coronary artery disease

CBF: Cerebral blood flow

CI: Confidence interval

CS: Conscious sedation

CT: Computed tomography

CTA: Computed Tomography Angiography

CTP: CT Perfusion

CTP : Computed tomography perfusion

DAWN: Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention

DEFUSE: DWI Evolution for Un- derstanding Stroke Etiology

DSA: Digital substration angiography

DWI : Diffusion weighted imaging

ECASS: European Cooperative Acute Stroke Study

EMA: European medicines agency

EMS: Emergency management of stroke

ESCAPE: Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times

EVT: Endovascular therapy

EXTEND-IA: EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy

FDA: Food and drug administration

FFA: First found abnormal

FLAIR: Fluid-attenuated inversion recovery

FR: Flow restoration

GA: General anesthesia

HDL: High density lipoprotein

HI: Hemorrhagic infarction

IA: Intraarterial

IAT: Intraarterial thrombolysis

ICA: Internal carotid artery

ICH: intracranial hemorrhagw

IMS: Interventional Management of Stroke

IQR: Interquartile range

ISC: International stroke conference

IVT: Intravenous thrombolysis

KO: Known onset

KO-LP: Late presenters

LDL: Low density lipoprotein

LSA: Lenticulo striated arteries

LSN: Last seen normal

LVO: Large vessel occlusion

MAT: Manual aspiration thrombectomy

MCA: Middle cerebral artery

MCA M1: Middle cerebral artery M1 segment

MCA M2: Middle cerebral artery M2 segment

MELT: Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial

MMT: Multimodal therapy

MR : Magnetic Resonance

MR CLEAN: Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

MR RESCUE: Magnetic Resonance and Reca- nalization of Stroke Clots Using Embolectomy

MRA: Magnetic Resonance Angiography

MRP: Magnetic Resonance perfusion

mRS: Modified Rankin scale

NIHSS: National Institutes of Health Stroke Scale

NINDS: National Institute for Neurological Disorders and Stroke

OR: Odds ratio

OTGP: Onset to groin puncture

OTR: Onset to recanalization

OTT: Onset to treatment

OTW: Outside the window

P2P: Picture to puncture

PH: Parenchymal hematoma

PISTE: The Pragmatic Ischaemic Stroke Thrombectomy Evaluation

PROACT: Prolyse in Acute Cerebral Thromboembolism

RCT: Randomized controlled trial

RESTORE: Reperfusion Therapy in Acute Ischemic Stroke With Unclear Onset

REVASCAT: Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset

ROC: Receiver operating characteristic curve

SAH : Subarachnoid hemorrhage

SD: Standard deviation

SICH: Symptomatic intracranial hemorrhage

SNIS: Sociedty of neurointerventional surgery

SPSS: Statistical Product and Service Solutions

ST: Stentrievers

SWIFT PRIME: Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment

SYNTHESIS EXPANSION: Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke

TCCS: Transcranial color coded sonography

TCD : Transcranial doppler

THERAPY: Assess the Penumbra System in the Treatment of Acute Stroke

THRACE: Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke

TICI: Thrombolysis in cerebral infarction

TIMI: Thrombolysis in myocardial infarction

TLSN: Time last seen normal

tPA: Tissue plasminogen activator

UKO: Unknown onset

UKO-nonWUS: Unknown onset non wake up stroke

UKO-WUS: Unknown onset-wake up stroke

UPMC: University of Pittsburgh medical center

US: United States

WTW: Within the window

ER: Emergency room

I

Introduction

1. BASIC CONCEPTS ON STROKE

1.1. Definition and epidemiology

The term stroke is relatively new from a historical perspective. It was first coined in the seventeenth century by Cole[1]. Until 1869, the term used was Apoplexy, and dates back to 400 BC when Hippocrates described it: *" when persons in good health are suddenly seized with pain in the head and straightaway are laid down speechless…."*, The definition provided by the World Health Organization is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin". [2] When the vascular cause is the rupture of an artery or vein it is a hemorrhagic stroke, when the cause is due to lack of blood supply, the stroke is called ischemic. The term ischemic stroke was recently revisited [3] when a different terminology was proposed. However, by the time this work is written, stroke continues to be the universal term used.

Ischemic Stroke is a devastating and frequent disease, and its incidence is growing due to the aging population.[4] The incidence of stroke varies across countries among 115.000 to 130.00 per 100.000 population.[5,6] According to the National Stroke Association, stroke occurs 152.000 times in a year, which means a stroke every 3 minutes and 27 seconds in the Europe.

Stroke is the second single most common cause of death after myocardial infarction in the world causing 6.7 million deaths each year.[7] The burden of disease (disability, illness and premature deaths) caused by stroke is set to double worldwide by 2030.[8] When a person survives a stroke, the next problem is usually disability. Stroke is the first cause of disability worldwide.

1.2. Pathophysiology

An ischemic stroke occurs when there is an interruption of blood supply to a focal area of brain parenchyma. This interruption is usually caused by the occlusion of an artery, but it could also be caused less often by other unusual mechanisms such as the occlusion of a vein, the steal from another territory, vasospasm or arterial wall diseases such as fibromuscular dysplasia or arterial injury such as a dissection.

Considering the occlusion of an artery as the most common mechanism, strokes can be classified according to the size of the occluded artery in:

1.2.1. Small artery occlusion

When the occluded artery is a lenticulostriate artery or perforating artery, the occlusion is caused by lipohyalinosis and the stroke is termed lacunar stroke or small vessel stroke. Sustained hypertension, hyperglycemia or both cause Lipohyalinosis. Lipohialinosis usually causes hardening of the vessel wall with a progressive occlusion, but it can also cause microaneurysms or dissections and microatheroma and may infrequently be a cause of hemorrhagic stroke. Lacunar strokes account for 20% of the strokes, and cause lesions smaller than 1.5mm, which can be silent or cause lacunar syndromes (there are over 100 clinical lacunar syndromes described). When these strokes happen repeatedly, they can cause leucoaraiosis and vascular dementia.

1.2.2. Large vessel occlusion (LVO)

When the occluded artery is a medium or large, the etiology is usually one of the following:

1.2.2.1. Atherosclerosis

This mechanism accounts for 20% of the strokes.[9] The atheroma plaque can cause progressive occlusion, which could lead to the development of collateral circulation before completely occluding which prevents the patient from having symptoms, or cause an ulcered or complicated

plaque that suddenly occludes the vessel causing symptoms. Atheromatosis can be extra or intracranial. Intracranial atherosclerosis occurs in 10% of the strokes and is more frequent in Asian populations.[10] Extracraneal atherosclerosis can occur in the carotid arteries but also in the aortic arch, which accounts for 10% of the strokes and can cause bilateral lesions.[11]

1.2.2.2. Embolism

The embolic source can be from an atheroma plaque (which is the previously mentioned etiology) from a cardiac source, or from other sources. The causes of cardiac emboli are multiple: hypokinetic area after silent ischemia or myocardial infarction, blood clot from a stagnant enlarged atrium after chronic or paroxistic atrial fibrillation or other arrhythmias. Other rare cardiac emboli are calcific emboly from calcified plaques or emboli from cardiac tumors such as mixomas. Another potential source of embolism are paradoxical emboli, which emerge from a clot in a vein and cross to the arterial bed through a patent foramen ovale.[12]

1.2.2.3. Thrombosis in situ

This mechanism is rare and usually due to blood dyscrasias or coagulation disorders. This can lead to an intracranial or extracranial occlusion.

1.3. Diagnostic of stroke due to large vessel occlusion

1.3.1. Clinical presentation

The clinical presentation differs on the occluded artery, with syndromes according to the occluded artery and side affected. Patients present with a significant neurological deficit, which usually scores higher than 8 in the (National Institutes of Health Stroke Scale (NIHSS). However, the studies that associate NIHSS and LVO differ with cut-off scores of 7, 8 and 9. Interestingly, the association between NIHSS and LVO is time dependent with higher NIHSS in earlier periods and lower NIHSS after 6 or 7.5 hours, depending on the study. Olavarria et al identified mean NIHSS cut off of 15 within 6 hours and 4 beyond 6 hours[13], while Heldner et al reported NIHSS

≥9 within 3 hours and NIHSS≥7 within 3 to 6 hours from symptom onset. [14] Additionally, a complete clinical history with comorbidities, premorbid status, risk factors and medication.

1.3.2. Confirmation of stroke

The first screening tool is usually a non contrast computed tomography (NCCT) to: 1) exclude a hemorrhage or other cause of acute neurological deficit (stroke mimic) that would preclude from treatment with IVT and 2) Quantify the extent of the image core by the Alberta Stroke Program Early CT Score (ASPECTS) score. This score divides the middle cerebral artery (MCA) territory in ten regions of interest, each of them is assigned one point, which will sum up for every region that is hypo attenuated on computed tomography (CT). Thus, a completed MCA infarct scores a 0 and very recent or well compensated by collaterals with no hypo attenuation scores 10. Although some authors have questioned the validity of this score [15] and recent studies have shown that Diffusion weighted imaging (DWI) ASPECTS is more reliable to assess than CT ASPECTS, ASPECTS remains the standard of care nowadays because it can precisely score the extremes, which is essential a fast first line screening tool. [16]

1.3.3. Confirmation of large vessel occlusion

Identification of the occluded site, which can be done based on transcranial Doppler (TCD), computed tomography angiogram (CTA) and magnetic resonance angiography (MRA). The gold standard is CTA, which scans from aortic arch to vertex and provides information on clot location and length, collaterals, supraaortic vessel status. MRA, because is slower to perform and has lower sensitivity and specificity, is the alternative for patients with allergy to iodinated contrast. TCD is another tool, but is operator dependent and thus not as accurate, neither is widely available. It is important not only to confirm that there is a LVO, but also to characterize it as much as possible (location, length or density are variables that are also related to outcome), to have a scenario of the natural history of that individual patient with that occlusion and that area or infarcted brain. To that regard, advanced neuroimaging helps in the decision-making; once the diagnosis of stroke due to LVO is confirmed.

1.3.4. Assessment of the infarct core

Although magnetic resonance (MR) DWI is the most accurate neuroimaging to detect early infarct core, it is not widely available and is time consuming. The maximal admission lesion volume compatible with favorable outcome is 70-100ml, so that reperfusion therapies on higher infarct volumes would result in futile recanalization.[17,18] However, Ribó et al recently shown that the volume threshold may be lower than traditionally estimated, as low as 39ml, and even lower in octogenarians with values of 15ml.[19]

CTA collateral score[20] has been advocated together with NCCT as a surrogate for infarct core.[16] In fact, it was the screening tool for the Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE) trial and has been favorably compared to DWI, so that a score of 0 represents a DWI volume<100ml. [21]

1.4. Management of stroke due to large vessel occlusion

1.4.1. Intravenous thrombolysis

It was 20 years ago in 1995, when the first ever treatment for stroke was first published. Since then, stroke became a treatable disease. The National Institute of Neurological Disorders and Stroke (NINDS) NINDS study published in 1995 offered the stroke victims a treatment option for the first time ever [22] : intravenous thrombolysis (IVT), which worked if administered in the first 3 hours. This fact radically changed the scenario and subsequently, stroke became an emergency and the term “stroke code” was coined. New structures were developed in the whole chain of stroke care: starting with public awareness, paramedics, stroke neurologist on call, stroke units and telemedicine[23] and other means to make the patients arrive on time to be treated. Later on came the primary and tertiary or comprehensive stroke centers, and the hub and spoke concepts. It all started in 1995 in terms of evidence based treatment with IVT and awareness of stroke as an emergency. Also in 2008, another milestone in stroke treatment was achieved: the

window of 3 hours was extended to 4.5hours.[24] The latest guidelines on the administration of IVT date back to 2013. Patients eligible for intravenous tPA should receive intravenous tPA even if endovascular treatments are being considered (Class I; Level of Evidence A). Numerous are the contraindications for IVT listed in tables 1 and 2. For this reason, its administration remains low with only 5-20%. Consequently, the contraindications have been recently revisited to increase its administration rate. [25]

Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours From Symptom Onset
Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 hours before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100 000/mm^3
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

Table 1. Inclusion and exclusion criteria for IVT for stroke within 3 hours.

Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptrom Onset
Inclusion criteria
Diagnosis of ischemic strokre causing measurable neurological deficit
Onset of symptoms within 3 to 4.5 hours before beginning treatment
Relative exclusion criteria
Aged > 80 years
Severe stroke (NIHSS> 25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and prior ischemic stroke

Table 2. Inclusion and exclusion criteria for IVT for stroke within 4.5 hours.

1.4.2. Endovascular therapy

1.4.2.1. Intraarterial thrombolysis

The first ever published report of intraarterial thrombolysis dates back to 1958[27], where an attempt was made to lyse a clot in the internal carotid artery with plasmin. In was not until 40 years later that the first randomized studies to pursue evidence in endovascular treatment were published, The Prolyse in Acute Cerebral Thromboembolism PROACT[28] in 1998 and PROACT-II[29] in 1999. In the first study, 48 patients with MCA M1 or M2 occlusions treated within 6 hours with intraarterial (IA) prourokinase and heparin achieved 67% of recanalization versus 18% in the control group treated with heparin only. However, that difference did not translate statistically significant in favorable outcomes, defined as modified Rankin scale (mRS) 0-1 (30.8% versus 21.4%, P=0.72). In the PROACT-II study 180 patients were recruited and the definition of favorable outcome was changed to mRS 0-2. Recanalization was again higher in the treatment group (66% versus 18%, p= 0.001) but again the differences in favorable outcomes were not significant (40% versus 25%). Due to the advent of mechanical thrombectomy in 2004, there was a silent period regarding studies on IAT until the publication of the MELT trial in 2007.[30] Because Japan did not have approval for the use of IVT, but could use prourokinase, a randomized a trial for patients with MCA M1 or M2 occlusions administering the drug IA within 6 hours was performed. When IVT was approved, the trial was prematurely aborted with 114 patients enrolled. Recanalization was achieved in 52.7% of the intraarterial thrombolysis

(IAT) patients without statistically significant difference in favorable outcome defined as mRS 0-2 (49.1% vs. 38.6%) Interestingly, a secondary analysis of mRS 0-1 did reach significance (42.1% vs. 22.8%, p=0.017). It is important to underline that the mean baseline NIHSS in the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) trial [31]were lower than in the PROACT [32]and PROACT II.[29]

As there was not enough evidence for intraarterial thrombolysis (IAT), advances were made to either combine IVT and IAT (bridging trials) or to pursue different means to achieve reperfusion, which would start the era of mechanical thrombectomy. The first trial combining IVT and IAT was the Emergency Management of Stroke (EMS) Bridging Trial Combining intravenous and intra-arterial tPA versus intra-arterial therapy of acute ischemic stroke[33]. Despite superior recanalization rates in the IA arm, it did not translate into a difference in clinical outcomes. The next bridging trial, the (Interventional management of stroke) IMS-II used historical controls from the NINDS and compared them with patients treated with IA t-PA and EKOS microinfusion catheter when possible. The treated patients had better outcomes than the NINDS placebo group but not different than the NINDS treatment group, with mRS 0-2 rates of 46%vs. 28% and 46% vs. 39%, respectively.[34] In 2009, the last bridging study was published. The RECANALISE study comparing 53 patients treated with IVT and IA tPA with 107 patients treated with IVT only, obtaining again higher rates in recanalization in the bridging group (87% vs. 52%, p<0.01) but not in outcomes (57% vs. 44%, p= 0.13). [35]

According to the current guidelines[36], EVT with ST is preferred over IAT. Nevertheless, its use as a salvageable adjunct to achieve a TICI 2b/3 grade is reasonable:

- *Initial treatment with intra-arterial fibrinolysis is beneficial for carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA (Class I; Level of Evidence B-R). However, these data derive from clinical trials that no longer reflect current practice, including use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial tPA is not established, and tPA does not have FDA approval for intra-arterial use. As a consequence, endovascular therapy with stent retrievers is*

recommended over intra-arterial fibrinolysis as first-line therapy (Class I; Level of Evidence E)

- *Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous tPA might be considered, but the consequences are unknown (Class IIb; Level of Evidence C).*
- *Use of salvage technical adjuncts including intra-arterial fibrinolysis may be reasonable to achieve these angiographic results, if completed within 6 hours of symptom onset (Class IIb; Level of Evidence B)*

1.4.2.2. Mechanical embolectomy

1.4.2.2.1. First generation devices

The first devices used for mechanical embolectomy for stroke were devices approved for foreign body retrieval: the Snare Goose and the Alligator device.[37] Other devices were specifically developed for stroke embolectomy: InTime and Attracter (Boston Scientific)[38], Catch [39], Neuronet [40] and Phenox[41], among others.

1.4.2.2.2. MERCI and Penumbra

However, the device that opened the era of mechanical thrombectomy was the MERCI retriever device[42], because it generated literature to support its use. This retriever was shaped as a corkscrew first, then with added filaments to catch the clot. This device was conceived to be used with proximal flow arrest using a balloon guide catheter. The importance of flow reversal had been previously described.[43] The Merci device was the first device approved for stroke mechanical thrombectomy by the FDA in 2004. The MERCI trial was published in 2005[44], with 46 % of recanalization assessed by TIMI2-3 and 27.7% favorable outcomes in patients ineligible for IVT who received mechanical thrombectomy within 8 hours. The multi MERCI [45], enrolled patients treated within 8 hours, with recanalization rates of 57.3% with the device only and 68.5% with adjunctive IAT, achieving favorable outcomes with mRS 0-2 in 36% of the patients. That same year, another new device using aspiration, the Penumbra Stroke System[46] was launched in the market and resulted in the Penumbra Pivotal trial [47], which achieved higher recanalization rates

than ever 81% with a surprisingly low good outcome rate of 25%. The latter Penumbra POST trial in 2010, achieved 87% recanalization rates with 41% good outcome rates[48]. Table x, shows a summary of the main trials on endovascular therapy for stroke using IAT and bridging therapy (IVT+IAT).

Trial, year	N	NIHSS	OTGP OTR	TIMI 2-3	mRS 0-2	Mortality	SICH
PROACT, 1998 [28]	26	17	276 330	58	NA	27	15
PROACT II, 1999[49]	121	17	NA 318	66	39.7	24.8	10
MELT, 2007[31]	114	14	NA 227	53	49.1	5.3	8.8
EMS 2004[50]	62	18		55	43	16	6
IMS II, 2007[34]	55	19		60	46	16	10

Table 3. Main interventional trials using IAT or bridging therapy.

NIHSS: National institutes of health stroke scale. OTGP: onset to groin puncture. Onset to recanalization, TIMI: thrombolysis in myocardial infarction, mRS modified Rankin scale, SICH: symptomatic intracranial hemorrhage.

1.4.2.2.3. Stenting

While the FDA approved mechanical thrombectomy devices, MERCI and PENUMBRA were used; the approach of angioplasty and stenting like in the coronary arteries was being attempted. The first report of a stent in an acutely occluded basilar artery dates back to 1999[51] using a balloon expandable stent, while that same approach but with a self expanding stent was used in an acutely occluded MCA in 2006[52]. The advantage of this approach was the rapid and effective recanalization clearly superior to the FDA thrombectomy devices, however, this was counterbalanced by the need of double antiplatelet therapy and the phenomenon of snow plowing.[53] The SARIS trial was an FDA approved prospective trial for stenting in acute stroke to answer this question.[54] However, another approach, which had both, the advantages of stent and clot retrievers emerged: the stentrievers. Since its first use in may 2008, and the publication of the early pilot trials to the later use in the randomized trials that have established EVT as the gold standard treatment.

1.4.2.2.4. Manual spiration Thrombectomy

In 2008, the distal access catheters were launched to the market, with the aim of enhancing mechanical thrombectomy with the Merci retriever. However, they started be used as stand alone technique, achieving as good results as retrievers, but sometimes even better and faster, which higher reperfusion rates that did translate into clinical outcomes. This approach, first described in 2010, which would later be widespread as suction thrombectomy, manual aspiration thrombectomy (MAT) or direct aspiration first pass technique and would be added to the thrombectomy procedures of stentrievers. Chronologically, it was in 2011, at the same time than the large series on stentrievers started to be reported, that the large series on MAT would be reported, achieving similar rates, not only in recanalization but also in outcomes.[55] This was a result of the fact that in Europe, the EMEA had authorized ST while in US they were not approved, so that the only way to improve the results was to add MAT to the approved Merci retrievers or to do it as a stand-alone technique, surprisingly, they lead to similar results. The role of stentrievers has been confirmed as gold standard by the guidelines, the role of MAT waits to be confirmed.

1.4.2.2.5. Stentrievers

The next milestone was the introduction of the stent retrievers in stroke treatment in 2009, which opened the stent-retriever era, and set the gold standard of mechanical thrombectomy with the five positive randomized trials.

Stentrievers (ST) were primarily designed used for aneurysm bridging treatment and first used in Europe 2009 in a case in which a Solitaire AB device was used after a retriever failed to recanalize an occlusion[56,57]. One of the specific features of stent retrievers is that they create a temporary endovascular bypass (TEB) from proximal to distal of the occlusion. This concept was first coined in 2008 by Kelly and colleagues, who deployed an Enterprise stent to create a temporary bypass in a stroke patient after failed attempts to recanalize with the Merci Retriever.[58] While the stent was deployed, IAT was performed and the occlusion successfully recanalized. It is worth mentioning that at that time, the Solitaire AB (Fig.1) was not approved for use in the United States, which would happen later in 2012.

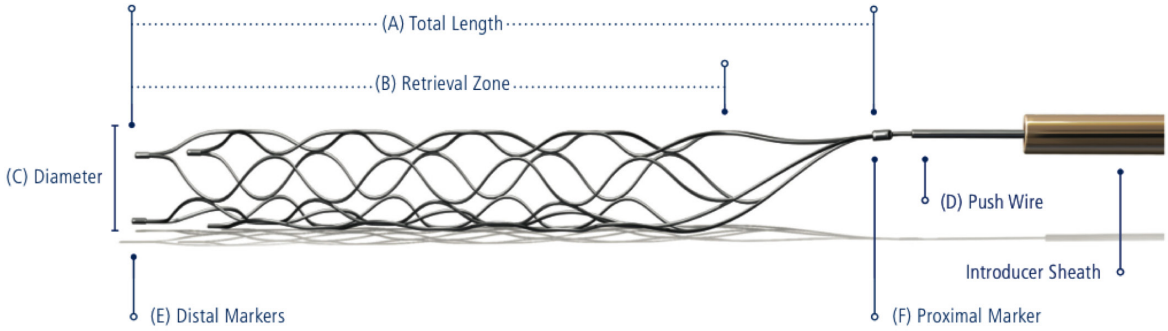

Figure 1. Solitaire AB.

Stent-retrievers, also named stentrievers, retrievable stents, stent-based clot retrievers, fully retrievable intracranial stent or stent retriever technology are unique because they compile the advantages from both the retrievers and the stents. Advantages from the stents include their fast deployment and ease of use as well as the establishment of a temporary bypass from proximal to distal part of the occlusion.

Advantages from the retrievers include that they are removed and, thus, do not require double antiplatelet therapy. As well as retrievers, they can be used in bifurcation occlusions first retrieving the thrombus in one branch and then in the other, which is technically easier and faster than the Y-stent technique using two stents [59]. The most important advantage is that stentrievers achieve higher recanalization rates and shorter procedural times, which has an impact on outcome as have shown the latter studies mounting the evidence. Due to its rapid learning curve, its use became widespread in Europe and they were presented for the first time in 2010 at the ISC and published the same year. [60,61] In the following years, new stent retrievers for stroke treatment were developed such as Trevo, Preset, Revive or Aperio among others and large series of different stentrievers were published.[62–66]

It was in 2013 when three ongoing randomized trials (MR RESCUE[67], IMS III[68] and SYNTHESIS EXPANSION[69]) would finish and be published failing to support evidence for the endovascular approach. One of the explanations for it was that the tools used for mechanical thrombectomy were not the most efficient. [70] It would not be until one year later that the

scenario would radically change when four positive trials (MR CLEAN[71], ESCAPE[72], EXTEND IA [73]and REVASCAT[74] using stent retrievers either yielded a positive result, or had to be stopped because of a clear benefit of EVT over standard treatment (IVT) or best medical therapy. All five recent RCT used ST in most of their enrolled patients and it is thought that its higher efficacy is responsible among other reasons for the positiveness of the trials. Since their first use in 2008, they have revolutionized EVT of stroke and are nowadays considered first line in the treatment and recommendation level A, class I if the treatment is started within 6 hours, the patient has a stroke due to occlusion of ICA or MCA M1 with an ASPECTS score ≥6, NIHSS ≥6, pre morbid mRS of 0 or 1, and over 18 years or age.

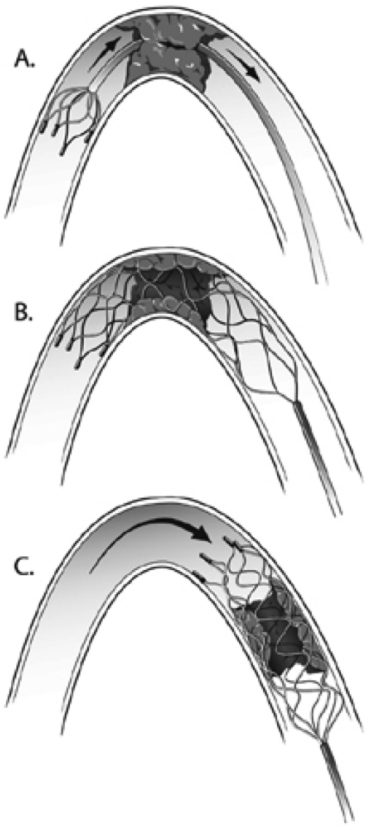

Figure 2. Solitaire FR: Thrombectomy procedure.

1.5. Outcome. Natural history of strokes due to large vessel occlusion

In this work, we will focus on ischemic strokes due to occlusion of a large artery, which have been reported to account for 46% of the ischemic strokes. [75] Strokes due to large artery

occlusion harbor a worse prognosis. When a large extra or intracranial artery, or both become occluded, a large cerebral territory becomes hypoperfused. So, if there is no compensation with collaterals or a timely treatment to revascularize the vessel and reperfuse the parenchyma, a large cerebral infarction will occur, which will likely leave the patient disabled. These strokes usually present with severe symptoms scoring high in the neurological scales (unless compensated by collateral circulation) and carry the worst prognosis. The natural history of these patients when left untreated implies an ominous prognosis with high disability and mortality rates, which obviously vary depending on the artery occluded and the supplied territory. Former publications from the 80´s and 90´s reported mortality rates of 42-53% in ICA terminus occlusion[76,77] and 35% in MCA occlusions.[78] Recent publications from the stroke-unit era in anterior circulation occlusions still yield rates of poor outcomes in ICA, proximal MCA and distal MCA in 92%, 87% and 47% and mortality rates of 23%, 12% and 3% respectively [79]. Regarding posterior circulation, the poor outcome rates range between 75-90%. Regardless the statistics taken into account, it is a fact that to leave a patient untreated is to lead the patient to a high level of disability if not mortality, however, until a year ago, the evidence to treat these patients only covered treatment with intravenous thrombolysis.

2. EVIDENCE ENDOVASCULAR THERAPY OF STROKE

2.1. Reasons to justify endovascular therapy

The reasons to pursue EVT will not be needed soon, according to the recently positive studies that will soon radically change patient management. Until 2015, the need of EVT could be justified based on the following reasons:

2.1.1. EVT is a Treatment option when IVT is contraindicated

Numerous are the contraindications to IVT according to the NINDS and ECASS III trials (Tables 1 and 2). Several reports in the literature have studied the reasons to exclude patients from IVT.[80] The first and more limiting is the narrow time window of 3 hours, which automatically excludes from treatment any patient presenting after 3 hours, or patients with unknown onset, or patients with wake-up strokes. Although the time window was extended to 4.5h, still more than 90 % of the patients are excluded from IVT.[25] Another contraindication of IVT is for patients with non-compressible potential bleeding sites (such as post surgery patients, or post trauma). Also, patients with any bleeding prone state (thrombocytopenia or anticoagulants) are excluded. These numerous contraindications limit the use of IVT in the emergency setting ranging from 5% to 18% in experienced centers. Also, after 20 years of experience, the number of patients treated off label is increasing. Several authors have reported on the complications of patients treated off-label.[81,82] EVT offers a treatment alternative in patients with stroke due to LVO in the numerous occasions when IVT is contraindicated.

2.1.2. Limitations of IVT in large vessel occlusions

Ultrasound studies have shown that the response to IVT in terms of recanalization is inversely related to the caliber of the occluded vessel, so that the larger is the artery occluded, the lower is the recanalization rate.[83] Another factor is the thrombus length, so that the longer the thrombus, the more difficult it is to be lysed with IVT, being the cut-off value 8mm length.[84] Recently, thrombus density in HU has been also reported to be a surrogate for recanalization.[85] The limited efficacy of IVT in these scenarios makes that even if the patients receive IVT in a timely manner, many would ultimately not benefit from it.

2.1.3. EVT is an On-site treatment

Due to its local effect, it is argued that the efficacy of intraarterial thrombolysis (IAT) to lyse the thrombus is not only more effective to recanalize the vessel, but also has fewer systemic hemorrhagic

side effects due to the lower dose of lytic needed, compared to systemic thrombolysis. EVT aims to recanalize large vessel occlusions by either lysing or removing the clot. In a metaanalysis of 33 studies and 989 patients, Rha et al concluded that mechanical thrombectomy is more effective than IAT to achieve recanalization.[86]

2.2. Summary of the Clinical trials that have mounted the evidence

Five clinical trials have finally mounted the evidence after almost 20 years of failure of EVT in randomized trials. There are three remaining trials that were stopped and wait to be published, THRACE (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke)[87], PISTE (Pragmatic Ischaemic Thrombectomy Evaluation Trial)[88] and the THERAPY (Assess the Penumbra System in the Treatment of Acute Stroke)[89] trials. It is worth it to mention that there are at least three major differences with the prior failed trials: 1) the use of more efficient devices (stentrievers), 2) the mandatory confirmation of large vessel occlusion and 3) the exclusion of patients with large areas of core.[90] A comparative summary of the five main trials is presented below based on two main categories:

2.2.1. Patient selection

Clinical criteria

- **Age**: the lower limit was 18 for all 5 trials. There was an upper threshold only in 2 trials, SWIFT PRIME and REVASCAT, up to ages of 80 and 85 respectively. ESCAPE, MR CLEAN and EXTEND- IA did not have a limiting age but required independency pre stroke. Premorbid status: MR CLEAN was the only trial that did not mandate a threshold. SWIFT PRIME and REVASCAT set a mRS of 0 to 1 and EXTEND- IA a mRS of 0 to 2 while ESCAPE did not use mRS but Barthel score of 90 to 100.

- **Clinical severity (NIHSS)**: While EXTEND- IA did not state any NIHSS cut-off; SWIFT PRIME established a range of 8-29 to receive IVT. The remaining 3 trials only

stated a lower NIHSS, which was ≥6 in REVASCAT and ESCAPE and ≥ 2 in MR CLEAN.

- **Time window**: was 6 hours in 3 trials (MR CLEAN, EXTEND- IA, and SWIFT PRIME), 8 hours in REVASCAT and 12 hours in ESCAPE.

Neuroimaging criteria

- Confirmation of LVO through a non-invasive study (CTA or MRA) was required in all studies. DSA was also allowed in MR CLEAN and REVASCAT. The site of occlusion CA or M1 was included in all trials. M2 occlusions were allowed only in 3 (MR CLEAN, ESCAPE and EXTEND- IA), while anterior cerebral artery occlusions (A1 or A2) were only allowed in MR CLEAN. Extracranial carotid occlusion, stenosis or dissection, were only allowed in MR CLEAN and REVASCAT.

- Assessment of infarcted tissue: All studies mandated a baseline non-enhanced CT or MRI. The required CT ASPECTS score was 6 or higher in ESCAPE and SWIFT PRIME and 7 or higher in the REVASCAT. MR CLEAN was the only trial without ASPECTS score threshold, thus the only that permitted ASPECTS<6. In MRI, an ASPECTS 6-10 in DWI was required in REVASCAT. Advanced perfusion imaging was required in addition to basal NECT or MRI in all studies except for MR CLEAN. In EXTEND- IA, CTP was required with ischemic core <70ml and mismatch ratio >1.2 or volume >10ml. SWIFT PRIME changed the criteria from either MRP or CTP for a mismatch ratio of ≥ 1.8 but ischemic core of <50ml to ASPECTS ≥6 in sites which did not have CTP. Interestingly, in the ESCAPE trial, the strategy to include patients was a NECT with ASPECTS≥6 + a multiphase CTA to evaluate for collaterals and mandated moderate to good collateral circulation (≥50% pial circulation).

2.2.2. Procedural details

- Stentrievers TREVO and SOLITAIRE were used in 81.5% in MR CLEAN; Solitaire was used in 86.7% of the ESCAPE trial. EXTEND- IA used Solitaire in 77.1% of

the patients. SWIFT PRIME used Solitaire FR and solitaire 2 in 89% of the cohort. Solitaire FR was used in 95.1% in REVASCAT.

- Intraarterial thrombolysis was not allowed as a rescue tool in REVASCAT or EXTEND-IA, while the other three trials did.

- None of the studies required specific instructions on the use of balloon guide catheter or large bore distal aspiration catheters for stent retrieval.

- Angioplasty and stenting: all the studies except fro SWIFT PRIME allowed inclusion of patients with carotid occlusion, stenosis or dissection. ESCAPE protocol did not recommend stenting.

- Regarding tandem occlusions, which were only included in the ESCAPE and REVASCAT trials, the treatment effect was very high with OR of 9.6 and 4.3 for the intervention group.

- Conscious sedation over general anesthesia: 91-94% of the procedures in ESCAPE and REVASCAT were performed under conscious sedation.

2.2.3. Summary of the most relevant results

Before comparing the results among studies, an overview can be obtained from a metaanalysis of the five randomized trials. This metaanalysis of 1287 patients showed a number needed to treat of 2.6, and a benefit of EVT to reduce disability (with adjusted cOR 2·49, 95% CI 1·76–3·53; p<0·0001). Another important message of is that there was not heterogeneity of treatment among subgroups, including age over 80, patients randomized beyond 5h from onset and patietns not eligible for IVT. Interestingly, SICH, parenchymal hematoma and mortality at 3 months did not differ either.[91,92]

2.2.3.1. Demographic and clinical variables

- **Age**: Although there was no difference in the treatment effect in the subgroup analysis of patients aged over 80, the ESCAPE trials did show a 24% mortality reduction in

the very old. The OR was 2.06 for age>80 versus OR 1.78 for age <80. In the MR CLEAN, patients aged >80 had an OR of 3.24.

- **NIHSS**: The median NIHSS at baseline was 13-18 in the control arms of the 5 trials and 16-17 in the EVT arm. The mean NIHSS in the treatment arm was 17 in all trials except for EXTEND-IA in which it was 15. The subgroup analysis from MR CLEAN and ESCAPE did not show differences in treatment effect across groups.

- **Time window**: Although the time window was different across trials ranging from within 12hours to within 6hours, the median onset to groin puncture time was <4.5 hours in all trials.[93]

- **Neuroimaging**: In MR CLEAN, the only trial that permitted ASPECTS <6, the treatment effect was favorable to intervention in all subgroups (0-4, 5-7 and 7-10), however, in the lower ASPECTs group the OR was 1.09, 95% CI, 0.14-8.46). EXTEND- IA did not report on ASPECTS and the other 3 trials reported subgroup analysis that offered greater benefit for patients in the 8-10 subgroup.

2.2.3.2. Procedural details

The patients with carotid stenosis or occlusions ranged between 18.6% in REVASCAT and 32.2% MR CLEAN. The outcomes of patients with carotid disease were reported in ESCAPE and MR CLEAN with OR, 9.6; (95% CI, 2.6–35.5) and adjusted OR, 1.43; (95% CI, 0.78–2.64), respectively.

Regarding general anesthesia or conscious sedation, the MR CLEAN study did not report differences between the EVT group under GA and the control group. (Adjusted OR, 1.09; 95% CI, 1.69–1.71.), but did find differences between the EVT group under CS and the control group (adjusted OR, 2.13; 95% CI, 1.46–3.11).

2.2.3.3. Safety and efficacy results

The five latter randomized trials showed superiority of EVT other IVT. This benefit was obtained through shorter times to treatment and modern devices like stentrievers that achieved

higher recanalization (58.7% to 88%) than the 25% to 42% achieved in previous trials with IAT or pre-stentriever devices (IMS III, MR RESCUE and SYNTHESIS EXPASION). This superior recanalization rates translated also in higher good outcome rates (32.6%-71%) than in the previous trials (30.4-40.8%) IMS-III and SYNTHESIS EXPANSION respectively. Interestingly, the global futile recanalization rates have notably decreased, with the lowest rates in the EXTEND- IA trial with 17% of patients who recanalized and did not achieve a favorable outcome.

The benefit across studies in OR was 1,67 in MR CLEAN, 2.6 in ESCAPE and 1.7 in REVASCAT. EXTEND- IA had different primary outcomes with 100% reduction in perfusion volume in the intervention group and 37% in the control group, and NIHSS reduction ≥8 or to 0-1 at day 3 in 80% versus 37% in the control group. The number needed to treat ranged from 2.5 to 7 to achieve an independent outcome at 3 months.

The SICH ranged between and 7, which is lower than the previous EVT trials, despite a high use of IVT in a high percentage of patients.

The median time to recanalization was < 6 hours in all trials. The main clinical, safety and outcome data are summarized in table 4.

	N	AGE	NIHSS	OTGP	TICI 2B-3	mRS 0-2	Mortality	SICH
MR CLEAN[94]	500	69	17	260	59	32.6/19.1	21/22	7.7
EXTEND IA[95]	70	65.8	15	210	86	71/40	9/20	0
ESCAPE[96]	315	69.4	17	200	72	53/29.3	10/19	3.6
SWIFT PRIME[97]	196	69.5	17	224	88	60/35	9/12	3
REVASCAT[96]	206	65.7	17	269	66	44/28	18/16	1.9

Table 4. Main results of the five positive randomized controlled trials.

NIHSS: National institutes of health stroke scale. OTGP: onset to groin puncture. Onset to recanalization, TICI: thrombolysis in cerebral infarction, mRS modified Rankin scale, SICH: symptomatic intracranial hemorrhage

Although there was no difference in the treatment effect in the subgroup analysis of patients aged over 80, the ESCAPE trials did show a 24% mortality reduction in the very old. The OR was 2.06 for age>80 versus OR 1.78 for age <80. In the MR CLEAN, patients aged >80 had an OR of 3.24.

2.3. Current Guidelines on EVT

2.3.1. Class I, level A recommendations

Endovascular therapy

Until two years ago, there was not enough evidence supporting endovascular therapy for stroke: pharmacological thrombolysis had Class I, level of evidence B and stent retrievers such as Solitaire FR and Trevo (which were preferred to coil retrievers such as Merci) had Class II; Level of Evidence B. For other mechanical devices, the evidence was Class II; level C. In the past 2 years, the scenario has completely changed due to positive results of five RCT that have confirmed the benefit of EVT. So now, the AHA guidelines establish EVT for stroke as Class I, level of evidence A recommendation for patients meeting the following criteria:

(a) PRESTROKE mRS score 0 to 1,

(b) Acute ischemic stroke RECEIVING INTRAVENOUS TPA within 4.5 hours of onset according to guidelines from professional medical societies

(c) SITE OF OCCLUSION: internal carotid artery or proximal MCA (M1)

(d) AGE≥18 years

(e) NIHSS score of ≥6

(f) ASPECTS of ≥6

(g) TIME: treatment can be initiated (groin puncture) within 6 hours of symptom onset

Intravenous thrombolysis

Always give IVT before EVT: *patients eligible for IVT should receive intravenous tPA even if endovascular treatments are being considered (Class I; Level of Evidence A). In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (Class IIa; Level of Evidence C). There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or non-time based (e.g., prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications)*.

2.3.2. Other recommendations

- **The faster the better (within 6h), thus, no *need to observe response after IVT***. *As with intravenous tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset (Class I; Level of Evidence B-R). Observing patients after intravenous tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended. (Class III; Level of Evidence B).*

- Patient selection and procedural details will be described below. Although these specific recommendations are not widely accepted, most scientific societies include them underlining their high limitations.[16]

2.3.2.1. Patient selection

- **Age**: there is no upper threshold for EVT, the lower threshold is 18, below that age: Endovascular *therapy with stent retrievers may be reasonable for some* patients with acute ischemic stroke who have demonstrated large vessel occlusion in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset, *but the benefits are not established in this age group (Class IIb; Level of Evidence C).*

- **Pre-Morbid Status mRS>1**: *Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score of >1, and causative occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence B-R). Additional randomized trial data are needed.*

- **Minor Strokes (NIHSS<6)**: *Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have NIHSS score <6 and causative occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence B-R). Additional randomized trial data are needed.*

- **Time Window>6h**: *When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence C). Additional randomized trial data are needed.*

- **Aspects<6**: *Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have ASPECTS <6, and causative occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence B-R). Additional randomized trial data are needed.*

- **Other Arterial Occlusion Sites**: *Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (Class IIb; Level of Evidence C).*

2.3.2.2. Procedural details

- **Thrombectomy Device**. *Use of stent retrievers is indicated in preference to the MERCI device. (Class I; Level of Evidence A). The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances (Class IIb, Level B-NR).*

- **Balloon Guide Catheter**. *The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial (Class IIa; Level of Evidence C). Future studies should examine which systems provide the highest recanalization rates with the lowest risk for non-target embolization*.

- **Stenting and Angioplasty**. *Angioplasty and stenting of proximal cervical atherosclerotic stenosis or complete occlusion at the time of thrombectomy may be considered but the usefulness is unknown (Class IIb; Level of Evidence C). Future randomized studies are needed.*

- **Intraarterialthrombolysis**. *The technical goal of the thrombectomy procedure should be a TICI 2b/3 angiographic result to maximize the probability of a good functional clinical outcome (Class I; Level of Evidence A). Use of salvage technical adjuncts including intra-arterial fibrinolysis may be reasonable to achieve these angiographic results, if completed within 6 hours of symptom onset (Class IIb; Level of Evidence B-R). Initial treatment with intra-arterial fibrinolysis is beneficial for carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA (Class I; Level of Evidence B-R). However, these data derive from clinical trials that no longer reflect current practice, including use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial tPA is not established, and tPA does not have FDA approval for intra-arterial use. As a consequence, endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy (Class I; Level of Evidence E). Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous tPA might be considered, but the consequences are unknown (Class IIb; Level of Evidence C)*.

- **Type of Anesthesia**. *It might be reasonable to favor conscious sedation over general anesthesia during endovascular therapy for acute ischemic stroke. However, the ultimate selection of anesthetic technique during endovascular therapy for acute ischemic stroke should be individualized based on patient risk factors, tolerance of the procedure, and other clinical characteristics. Randomized trial data are needed (Class IIb; Level of Evidence C).*

2.4. Unresolved issues in the current guidelines

There are some limitations of the guidelines, which will be presented in the same categories as were described in the summary of the clinical trials: Patient selection and procedural details.

2.4.1. Patient selection

One general criticism of the current guidelines is that they include a minority of patients, mainly because of the stringent criteria regarding: 1) time, which is 6 hours instead of the previous 8 hour window for mechanical thrombectomy and 2) site of occlusion, because only MCA M1 and ICA are considered in the Class I level A recommendation. However, there are other clinical criteria which are less stringent than previous guidelines: 1) NIHSS, which surprisingly has a lower threshold of ≥6 than the NIHSS of 8 threshold traditionally used in previous randomized EVT trials. Traditionally, EVT was restricted for patients with NIHSS ≥8 or ≥10[99] based on studies that correlated 8 or 10 with large vessel occlusion[100] and that strokes with NIHSS ≥10 due to LVO harbor a significant worse outcome and thus should be amenable to EVT, with a favorable benefit/risk ratio. While it is widely accepted that minor strokes should be treated with IVT with tPA or even other lytics[101,102] because at least one third of patients not treated will be disabled[103]; it remains unknown whether these patients should all be treated with EVT. 2) The age criteria has become less strict as there is currently no upper age limit, because some of RCT obtained a higher benefit of treatment in the older patients. The lower age limit of 18 years old persists.

Altogether, despite more relaxing criteria of NIHSS and age some authors have stated that the new guidelines would decrease in almost 50% the number of patients eligible for EVT[104] mainly due to the shortening of the time window.

One of the limitations of the current guidelines is that EVT is recommended only for patients with occlusion of the ICA or MCA-M1. For patients with *occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries, EVT with ST may be reasonable within 6 hours of symptom onset, although the benefits are uncertain. (Class IIb; Level of Evidence C).* This limitation is particularly evident for posterior circulation strokes. Posterior circulation strokes have usually a dismal outcome with mortality rates of 40-80% and high disability rates, however there is currently a lack of evidence because these types of strokes have been consistently excluded from the trials due to their low incidence. Posterior circulation strokes were not included in the five randomized trials and the only randomized controlled trial to prove the superiority of EVT was stopped because of poor recruitment.[105] This is a very controversial aspect because randomized evidence will be difficult to establish. There is an ongoing registry aimed to basilar artery occlusion.

- **Time window**: The current guidelines state a 6hour window from symptom onset. The controversy here is that the guidelines are based on time rather than pathophysiology[106,107], so that the tissue clock is not regarded. This paradigm states that the rate at which the brain tissue dies varies among patients. Taking this into account completely changes the scenario because patients with unknown onset o beyond the stated time windows could benefit from EVT provided there is salvageable tissue on neuroimaging. Conversely, this paradigm explains why patients with short onset to door times cannot benefit from reperfusion therapies if they already have a large infarcted area. This hypothesis might offer a treatment opportunity not only for patients which wake up stroke, but also for patients whose stroke onset is unknown because the patient is aphasic or unconscious and not able to say the onset and there was no witness on site and represent 15-30% of the patients. Thus, the question is of the essence, as these patients would be otherwise excluded from reperfusion therapies according to the guidelines. Following the tissue based approach, the MR WITNESS

trial[108] recently presented its results concluding that IVT was safe and effective beyond 4.5hhours in patients selected with MR, but there is still no evidence for EVT on wake up stroke or unknown onset or late presenting patients. Traditionally, the time window for mechanical thrombectomy trials was 8 hours. Thus, the studies to support this hypothesis were done comparing patients treated within and beyond 8 hours with an endovascular approach,[109,110] concluding that the treatment of late presenting patients or unknown window was as safe and efficient as treating patients within the 8 hour time window. A second unresolved issue, which is currently under work, is that the workflow and the metrics must be radically changed to shorten in- hospital delays. The Society of Neurointerventional Surgery (SNIS) has recommended new metrics to that regard. In this thesis, we will focus on the first issue, that of the time window, studying the controversy of EVT of strokes without unknown onset with a study that was performed in our center. What our study added is that the tools used for thrombectomy were stentrievers, which had not been reported previously. The first chapter of this work presents this study and compares it with the current literature.

2.4.2. Procedural details

Another critical point is the device-specific recommendation, which restricts the use of EVT only to stentrievers. That hinders and slows the development of other devices that may be better than ST but would necessarily need to be compared face to face with them.[90]

- **Thrombectomy devices**: One of the main limitations of the current guidelines is to recommend that EVT should be performed with stentrievers. This is a controversial issue because 1) several years ago, other techniques such as manual aspiration thrombectomy [55] or ST combined with MAT which may be as efficient in recanalizing the vessel; 2) the rapidly evolving field on neurointervention may well develop a better tool soon; 3) Stentrievers are not perfect devices and as have their inconveniences and complications. Consequently, to strictly restrict EVT to the use of one specific devices is currently under controversy and may not correspond to the better therapeutic option. Currently, there are other which maybe as efficient as devices under investigation or already launched

to counteract one of the downsides of ST which is distal embolization. [111,112]4) these recommendations force to compare face to face any new device with ST;[90] and last, the current guidelines do not recommend other tools than ST, however, if they were to be used, they should be used in conjunction with ST. *The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial (Class IIa; Level of Evidence C). Future studies should examine which systems provide the highest recanalization rates with the lowest risk for non target embolization.*

3. JUSTIFICATION OF THIS THESIS

"*It was 2008 when I first saw the endovascular treatment of a stroke patient who was last seen normal 16 hours ago. I could not believe it. The patient fully recovered and was able to walk. Then I thought of the fate of the patients back in my home country with the same artery occlusion. I thought - this can only happen in the United States (US)- , but I was completely wrong. Later on, I found out that most US centers would not have taken that approach. Then, I was taught the research behind this approach, the hours and nights of Tudor Jovin being a fellow spent with Xenon-CT to calculate the cerebral blood flow, the work of Howard Jonas… I was taught the background by Wolf Dieter Heiss, Jean Claude Baron, R.G. Gonzalez and others from MGH; supporting the great variability of speed at which the ischemia evolves among individuals, the concept of fast and slow progressors. For us as fellows, it was a usual approach to consider these patients for treatment and then I realized it was an exception, even in the US".* The time-based approach is based on the assumption that the rate at which the ischemic core progresses is similar across individuals. However, it has been demonstrated that there is a high variability in the ischemic core progression, which backgrounds the tissue- based approach. This approach was described over 20 years ago [107]and has been confirmed over time with recent advanced neuroimaging trials[113] assessing tissue viability in extended windows up to 12 hours, 24 hours[114] and even 48 hours.[115] The first background papers date back to 2006 [116] when case reports were published [116] and would be followed small series in 2009 [117]and large, multicentric series to support the principle in 2011[118]. Parallel to the attempts to proof that

these patients could be safely treated, several trials failed to demonstrate first the basics: that endovascular therapy was the treatment for stroke due to large artery occlusion. Fortunately, the stentrievers took over the angiosuites changing the recanalization rates, procedural times and most important, the outcomes of patients. It took another 1- 2 years for five randomized trials to finally confirm that Endovascular therapy with stentrievers was the recommended treatment. Now it is the time to get back to the patients with unknown onset or the late presenters. Now that we can offer an accepted treatment for a patient with a dismal natural history, we can move forward to research whether it can also be offered to patients with unknown onset, or to patients who present late in the time window. Most of the work has been previously done in basic research and in clinical research, however the tools used in most large series or randomized studies were not stentrievers, and the current RCT did not include this type of patients, with the exception of ESCAPE that enrolled patients within 12 hours. Thus, it remains to be described what happens to these patients when they are treated with the gold standard treatment, and to know if they have similar outcomes than patients within the window. That is the question that this work wants to answer. This thesis aims to shed some light on the matter, while waiting for the results of the trials like DAWN addressing this issue now with stentrievers. It is also a tribute to those who taught me the thought process of treating stroke as well as how to use a catheter, a tribute to the patients who unfortunately were not at the right time and right place to be treated and a tribute to the researchers who devoted their time to this subject despite of not being understood and the pioneers who started to treat these patients and began to slowly mount the evidence.

Unfortunately the situation of this patient was not an exception. It was not an exception back then in 2008 and it is not an exception now in 2016, when we finally have evidence for EVT and management of patients with endovascular therapy is going to exponentially widespread. Moreover, because the current guidelines establish as shorter time window of 6 hours, the exclusion of patients due the time window is likely going to be a focus of interest in the near future.

It is known that approximately up to one in four patients that arrive at the emergency room has a wake up stroke (WUS).[119] If we add to the wake up strokes, the patients with daytime unwitnessed stroke who cannot state the onset time (because they may be aphasic or unconscious) and in

whom no witness is available the rate is becomes higher than one in four. According to the largest series, it can be estimated that over one in three patients have an unknown onset (UKO). Silva et al described a series of 676 patients in which 38%(256) had an unknown onset, from those, 51%(13) had wake up strokes (UKO-WUS) and 49% had unknown onset strokes while awake (UKO-non WUS).[120] So, in their study the incidences of wake up stroke and daytime unwitnessed stroked were 19.3% and 18.4% respectively. In a recent study of 762 patients, 36,2% had and unknown onset and 63.8% known onset. From the patients with UKO, 172 (62.1%) patients were classified as having WUS and 104 patients (37.7%) as having daytime unwitnessed onset, which represents and incidence of WUS of 14% and UKO-nonWUS of 23% which is higher than previously reported series.[121] So, as a rule of thumb, it could be roughly estimated that two thirds of the patients have a known onset, and one third has a unknown onset, and that from those with unknown onset, two thirds have unknown onset due to wake up stroke and one third corresponds to unknown onset due to daytime unwitnessed stroke, in other words, an UKO-nonWUS.

In both situations, the stroke has an unknown onset (due to wake up or to unwitnessed daytime) and the definition for the time of stroke onset has traditionally been considered the last time seen normal (LSN).

Since stroke became a treatable disease over 20 years ago, time of onset (and the time LSN if onset was not available) has been a critical point to determine whether a patient should be treated or not. The reasons to choose time as a surrogate for stroke were that 1) time it is an easy metric to obtain in the field, to compare and to recommend in guidelines (time of onset for witnessed strokes and LSN for unknown onset) and 2) because ischemia evolves over time so, time is brain, so there faster the patient is treated the better.

Consequently, patients beyond the time window, have been traditionally excluded from reperfusion therapies, based on the thought that patients out of the window would first, be at greater risk of bleeding and second, would not benefit from reperfusion because the infarct would be already established.

The time last seen normal (TLSN) has lately been questioned because it excludes patients from treatment because most are outside the time window. TLSN is based on the assumption that the patient had the onset at earliest time seen normal, while the onset may have occurred later in time, and thus within the time window. [122] In fact, alternative methods for establishing stroke onset (like first known abnormal (FKA) or midpoint between LSN and FKA) have been proposed based on the conservative nature of the LSN and also on the individual variation of the ischemic penumbra which would not be consistent with a fixed time limit (neither for a known onset, nor for a surrogate of onset in an unknown onset stroke as LSN). The proposed alternatives since stroke onset, were analyzed and the authors concluded eligibility for trials significantly increased and may be close to the dynamic and individual process of ischemic stroke.[123]

Therefore, in patients with unclear time of onset, because TLSN assumes the earliest possible onset, patients are very often excluded from reperfusion because they are supposedly too late to be treated according to the TLSN. The same situation occurs when a patient experiences a stroke with a known onset but arrives late at the hospital, usually beyond the narrow time window. These patients will also be excluded because they are too late to be treated.

Given that the current guidelines shorten the window from 8 to 6 hours, and taking into account that the 6 hours are not from onset to arrival but from onset to groin puncture, the amount of patients out of the window due to late presentation or unknown onset, is likely going to increase.

If we consider any of the previous scenarios: wake up stroke, unknown onset during awake or late presenting stroke, the number of patients excluded due to time window would considerably increase. In the current era of wide spreading EVT as the first line therapy, the study of patients treated beyond the time window becomes paramount and the frequencies of each reason to be excluded (UKO-WUS, UKO-nonWUS and LP) should be quantified in future studies. For that purpose, the rate of patients with stroke due to large vessel occlusion should be studied in order to estimate the patients that would be excluded from EVT. Unfortunately, the frequency of patients with a stroke due large artery occlusion that present beyond the time window due to unknown or late presentation, has not been specifically assessed However, there are some data that can be extracted either from descriptive studies on unknown or wake up strokes. Accordingly, the above

mentioned study by Silva et al showed that the percentage of anterior or posterior circulation LVO was 38.6% in Known onset (KO) strokes, 35.1% in UKO due to WUS, and 45.6% in UKO-nonWUS In that study, the patients amenable to EVT were calculated according to LVO and mismatch criteria, yielding the highest rates of EVT for UKO-nonWUS with 8.8%(11) and the lowest 1.5%(1.96) for UKO-WUS with mid rates of 5.8%(24.36) for KO strokes. However, the rate of late presenting patients is not detailed, furthermore, it depends on the established time window, which at that time was 8 hours. The information on the percentage of patients with LVO is of the essence to be able to calculate the impact of the exclusion of these patients.

Because the estimation of potential eligible patients for EVT beyond the therapeutic time windows based on advanced neuroimaging, in case it was proven effective has not been studied specifically, an indirect source of information comes from series of patients already treated with EVT. However, due to selection bias, differences among patient selection and treatment protocol of each hospital, and the inclusion or exclusion of patients with anterior or posterior circulation; the results of these studies should be interpreted with caution and cannot be generalized.

Because EVT was not approved until recently, there are few large studies on EVT for patients with unknown or late onset stroke, from with the rate of each condition could be approximately estimated. In a study of 859 patients with anterior and posterior circulation strokes treated with EVT with first and new generation devices, 23.8% of the patients would not have been treated if the time window criteria had been applied. The group of patient treated outside the 6 hour time window included: 128 (14.9%) patients with known stroke onset beyond 6 hours and 77 (8.9%) with unknown onset, from which 55 had WUS. [124] Gralla et al, analyzed 227 patients with anterior circulation strokes treated with stentrievers within and without standard inclusion criteria for EVT. Surprisingly, 35.7% fewer patients fulfilled the standard criteria and 63.9% did not. The rate of patients beyond the time window of 8 hours was 9.7% (22 patients). Jovin et al, published a multicenter study of 237 patients treated beyond 8hours from time LSN, data on the type of presentation was only available in 77 patients because many centers “equalized time LSN to time of onset”. From these 77 patients, 63(81%) were witnessed onset beyond 8 hours, 10(13%) were wake up strokes and 4(5%) were unknown onset strokes. Aghaebrahim published a study on 206 patients treated beyond 8 hours from LSN, from which 128(62%)

had a witnessed onset beyond 8 hours and 78(38%) wake up stroke. In the MERCI REGISTRY, from 1000 patients treated, follow up data from 112 (11.2%) patients treated beyond 8 hours from LSN were available.[125]

Although there are likely differences among the patients outside of the time window according to stroke presentation (unknown strokes while awake or wake up strokes of late presenting strokes), all these patients share the exclusion of treatment because they are too late to be treated and they also share the selection based on advanced neuroimaging, to potentially be treated provided there is salvageable tissue. We have thus studied/pooled together the patients beyond the time window for any of the reasons and compared them with patients treated within the time window.

Regarding the selection of patients for EVT with neuroimaging, two different approaches have been described for unknown onset strokes: 1) to estimate the time of onset by advanced neuroimaging, mainly by FLAIR-DWI mismatch, and 2) to disregard the time window and consider that every patient has an individual tissue clock. For patients with late presenting strokes, only the second approach would consider them for treatment provided salvageable tissue is present. We propose this latter approach for patients outside the time window, which makes every patient a potential candidate for screening; regardless time is unknown or too late.

In our opinion, the first approach is still a time-based approach of stroke, and its drawback is that still aims to calculate the time since symptom onset, implying that the speed at which the parenchyma becomes infarcted is universal among individuals. This does not accurately reflect the underlying physiology of stroke in which the ischemia evolves at different speed across individuals, which can be explained by patient anatomy, collateral status, hemodynamic and temperature conditions, metabolic milieu an others.[126] This concept has been proposed in basic research as well as in clinical research. Shortly after the first treatment for stroke was available, the concept of a rigid time window was challenged. [107] Recently, the DEFUSE 2 study[127] has added evidence to the concept of a tissue clock rather than time clock showing that for patients that presented at similar times and with similar sites of occlusion, the DWI lesions were highly variable. This study also showed that Target mismatch patients who reperfused achieved less

infarct volume and better clinical outcomes. However, in patients without Target mismatch this association between reperfusion and infarct volume on outcome was not observed. Interestingly, in patients treated within 6-12 hours from onset, the positive association between clinical outcome and decrease of infarct volume did not change. In fact that target mismatch patients treated in the late time window had similar outcomes than patients treated with EVT within the early windows. One likely explanation is that in later windows, the speed of recruiting core is slow (slow progressors). However, the fact that the ischemic tissue progresses slowly, does not preclude from a poor outcome. In fact, when reperfusion was not achieved in DEFUSE-2 trial, there was a substantial infarct growth.[128] These findings suggested that imaging was as important or more than time, to select patients for EVT. The variable speed, at which the ischemic core progresses, depends mainly on the collateral status. It is known that infarct volume is a biomarker of clinical outcome even exceeding the predictive capacity of recanalization, so, the larger the infarct volume, the more difficult is to achieve a good outcome.[17,129] Furthermore, the faster the infarct grows, the more difficult it is to achieve a good outcome after reperfusion or conversely in slow progressors, the slower the infarct core grows the more likely it is to achieve a good outcome if reperfusion is achieved.

Magnetic resonance based studies have proved the existence of mismatch beyond 9 hours up to 24 hours, and that this was more frequent in patients with proximal artery occlusion that in those without proximal artery occlusion.[130] Another recent study found the existence of mismatch up to 48 hours from onset. [115]

For patients with late presenting strokes, only the tissue clock approach would consider them for treatment provided salvageable tissue is present. We propose this latter approach for all patients outside the time window, thus making every patient a potential candidate for screening regardless time is unknown or too late.

Regardless of the reason (unknown or late) to be out of the time window, these patients are automatically ineligible for reperfusion therapies according to the guidelines. Regarding IVT, there are plenty of reports, large studies and RCT to treat patients beyond the therapeutic windows. For IVT, for which the time window is shorter than for EVT, (3h and lately 4.5h),

approximately 35-39% of wake up stroke (WUS) patients could have benefited from thrombolysis if time had not been an exclusion criterion[131]**.** There are several large series and ongoing trials investigating the approach of IVT for patients out of the time window and based on imaging, which are beyond the scope of this work. One of the most robust trials on this approach is the recently presented MR WITNESS trial, which has not been published to date, that supported IVT beyond the 4.5-hour time window with similar safety and efficacy results in a cohort of 80 patients in whom the median time from onset to treatment was 11.3 hours from TLSW and median time from first known abnormal to treatment of 3.85h(2.83-4.25) with promising rates of favorable outcomes at 3 months, including 44% excellent outcome (mRS 0-1) and 57.6% good outcome (mRS o to 2). The investigators did not target proximal occlusions, for which EVT is the first line therapy, but insisted on the impact of the novel approach of the tissue-clock, which might increased the patients treated with IVT in a likely15-20%.

Regarding EVT, the treatment of all those patients represents a therapeutic dilemma because EVT is not any more an experimental therapy and in fact, it has demonstrated an overwhelming benefit for patients with a number needed to treat of 4. So, it is certainly controversial to leave a patient untreated when 1) EVT is available 24x7, 2) there are studies supporting that EVT in selected patients beyond the 6 hour window is as safe and as effective than EVT within the window 3) the prognosis without treatment is devastating for the patient, the family and the society. For that reason, there are ongoing RCT studies to prove the treatment in these patients. Until the results of those RCT become available, studies should be directed to 1) estimate the increase in the number of patients eligible if proved effective beyond the window 2) study the differences among these patients who share the fact of being "*too late to be treated"* 3) pursue population studies to find out the real incidence of patients with UKO-WUS or UKO-non WUS or late presenting and their percentage of large artery occlusion 4) to gather knowledge on the natural history of these patients when untreated to know whether there are differences with patients within the window and 5) to support or question the non randomized allocation to EVT for these patients in high volume centers in front of large comparative studies, and according to the latest devices and latest guidelines. This thesis is part of this effort, and a small contribution until the RCT yield their results**.**

Considering the time window of 6 hours from the latest guidelines and the recommendations to treat patients with EVT with stentrievers, we sought to report our experience with EVT using stentrievers for strokes due anterior circulation occlusion and compare the safety and efficacy results of patients within and beyond the therapeutic window with EVT using stentrievers.

II

Hypothesis

Primary hypothesis

The primary hypothesis of this work is that endovascular therapy with stentrievers in patients with a stroke due to anterior circulation occlusion, outside of therapeutic time window and selected by neuroimaging, is as efficient and safe as in those patients with a stroke due to anterior circulation occlusion within the therapeutic time window.

Secondary hypothesis

The secondary hypothesis is that patients within and outside the established therapeutic window share the same predictors of favorable outcome and that time is not a predictor of outcome. .

Additional comments

It should be noticed that patients outside of the therapeutic time window include two types of stroke according to symptom onset:

- Patients with unknown onset stroke (UKO), that may have happened during sleep, a wake up stroke (UKO-WUS) or while awake (UKO-nonWUS)
- Patients who have a known onset but present late (late presenters) beyond the time window recommended for endovascular stroke treatment (KO-LP). The time window is currently 6 hours according to the latest guidelines that recommend: *treatment can be initiated (groin puncture) within 6 hours from symptom onset*.[36]

The rationale to study these patients together is that patients belonging to both groups would automatically be excluded from reperfusion therapies if based on the current guidelines or to be enrolled in a clinical trial, which are both time based. In most studies on wake up, unknown onset of late presenting strokes, the time last seen normal (LSN) was considered a surrogate for stroke onset. However, we decided not to use this surrogate because 1) it is irrelevant as to the management according to imaged based selection 2) the concept of LSN is currently being questioned because it might unnecessarily exclude patients that may have been within the time window. [122]

As of today, the guidelines do not recommend a time window from onset to arrival, which could be explained by the wide variety and constant evolution in the in-hospital time metrics. Thus, if a patient arrives beyond 6 hours from onset is excluded, while if the patient arrives earlier, the patient can be treated or not within the time window depending on those metrics. So, according to this fact, we decided to include in the study group, the patients that fell undoubtedly out of the treatment window as per onset to groin. If they were late presenters on arrival or became late presenters during the in-hospital stay is beyond the scope of this work and in fact challenges the principle of time-based approach, which is questioned in this work. It should be noticed that when the time-based approach is questioned, it does not refer to ignoring the time, but to ignore the time as an exclusion or inclusion criteria. It should be underlined that the time is of the essence, especially when referring to time in the metrics and performance and fast track protocols make the difference, which regards to outcomes.

III

Objectives

Primary aim

The primary aim of the study was to compare the outcomes and safety of EVT using ST in patients with acute ischemic stroke (AIS) due to anterior circulation artery occlusion beyond the therapeutic time window of 6 hours and selected by neuroimaging, with the outcomes of patients treated within the therapeutic time window.

Secondary aims

The secondary aims were:

1. To identify predictors of good functional outcome and mortality for patients within (WTW) and outside the therapeutic window (UKO group and KO-LP group).
2. To investigate whether some workflow time metrics in these selected patients are predictors of poor outcome

IV

Materials and methods

1. STUDY DESIGN

This is a retrospective cohort study (multipurpose cohort) on two prospectively collected databases of consecutive patients who underwent endovascular therapy for acute ischemic stroke at comprehensive stroke centers between September 1st, 2007 and April 6th, 2016. The first database from Hospital Vall de Hebron included 529 patients treated from January 1st, 2011 and April 3rd 2016. The second data set from Hospital Universitari Germans Trias i Pujol, included 439 patients treated from September 1st, 2007 to April 6th, 2016. Early follow up was performed within 7 day from intervention using neuroimaging and clinical pre-established protocols. Late follow up was performed at 90 days using functional outcome scales.

2. STUDY POPULATION

The merged database from both centers yielded a total of 964 patients. The following inclusion and exclusion criteria were applied:

Inclusion criteria

- Stroke due to anterior circulation large artery occlusion (MCA, intracranial ICA) with or without cervical carotid occlusion.
- EVT with stentrievers (adjunctive therapy allowed provided that ST were used).

Exclusion criteria

- Posterior circulation.
- Intraarterial thrombolysis only.
- Mechanical thrombectomy with other than stentrievers (Merci, stenting.)

- ASPECTS< 6

Rational for the inclusion/exclusion criteria

The rational to exclude posterior circulation strokes was the different natural history of anterior and posterior circulation strokes as well as to the different resistance to ischemia in posterior circulation strokes.

Because the current gold standard is EVT with stentrievers due to their better and faster reperfusion rates and thus better outcomes, we did not want to include other treatment tools that may act as confounders in safety and efficacy of the treatment.

The reasons to exclude patients with ASPECTS score less than 6 were: 1) the AHA/ASA guidelines recommend this threshold based on the trials that have mounted the evidence for EVT and 2) there are some studies supporting that the outcomes in patients with lower ASPECTs are somewhat worse than the good outcomes and thus, we did not want ASPECTs to act as a confounder when our dependent variable is outcome. [132133]

However, is should be said that the concept of excluding patients with low ASPECTs is recently being challenged as the outcomes of these patients treated with EVT may still be better than the natural history of the patients untreated. [134] [135]

Study population

After applying the above-mentioned criteria, the study population resulted in 468 patients with acute stroke due to anterior circulation large artery occlusion that presented out of the therapeutic time window and treated with EVT with stentrievers:

For the purpose of the study, the total sample was divided in two groups:

- **Group 1**. Patients WITHIN THE TIME WINDOW (WTW), defined as time from onset to groin puncture less or equal to 6 hours, according to the latest guidelines in which the Class I, Level A recommendation is that patients should be treated within 6 hours.

- **Group 2**. Patients OUTSIDE THE TIME WINDOW (OTW) were considered those in whom time from onset to groin puncture was estimated longer than 6 hours. Patients outside the time window included two subgroups:

    - **Group 2A**: Patients with UNKNOWN ONSET (UKO), defined as stroke with uncertain onset. The time of stroke onset was estimated as the time the patient was last seen normal (TLSN). Patients in whom the TLSN was within 4.5 hours were considered within the time window.

      The UKO group includes patients with wake up strokes (UKO-WUS) and patients with strokes during awake that happened unwitnessed or in whom onset could not be stated (UKO-nonWUS). In our study however, the UKO group was presented as one group, as details regarding presentation to sub classify the patients into UKO-WUS or UKOnon-WUS), were not available in all patients.

    - **Group 2B**: Patients presenting late, also called LATE PRESENTERS (KO-LP), were defined as patients with a known onset (KO), in whom the groin puncture was performed beyond 360 minutes.

The rational to include both UKO and KO-LP was that in both situations, the endovascular treatment of the patient is a dilemma. In both scenarios, patients would be excluded and thus left untreated according to time-based criteria (beyond 6 hours in the current guidelines), because they are usually too late to be treated either according to the TLSN in patients with UKO or due to known onset beyond the window. However, applying physiology-based criteria, both groups are managed similarly; regardless whether the time elapsed from symptom onset is unknown or too late for the accepted time windows, both groups will be selected for EVT if viable tissue is present.

For that purpose, we analyzed previously whether these two subgroups treated OTW, UKO and KO-LP, were comparable in baseline characteristics and outcomes.

3. INTERVENTIONS

The intervention was endovascular therapy, according to the treatment protocol in each comprehensive stroke center.

3.1. Treatment algorithm (Hospital Universitari Germans Trias i Pujol)

All patients were evaluated with cranial CT scan or multimodal MR, and the confirmation of ACLVO was assessed by CT angiography (CTA), MR angiography (MRA) or transcranial color-coded Duplex sonography (TCCS). IVT with tPA was administered to all patients admitted within 4.5 hours who fulfilled the approved criteria. Moreover, a few UKO patients were also initially treated with IV tPA based on the MRI mismatch criteria. Monitoring of vessel patency by TCCS was performed during the drug infusion. EVT was indicated when the patient 1) had a documented ACLVO refractory to IVT, 2) was ineligible for the use of IV tPA (I this included stroke onset >4.5 h, unknown onset or wake-up stroke) and 3) did not present large signs of ischemia in the neuroimaging tool performed just before EVT. Alberta Stroke Program early CT score (ASPECTS) ≥7 was used in CT, whereas MRI criteria were a DWI lesion <50% of the affected arterial territory or DWI ASPECTS ≥6, absence of patent hyperintensity in the ischemic region in FLAIR and at least 20% PWI/ DWI mismatch evaluated by visual inspection. Angio-DWI mismatch was used when PWI maps could not be performed due to the patient's condition or low quality of images. DWI volume was post hoc calculated by using the PerfScape and NeuroScape from the Olea Program in the MRI-selected population. A non contrast CT was recommended in patients within 4.5 h of stroke onset, whereas multimodal MRI was the neuroimaging of choice if available for patients with >4.5 h of symptom onset,

including those with UKO. Patients were managed after the procedure following the European Stroke Organization Guidelines[136].

3.2. Treatment algorithm (Hospital Vall d´Hebron)

All patients were evaluated with cranial CT scan or multimodal MR, and the confirmation of ACLVO was assessed by MR angiography (MRA), CTA or transcranial color-coded Duplex sonography (TCCS). IVT with tPA was administered to all patients admitted within 4.5 hours who fulfilled the approved criteria. Moreover, a few UKO patients were also initially treated with IV tPA based on the MRI mismatch criteria. EVT was indicated and immediately performed when the patient 1) had a documented ACLVO and the following findings on admission neuroimaging: Alberta Stroke Program early CT score (ASPECTS) ≥7 was used in CT and in selected cases CTP was used to confirm the CT findings. A non contrast CT was recommended in patients within 4.5 h of stroke onset, whereas multimodal CTP/MRI was the neuroimaging of choice if available for patients with >4.5 h of symptom onset, including those with UKO. Patients were managed after the procedure following the European Stroke Organization Guidelines.[136]

3.3. Criteria for endovascular therapy

The criteria for primary or rescue EVT were predefined (Table 1) and approved by the local ethics committee of each hospital. From 2012 onwards investigators used common criteria defined by the Stroke Program of the Public Health Hospitals in Catalonia.

INCLUSION CRITERIA

1. Informed consent
2. Acute ischemic stroke refractory or ineligible for the use of intravenous tPA
3. Documented large arterial occlusion in the anterior circulation cerebral arteries that corresponds to the acute clinical deficit
4. Pre-Stroke mRS ≤2
5. Signs of limited early infarction on CT or MRI (ASPECTS ≥6)

EXCLUSION CRITERIA

- Anticoagulation with international normalized ratio >3 or prolonged partial thromboplastin time that exceeded twice the upper limit of the normal range
- Platelet count 400 mg/dl
- Uncontrolled hypertension defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg or blood pressure that required aggressive treatment to reduce it to within these limits
- Another stroke within the previous 6 weeks
- Hereditary or acquired hemorrhagic diathesis
- Baseline blood glucose concentrations 400 mg/dl
- Well-developed parenchymal hyperintensity seen on FLAIR or pronounced hypodensity on CT affecting the ischemic region
- ASPECTS <6 or DWI abnormality involving > 50% of the affected territory
- No evidence of large arterial occlusion on MR angiography or TCCS or angiography

4. OUTCOME VARIABLES

The main efficacy variables were good outcome evaluated as mRS≤2 and successful recanalization defined as a TICI≥2b.

The main safety variables were symptomatic intracerebral hemorrhage (SICH) on follow-up CT and mortality at 3 months.

4.1. Clinical variables

In all patients, demographic data, vascular risk factors, previous medical history and medications were collected as follows:

- **Demographic data**: Age and gender, patient name and initials were collected.

- **Vascular risk factors**: smoking, diabetes mellitus defined as basal glycaemia above 126mg/dl in two samples or use of antidiabetic drugs, history of atrial fibrillation or newly diagnosed atrial fibrillation during admission, hypertension defined as BP>140/90 or hypotensive drugs, hypercholesterolemia defined as total cholesterol levels >200mg/dl, LDL-col>130mg/dl, HDL-col<35mg/dl, TG>170mg/dl or lipid-lowering drugs, history of coronary artery disease or stroke.

- **Medications**: Antiplatelet or anticoagulant therapy and statins were collected.

- **Vital signs**: systolic and diastolic blood pressure on admission, body temperature were systematically collected.

- **Stroke subtype**: as per the TOAST Criteria *(Trial of Org 10172 in Acute Stroke Treatment)* (see Appendix 3) *was* divided in cardioembolic, atherothombotic, and lacunar, undetermined and unusual.

- **Stroke severity** was assessed at baseline by certified neurologists using the NIHSS score was measured at 24 h and at day 7.

- **Time metrics were defined in minutes**: time from symptom onset to arrival, time from onset to groin puncture, time from onset to neuroimaging and time from neuroimaging to groin puncture (Picture to puncture: P2P), time from arrival to groin puncture, time from onset to recanalization and procedure duration (groin puncture to end time).

4.2. Neuroimaging variables at baseline

In most cases, the first neuroimaging performed was a NCCT, in which a neurologist or radiologist assessed the ASPECTS Score.137 The ASPECTS score evaluates the early ischemic signs in a 0 to 10 scale according to the MCA territory that is divided in 10 areas. One point is subtracted for every affected area, so that a score of 10 is a CT without ischemic signs and a score of 0 is a patient with ischemic signs in the whole MCA area. In the study, patients with an ASPECTS <6 were excluded.

4.3. Angiographic variables

- Recanalization: successful arterial recanalization was defined as thrombolysis in cerebral infarction grade 2b or 3[138].

- Complications: Pre-established periprocedural complications were: arterial dissection, device fracture, hemodynamic complications (bradycardia or hypotension requiring treatment), vascular perforation, embolization of a previously uninvolved territory, vasospasm requiring treatment, reocclusion, SAH, other.

4.4. Clinical follow-up and outcome variables

- Stroke severity was assessed by NIHSS, which evaluated at baseline 24 hours and at day 7.

- Dramatic early neurological improvement was defined as NIHSS score 0 or 1 or improvement of 10 points or more at 24 h.

- Neurological improvement (or good early neurological outcome) was defined as a decrease in 4 or more points in the NIHSS score at discharge or 7days.

- -Functional independence was evaluated at 90 days according to the modified Rankin Scale (mRS) score (see Appendix 1) and was defined as a mRS ≤2 and excellent outcome as mRS 0 or 1 at day 90. Moreover, the ordinal distribution of the mRS scores was also evaluated. Patients without functional independence mRS>2 before treatment were excluded from the analysis.

4.5. Neuroimaging follow-up

A CT scan was routinely performed at 24–36 h after treatment, or before if any neurological worsening ≥4 points in NIHSS score occurred.

Radiological outcome was assessed in all patients by a 24h follow up NCCT scan reviewed by a neuroradiologist.

Hemorrhagic transformation (any ICH) was classified into hemorrhagic infarction type 1 and 2 and parenchymal hematoma type 1, type 2 and remote, according to ECASS II definitions.[139]

Symptomatic intracranial hemorrhage (SICH) was defined as any hemorrhagic transformation or subarachnoid hemorrhage associated with a decline of ≥4 points in the NIHSS score within 24 h or leading to death.

The previously described variables were entered into a prospective database for statistical analysis.

5. STATISTICAL ANALYSIS

5.1. Preliminary analysis

Because group OTW includes two types of patients, unknown onset (UKO) and known onset but late presenting patients (KO-LP), a previous comparative analysis was done to know whether there were significant differences among these patients that could prevent from grouping them into the same category.

According to this latter analysis, the patients OTW could not be pooled into the same group, because UKO and KO-LP had different characteristics in our study. Thus, for the purpose of the study patients were initially classified in 2 groups (WTW and OTW) but comparisons were made and presented in 3 groups:

- **Group 1**. Patients within the window (WTW) defined as Onset to Groin puncture <360 minutes.

- **Group 2**. Patients outside the window (OTW).
    - **Group 2A**. Patients outside the time window (OTW) due to unknown onset (UKO). In this group, al patients were merged because it was not possible to classify the patients from Hospital 2 in UKO-WUS or UKO-nonWUS.
    - **Group 2B**. Patients outside the time window (OTW) due to late presentation (KO-LP).

5.2. Main analysis

The statistical analysis performed for the whole sample as well as for subgroup (WTW, UKO and KO-LP) analysis was as follows:

Qualitative variables were presented with their frequency distribution. Quantitative variables were summarized in median and standard deviation (SD). In all cases, the variable distribution was compared with the theoretical models and, in case of asymmetry; the median and interquartile range was calculated (IQR).

Initial comparability among groups was performed among qualitative variables, with the ji2 or Fisher´s exact test, in case of more than 25% of expected values were inferior to 5. Quantitative variables were analyzed in groups by the analysis of variance (ANOVA). For contrasts in multiple comparisons, the level of signification was corrected by the Bonferroni test. To evaluate the results, the above-mentioned tests were used according to the variable type.

To evaluate the primary aim of the study, the efficacy variables (mRS0-2, mRS 0-1, NIHSS at day 7, neurological improvement, dramatic recovery and recanalization) and the safety variables (any ICH, SICH, and mortality at 3 months) were compared between the WTW and the UKO groups and between the WTW and the KO-LP groups using univariate analyses.

Binary and ordinal logistic regression models were used to evaluate the independent effect of subgroups on binary (mortality and dichotomized mRS) or ordinal variables (shift analysis of the mRS). The effects relative to adjusted odds ratio (OR) and 95% confidence intevals were estimated.

To evaluate the secondary aim of the study, potential predictors of good functional outcome and mortality were analysed by binary logistic regression models in the global series and in the subgroups, WTW, UKO and KO-LP. The factors included in the model were those in which in the raw analysis of the contrast showed p results of less than 0.05. This model allows identifying the relation among a set of explicative variables and the probability of control of the studied variables. The discriminative capacity were studied with ROC curves of the predicted probability and Hosmer- Lemeshow test were calculated to evaluate de goodness of model

Finally, to investigate whether some workflow time metrics in these selected patients were predictors of poor functional outcome and mortality the median values and IQR of the time from onset to groin and the time from neuroimaging to groin were compared and represented in box plots for each subgroup (UKO and KO-LP) in comparison with the reference group (WTW).

6. ETHICAL CONSIDERATIONS

Patients or their relatives or his/her legal representative signed an informed consent for the endovascular procedure and a general informed consent to participate in studies derived from the analysis of the collected data.

V
Results

1. SELECTION OF THE STUDY POPULATION

From the merged database of 964 patients, 468 patients fulfilling study criteria were selected. The exclusion criteria included 496 patients (455 with general exclusion criteria: 29 patients with no occlusion on angiography and 21 patients in whom occlusion was not accessible, 92 in whom mRS was not available and 279 in whom device was not specified and with 105 study specific exclusion criteria: 68 patients with posterior circulation strokes; 5 patients with ASPECTS ≤5, 11 patients with mRS>2 , 21 patients treated with other devices than strentrievers or IAT only. (Figure 3).

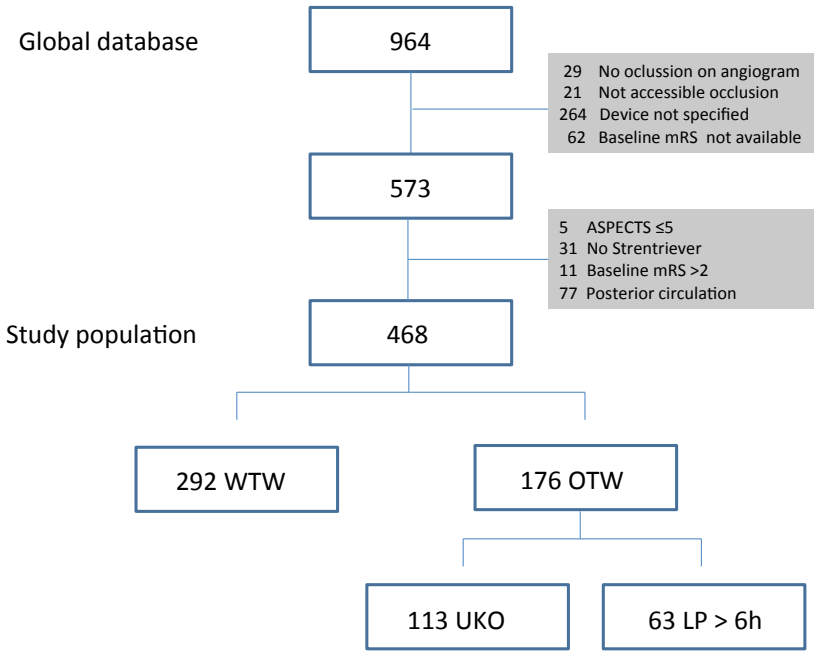

Figure 3. Selection process for the study population.

2. DESCRIPTION OF THE STUDY POPULATION

A total of 468 patients fulfilled study criteria, from which 292 (63.4%) were patients within the time window (WTW), and 176 (37.6%) outside the time window (OTW). The group OTW was divided in two subgroups according to onset: unknown time of onset (UKO) in 113 (24.1%) patients and known onset but late presenters (KO-LP) in 63 (13.5%) patients. These latter subgroups could not be merged because previous statistical analysis showed that their baseline characteristics and outcomes were not comparable as shown in Tables 5 to 8.

		Outside the Time Window (OTW)				p
		Unknown onset (UKO)		Known onset- late presenters (KO-LP)>6h		
		Nº of cases	%	Nº of cases	%	
Number of patients		113	24.1%	63	13.5%	
Sex	Male	59	52,20%	32	50,80%	0.857
	Female	54	47,80%	31	49,20%	
Age, years	Mean (SD)	67,5	12,8	68,4	11,1	0.648
NIHSS at baseline	Median (IQR)	17	12-20	17	13-21	0.940
mRS baseline	Median (IQR)	0	0-1	0	0-1	0.478
Hypertension	No	45	39,80%	23	36,50%	0.665
	Yes	68	60,20%	40	63,50%	
Atrial fibrillation	No	63	55,80%	40	64,50%	0.260
	Yes	50	44,20%	22	35,50%	
Diabetes	No	87	77,00%	53	84,10%	0.261
	Yes	26	23,00%	10	15,90%	
Smoking habit	No	92	81,40%	54	85,70%	0.467
	Yes	21	18,60%	9	14,30%	
Dyslipidemia	No	60	53,10%	36	57,10%	0.267
	Yes	53	46,90%	27	42,90%	
CAD	No	93	82,30%	52	82,50%	0.968
	Yes	20	17,70%	11	17,50%	
Prior stroke	No	104	92,00%	56	88,90%	0.486
	Yes	9	8,00%	7	11,10%	
Prior antiplatelet therapy	No	52	83,90%	378	81,10%	0.541
	Yes	10	16,10%	88	18,90%	
Prio anticoagulants	No	94	83,20%	52	83,90%	0.907
	Yes	19	16,80%	10	16,10%	
Prior NACOs	No	110	97,30%	63	100,00%	0.192
	Yes	3	2,70%	0	0,00%	
Statins	No	79	70,50%	41	66,10%	0.547
	Yes	33	29,50%	21	33,90%	
Systolic BP, mm Hg	Mean (SD)	144,5	23,7	145	24	0.912
Diastolic BP, mm Hg	Mean (SD)	78,5	14,9	77,7	16,6	0.750
Body temperature	Mean (SD)	36,1	0,5	35,9	0,5	0.104
Blood glucose, mg/dl	Mean (SD)	133,6	40,3	136,6	38,6	0.659

Table 5. Comparison of baseline characteristics between groups (I).

CAD: Coronary artery disease. NACOs: novel anticoagulant agents. BP: blood pressure. SD: standard deviation.

		Unknown onset		KO-LP >6h		
		Nº of cases	%	Nº of cases	%	p
Stroke Subtype (TOAST)	Atherothrombotic	20	17.9%	14	23%	0.721
	Cardioembolic	60	53.6%	32	52.5%	
	Other	7	6.3%	5	8.2%	
	Undetermined	25	22.3%	10	16.4%	
Site of arterial occlusion	ACA	1	.9%	0	0%	0.078
	ICA	1	.9%	1	1.6%	
	M1 MCA	55	48.7%	33	52.4%	
	M2 MCA	14	12.4%	3	4.8%	
	Tandem	19	16.8%	10	15.9%	
	TICA	23	20.4%	16	25.4%	
Intravenous tPA	No	93	82.3%	30	47.6%	<0.001
	Yes	20	17.7%	33	52.4%	
Side	bilateral	0	0%	0	0%	0.493
	Right	60	53.6%	31	49.2%	
	Left	52	46.4%	32	50.8%	
ASPECTS**	Mean (SD)	8.28	1.31	8.00	1.22	0.005
ASPECTS	=>8	91	89.2%	58	92.1%	0.069
	<8	11	10.8%	5	7.9%	
Advanced neuroimaging	No	20	17,7%	24	38,1%	<0.001
	CTP	18	15,9%	8	12,7%	
	MR	75	66,4%	31	49,2%	
Onset to arrival, mins (without LSN)	Median (IQR)			301	255-384	
Onset to arrival, mins (with LSN)	Median (IQR)	470	330-617	301	255-384	<0.001
Onset to NI. mins (includes LSN)	Median (IQR)	451	326-650	231.0	135-330	<0.001
0nset to NI, mins (no LSN)	Median (IQR)			231.0	135-330	
P2P, mins	Median (IQR)	59	37-97	64	50-104	0.806
Door to groin, mins	Median (IQR)	107	77-133	102.5	79-140	0.001
OTGP mins (with LSN)	Median (IQR)	605	455-780	420	380-476	<0.001
OTGPmins (without LSN)	Median (IQR)			390	370-470	
Onset to recanalization. mins (with LSN)	Median (IQR)	630	472-835	465	422-520	<0.001
Onset to recanalization. mins (without LSN)	Median (IQR)			465	422-520	

Table 6. Comparison of baseline characteristics between groups (II).

ACA:Anterior Cerebral Artery ICA: Internal carotid artery TICA:terminal internal carotid artery CTP: Computed tomography perfusión MR: magnetic resonance LSN: last seen normal, NI: Neuroimaging OTGP: Onset to Groin puncture, OTR: Onset to recanalization.

		Outside the Time Window (OTW)				p
		Unknown onset (UKO)		KO-LP >6h		
		Nº	%	Nº	%	
Number of patients		113	24.1%	63	13.5%	
Treatment modality	MT+IAT	3	2.7%	1	1.6%	0.649
	Trombectomía mecánica MT	110	97.3%	62	98.4%	
Extracranial ICA treatment	No	94	83,90%	47	74,60%	0.187
	PTA	11	9,80%	7	11,10%	
	Stent ±PTA	7	6,30%	9	14,30%	
Procedure duration, mins	Median (IQR)	55	35-95	56	40-85	0.819
General Anesthesia	Yes	89	80.2%	47	83.9%	0.556
	No	22	19.8%	9	16.1%	
TICI pre	TICI 0	110	97.3%	60	95.2%	0.396
	TICI 1	3	2.7%	2	3.2%	
	TICI 2a	0	0.0%	1	1.6%	
	TICI 2b	0	0.0%	0	0.0%	
TICI post	TICI 0	12	10.6%	4	6.3%	0.150
	TICI 1	3	2.7%	1	1.6%	
	TICI 2a	15	13.3%	5	7.9%	
	TICI 2b	25	22.1%	8	12.7%	
	TICI 3	58	51.3%	45	71.4%	
Complications	No	80	72.7%	35	62.5%	0.170
	Arterial dissection	1	.9%	2	3.6%	
	Device fracture	0	0.0%	0	0.0%	
	Distal embolism	6	5.5%	3	5.4%	
	Hemodynamic complications	6	5.5%	2	3.6%	
	Vascular perforation	0	0.0%	3	5.4%	
	Reoclussion	1	.9%	0	0.0%	
	SAH	0	0.0%	1	1.8%	
	Others	1	.9%	0	0.0%	
	Vasospasm	15	13.6%	10	17.9%	
ICH	No	67	60.4%	31	49.2%	0.154
	HI 1	11	9.9%	8	12.7%	
	HI 2	20	18.0%	10	15.9%	
	PH1	9	8.1%	3	4.8%	
	PH2	1	0.9%	9	14.3%	
	PH r	0	0.0%	0	0.0%	
	remote/extraaxial	2	1.8%	0	0.0%	
	SAH	1	0.9%	2	3.2%	
Any ICH	No	67	60.4%	31	49.2%	0.154
	Yes	44	39.6%	32	50.8%	

Table 7. Comparison of procedural details between groups.

MT: mechanical thrombectomy IAT: intraarterial thrombolysis PTA: Percutaneous transluminal angioplasty, TICI: thrombolysis in cerebral infarction. HI: Hemorrhagic infarction, PH: Parenchymal hematoma, SAH: subarachnoid hemorrhage.

		Outside the Time Window (OTW)				p
		Unknown onset		KO-LP >6h		
		Nº	%	Nº	%	
Recanalization (TICI)	0-2a	30	26.5%	10	15.9%	0.008
	2b-3	83	73.5%	53	84.1%	
NIHSS at 7 day or discharge	Median (IQR)	5	1-15	6	2-16	0.299
Neurologic improvement	No	44	39.3%	29	47.5%	0.772
	Si	68	60.7%	32	52.5%	
Dramatic Recovery	no	78	69.0%	45	73.8%	0.027
	si	35	31.0%	16	26.2%	
Any ICH	No	67	60.4%	31	49.2%	0.059
	Yes	44	39.6%	32	50.8%	
SICH	No	108	97.3%	57	90.5%	0.109
	si	3	2.7%	6	9.5%	
Favorable Outcome (mRS at 3 months)	>2	59	57.8%	37	62.7%	0.241
	=<2	43	42.2%	22	37.3%	
Mortality day 7	No	104	92.9%	60	95.2%	0.628
	Si	8	7.1%	3	4.8%	
Mortality at 3 months	No	86	84.3%	44	74.6%	0.787
	Si	16	15.7%	15	25.4%	

Table 8. Comparison of safety and outcome variables between groups.

NIHSS: National Institutes of Health Stroke Scale. ICH: intracranial hemorrhage. SICH: symptomatic intracranial hemorrhage.

2.1. Baseline characteristics

Baseline characteristics are summarized in Tables 9 and 10. The mean age was 67.8 (SD 12.7), range 21-88, and the mean ages at subgroups were similar; 67.8 years in patients WTW, 67.5 in patients with UKO and 68.4 in KO-LP. The median baseline NIHSS score was 18 (IQR 13-21) with similar scores across subgroups 18 (WTW), 17 (UKO) and 17 (KO-LP). From the total sample, 248 (53.0%) of the patients were males. Patients with and beyond the time window were comparable in pre-stroke functional status, vascular risk factors, previous medications, vitals, basal glycemia, stroke subtype by TOAST or site of occlusion. Comparisons were made to rule out differences among subgroups (UKO versus WTW, and KO-LP versus WTW).

Intravenous tPA was administered in nearly half (47.4%) of the total sample. There were significant differences between IVT use in patients WTW and with UKO (66.1% versus 17.7%, p>0.001) and between the UKO and the KO-LP group (52.4%; p=0.040).

The mean ASPECTS score was 8.5 (SD 1.3) with subgroups scores of 8.7 (WTW), 8.3 (UKO) and 8.0 (KO-LP) with statistically significant difference which was not clinically relevant between the WTW and KO-LP groups. However, the dichotomized ASPECTS ≥8 did not differ statistically among subgroups. Regarding advanced neuroimaging, significant differences were found among subgroups, with fewer patients selected by advanced neuroimaging in the WTW group (39.0 %) and more patients in the OTW groups (82.3% in UKO and 63.9% in KO-LP). All pre-hospital workflow time metrics and those in-hospital workflow time metrics including stroke onset, differed significantly among or between groups, while the picture to puncture time and time to groin puncture did not.

		Total		Within the window (WTW)		Outside the Time Window (OTW)				p	p
						Unknown onset (UKO)		KO-LP >6h		UKO vs WTW	KO-LP >6h vs WTW
		Nº of cases	%	Nº of cases	%	Nº of cases	%	Nº of cases	%		
Number of patients		468	100.0%	292	63.4%	113	24.1%	63	13.5%		
Sex	Male	248	53,0%	157	53,8%	59	52,2%	32	50,8%	0.778	0.668
	Female	220	47,0%	135	46,2%	54	47,8%	31	49,2%		
Age, years	Mean (SD)	67,8	12,7	67,8	13,0	67,5	12,8	68,4	11,1	0.832	0.746
NIHSS at baseline	Median (IQR)	18	13-21	18	14-21	17	12-20	17	13-21	0.768	0.963
mRS baseline	Median (IQR)	0,0	0-1	0,0	0-1	0,0	0-1	0,0	0-1	0.478	0.659
Hypertension	No	175	37,4%	107	36,6%	45	39,8%	23	36,5%	0.553	0.984
	Yes	293	62,6%	185	63,4%	68	60,2%	40	63,5%		
Atrial fibrillation	No	274	58,7%	171	58,6%	63	55,8%	40	64,5%	0.608	0.385
	Yes	193	41,3%	121	41,4%	50	44,2%	22	35,5%		
Diabetes	No	362	77,4%	222	76,0%	87	77,0%	53	84,1%	0.838	0.163
	Yes	106	22,6%	70	24,0%	26	23,0%	10	15,9%		
Smoking habit	No	363	77,7%	217	74,6%	92	81,4%	54	85,7%	0.145	0.058
	Yes	104	22,3%	74	25,4%	21	18,6%	9	14,3%		
Dyslipidemia	No	262	56,0%	166	56,8%	60	53,1%	36	57,1%	0.495	0.966
	Yes	206	44,0%	126	43,2%	53	46,9%	27	42,9%		
CAD	No	389	83,1%	244	83,6%	93	82,3%	52	82,5%	0.761	0.843
	Yes	79	16,9%	48	16,4%	20	17,7%	11	17,5%		
Prior stroke	No	427	91,2%	267	91,4%	104	92,0%	56	88,9%	0.846	0.522
	Yes	41	8,8%	25	8,6%	9	8,0%	7	11,1%		
Prior antiplatelet therapy	No	232	79,7%	94	83,2%	52	83,9%	378	81,1%	0.186	0.734
	Yes	59	20,3%	19	16,8%	10	16,1%	88	18,9%		
Prio anticoagulants	No	378	81,1%	232	79,7%	94	83,2%	52	83,9%	0.429	0.455
	Yes	88	18,9%	59	20,3%	19	16,8%	10	16,1%		
Prior NACOs	No	459	98,1%	286	97,9%	110	97,3%	63	100,0%	0.713	0.251
	Yes	9	1,9%	6	2,1%	3	2,7%	0	0,0%		
Statins	No	308	66,1%	188	64,4%	79	70,5%	41	66,1%	0.242	0.794
	Yes	158	33,9%	104	35,6%	33	29,5%	21	33,9%		
Systolic BP, mm Hg	Mean (SD)	144,9	24,3	144,9	24,7	144,5	23,7	145,0	24,0	0.889	0.991
Diastolic BP, mm Hg	Mean (SD)	77,9	14,8	77,8	14,4	78,5	14,9	77,7	16,6	0.657	0.976
Body temperature	Mean (SD)	36,0	0,5	36,0	0,4	36,1	0,5	35,9	0,5	0.227	0.252
Blood glucose, mg/dl	Mean (SD)	136,1	47,4	137,0	51,9	133,6	40,3	136,6	38,6	0.556	0.956

Table 9. Baseline characteristics of the study population (I).

CAD: Coronary artery disease. NACOs: novel anticoagulant agents. BP: blood pressure. SD: standard deviation.

		Total		Within the window (WTW)		Outside the Time Window (OTW)				p UKO vs WTW	p KO-LP >6h vs WTW
						Unknown onset (UKO)		KO-LP >6h			
		Nº of cases	%	Nº of cases	%	Nº of cases	%	Nº of cases	%		
Stroke Subtype (TOAST)	Atherothrombotic	76	16.5%	42	14.6%	20	17.9%	14	23%	0.721	0.308
	Cardioembolic	264	57.3%	172	59.7%	60	53.6%	32	52.5%		
	Other	28	6.1%	16	5.6%	7	6.3%	5	8.2%		
	Undetermined	93	20.2%	58	20.1%	25	22.3%	10	16.4%		
Site of arterial occlusion	ACA	3	.6%	2	.7%	1	.9%	0	0%	0.078	0.070
	ICA	10	2.1%	8	2.7%	1	.9%	1	1.6%		
	M1 MCA	247	52.8%	159	54.5%	55	48.7%	33	52.4%		
	M2 MCA	60	12.8%	43	14.7%	14	12.4%	3	4.8%		
	Tandem	52	11.1%	23	7.9%	19	16.8%	10	15.9%		
	TICA	96	20.5%	57	19.5%	23	20.4%	16	25.4%		
Intravenous tPA	No	222	47.4%	99	33.9%	93	82.3%	30	47.6%	<0.001	0.040
	Yes	246	52.6%	193	66.1%	20	17.7%	33	52.4%		
Side	bilateral	1	.2%	1	.3%	0	0%	0	0%	0.493	0.882
	Right	230	49.4%	139	47.8%	60	53.6%	31	49.2%		
	Left	235	50.4%	151	51.9%	52	46.4%	32	50.8%		
ASPECTS**	Mean (SD)	8.50	1.26	8.69	1.22	8.28	1.31	8.00	1.22	0.005	<0.001
ASPECTS	=>8	424	93.0%	275	94.5%	91	89.2%	58	92.1%	0.069	0.458
	<8	32	7.0%	16	5.5%	11	10.8%	5	7.9%		
Advanced neuroimaging	No	221	47,4%	177	61,0%	20	17,7%	24	38,1%	<0.001	<0.001
	CTP	87	18,7%	61	21,0%	18	15,9%	8	12,7%		
	MR	158	33,9%	52	17,9%	75	66,4%	31	49,2%		
Onset to arrival, mins (without LSN)	Median (IQR)	135	60-235	105	55-194			301	255-384		<0.001
Onset to arrival, mins (with LSN)	Median (IQR)	190	69-307	105	55-194	470	330-617	301	255-384	<0.001	<0.001
Onset to NI. mins (includes LSN)	Median (IQR)	140	80-293	103	70-157	451	326-650	231.0	135-330	<0.001	<0.001
0nset to NI, mins (no LSN)	Median (IQR)	116	72-174	103	70-157			231.0	135-330		<0.001
P2P, mins	Median (IQR)	60	40-94	60	38-92	59	37-97	64	50-104	0.806	0.658
Door to groin, mins	Median (IQR)	95	63-126	83	52-120	107	77-133	102.5	79-140	0.001	0.020
OTGP mins (with LSN)	Median (IQR)	285	195-405	235	175-290	605	455-780	420	380-476	<0.001	<0.001
OTGPmins (without LSN)	Median (IQR)	194	142-270	190	139-259			390	370-470		0.048
Onset to recanalization. mins (with LSN)	Median (IQR)	330	240-460	270	218-345	630	472-835	465	422-520	<0.001	<0.001
Onset to recanalization. mins (without LSN)	Median (IQR)	295	225-384	270	218-345			465	422-520		<0.001

Table 10. Baseline characteristics of the study population (II).

ACA:Anterior Cerebral Artery. ICA: Internal carotid artery. TICA:terminal internal carotid artery. CTP: Computed tomography perfusion. MR: magnetic resonance. LSN: last seen normal. NI: Neuroimaging. OTGP: Onset to Groin puncture. OTR: Onset to recanalization.

2.2. Procedure-related variables

Mechanical thrombectomy with stentrievers was performed in the majority of the patients in each subgroup, with similar percentages above 97%. Mechanical thrombectomy and adjunt intraarterial thrombolysis was used in the rest of the cases, with similar rates across subgroups. All other procedural variables including recanalization, procedure duration, treatment of extracranial carotid artery and the use of anesthesia did not differ across subgroups. The only significant difference was found in the occurrence of any ICH, which was higher in KO-LP group compared with WTW. This did not translate to SICH, where no differences were detected between the subgroups groups OTW and WTW, which rates of 6.8% in WTW, 2.7% UKO and 9.5% in the KO-LP group.

		Total		Within the window (WTW)		Outside the Time Window (OTW)				p	p
						Unknown onset (UKO)		KO-LP >6h		UKO vs WTW	KO-LP >6h vs WTW
		Nº	%	Nº	%	Nº	%	Nº	%		
Number of patients		468	100%	292	63.4%	113	24.1%	63	13.5%		
Treatment modality	MT+IAT	11	2.4%	7	2.4%	3	2.7%	1	1.6%	0.881	0.694
	Trombectomía mecánica MT	457	97.6%	285	97.6%	110	97.3%	62	98.4%		
Extracranial ICA treatment	No	390	84,20%	249	86,50%	94	83,90%	47	74,60%	0.626	0.053
	PTA	38	8,20%	20	6,90%	11	9,80%	7	11,10%		
	Stent ±PTA	35	7,60%	19	6,60%	7	6,30%	9	14,30%		
Procedure duration, mins	Median (IQR)	50	35-85	48	33-79	55	35-95	56	40-85	0.559	0.112
General Anesthesia	Yes	352	77.5%	216	75.3%	89	80.2%	47	83.9%	0.298	0.161
	No	102	22.5%	71	24.7%	22	19.8%	9	16.1%		
TICI pre	TICI 0	451	96.4%	281	96.2%	110	97.3%	60	95.2%	0.841	0.649
	TICI 1	14	3.0%	9	3.1%	3	2.7%	2	3.2%		
	TICI 2a	2	.4%	1	.3%	0	0.0%	1	1.6%		
	TICI 2b	1	.2%	1	.3%	0	0.0%	0	0.0%		
TICI post	TICI 0	32	6.9%	16	5.5%	12	10.6%	4	6.3%	0.115	0.140
	TICI 1	9	1.9%	5	1.7%	3	2.7%	1	1.6%		
	TICI 2a	43	9.2%	23	7.9%	15	13.3%	5	7.9%		
	TICI 2b	115	24.7%	82	28.3%	25	22.1%	8	12.7%		
	TICI 3	267	57.3%	164	56.6%	58	51.3%	45	71.4%		
Complications	No	308	68.3%	193	67.7%	80	72.7%	35	62.5%	0.664	0.364
	Arterial dissection	8	1.8%	5	1.8%	1	.9%	2	3.6%		
	Device fracture	4	.9%	4	1.4%	0	0.0%	0	0.0%		
	Distal embolism	26	5.8%	17	6.0%	6	5.5%	3	5.4%		
	Hemodynamic complications	23	5.1%	15	5.3%	6	5.5%	2	3.6%		
	Vascular perforation	7	1.6%	4	1.4%	0	0.0%	3	5.4%		
	Reoclussion	5	1.1%	4	1.4%	1	.9%	0	0.0%		
	SAH	4	.9%	3	1.1%	0	0.0%	1	1.8%		
	Others	9	2.0%	8	2.8%	1	.9%	0	0.0%		
	Vasospasm	57	12.6%	32	11.2%	15	13.6%	10	17.9%		
ICH	No	303	65.0%	205	70.2%	67	60.4%	31	49.2%	0.059	<0.001
	HI 1	37	7.9%	18	6.2%	11	9.9%	8	12.7%		
	HI 2	59	12.7%	29	9.9%	20	18.0%	10	15.9%		
	PH1	26	5.6%	14	4.8%	9	8.1%	3	4.8%		
	PH2	21	4.5%	11	3.8%	1	0.9%	9	14.3%		
	PH r	2	0.4%	2	0.7%	0	0.0%	0	0.0%		
	remote/extraaxial	9	1.9%	7	2.4%	2	1.8%	0	0.0%		
	SAH	9	1.9%	6	2.1%	1	0.9%	2	3.2%		

Table 11. Procedure related variables.

MT: mechanical thrombectomy. IAT: intraarterial thrombolysis. PTA: Percutaneous transluminal angioplasty. TICI: thrombolysis in cerebral infarction. HI: Hemorrhagic infarction. PH: Parenchymal hematoma. SAH: subarachnoid hemorrhage.

3. PRIMARY OBJECTIVE: SAFETY AND EFFICACY OUTCOMES WITHIN AND BEYOND THE THERAPUTIC WINDOW

Safety and efficacy outcomes within and beyond the theraputic window

We first evaluated between groups the effect of mechanical thrombecotmy on functional outcome (mRS) and mortality at 3 months by using univariate analyses. The two OTW subgroups (UKO and KO-LP) were separately compared to the WTW as the reference group (Table 12). Efficacy in terms of recanalization and favorable outcome was not significantly different across subgroups. Favorable outcome at 3 months was achieved in 49% WTW, 42.2%% in UKO and 37.3% in KO-LP. Dramatic recovery was significantly lower while any type of ICH was higher in the OTW subgroups compared to the WTW group, particularly in the KO-LP subgroup. This difference in the rate of global ICH, was not found according to the definition of SICH between groups.

						Outside the Time Window (OTW)				p	p
		Total		Within the window (WTW)		Unknown onset (UKO)		KO-LP >6h		UKO vs WTW	KO-LP >6h vs WTW
		Nº	%	Nº	%	Nº	%	Nº	%		
Recanalization (TICI)	0-2a	84	18.0%	44	15.2%	30	26.5%	10	15.9%	0.008	0.889
	2b-3	382	82.0%	246	84.8%	83	73.5%	53	84.1%		
NIHSS at 7 day or discharge	Median (IQR)	4	1-12	3	1-11	5	1-15	6	2-16	0.299	0.127
Neurologic improvement	No	182	39.4%	109	37.7%	44	39.3%	29	47.5%	0.772	0.154
	Si	280	60.6%	180	62.3%	68	60.7%	32	52.5%		
Dramatic Recovery	no	289	62.2%	166	57.0%	78	69.0%	45	73.8%	0.027	0.015
	si	176	37.8%	125	43.0%	35	31.0%	16	26.2%		
Any ICH	No	303	65.0%	205	70.2%	67	60.4%	31	49.2%	0.059	<0.001
	Yes	163	35.0%	87	29.8%	44	39.6%	32	50.8%		
SICH	No	437	93.8%	272	93.2%	108	97.3%	57	90.5%	0.109	0.460
	si	29	6.2%	20	6.8%	3	2.7%	6	9.5%		
Favorable Outcome (mRS at 3 months)	>2	226	54.3%	130	51.0%	59	57.8%	37	62.7%	0.241	0.104
	=<2	190	45.7%	125	49.0%	43	42.2%	22	37.3%		
Mortality day 7	No	429	92.3%	265	91.4%	104	92.9%	60	95.2%	0.628	0.304
	Si	36	7.7%	25	8.6%	8	7.1%	3	4.8%		
Mortality at 3 months	No	342	82.2%	212	83.1%	86	84.3%	44	74.6%	0.787	0.127
	Si	74	17.8%	43	16.9%	16	15.7%	15	25.4%		

Table 12. Efficacy, safety and outcome results.

NIHSS: National Institutes of Health Stroke Scale. ICH: intracranial hemorrhage. SICH: symptomatic intracranial hemorrhage.

We used ordinal logistic regression analysis to estimate the sugroup effect on the distribution of the mRS scores at 3 months (shift analysis) after mechanical thrombectomy. The common OR was 1,17 (95%CI 0.74-1.83; p=0.504) towards better outcome for the WTW group compared to the UKO group and 1.65 (95%CI 0.97-2.81; p=0.067) for WTW group compared to the KO-LP >6h group, adjusted by age, mRS baseline and intravenous tPA. Table 13 shows the relative effects of each category of mRS at 3 months and the cumulative ordinal ORs. When good functional outcome (mRS at 3 months ≤2) was analyzed, binary logistic regression showed a relative effect of 0.74 (95%CI 0.43-1.26; p=0.264) in the UKO versus WTW. and a non-significant relative reduction of good outcome of 42% in the KO-LP>6h versus WTW (OR, 0.58; 95%CI 0.31-1.10; p=0.096), adjusted by age, mRS baseline and intravenous tPA.. Figure xx shows the distribution of the mRS scores at 3 months in each subgroup. Regarding mortality at 3 months, a relative effect 0.96 (95%CI 0.48-1.93; p=0.916) was found in the UKO versus WTW and 1.51 (95%CI 0.71-3.20; p=0.282) in the KO-LP>6h versus WTW, adjusted by age, prior mRS and intravenous tPA.

		Univariate				**Adjusted***			
				95% CI OR				**95% CI OR**	
Outcome mRS 3 months	**Groups**	**p**	**OR**	**Lower Bound**	**Upper Bound**	**p**	**OR**	**Lower Bound**	**Upper Bound**
1	UKO/WTW	0.927	0.96	0.39	2.36	0.829	1.12	0.40	3.18
	LP>6h/WTW	0.899	0.92	0.27	3.19	0.648	0.73	0.19	2.79
2	UKO/WTW	0.646	0.81	0.33	1.98	0.833	0.90	0.32	2.50
	LP>6h/WTW	0.854	1.12	0.35	3.58	0.904	1.08	0.32	3.58
3	UKO/WTW	0.399	1.46	0.61	3.50	0.424	1.51	0.55	4.18
	LP>6h/WTW	0.603	1.37	0.42	4.54	0.543	1.47	0.43	5.02
4	UKO/WTW	0.466	1.39	0.58	3.35	0.503	1.42	0.51	3.93
	LP>6h/WTW	0.917	1.07	0.31	3.71	0.822	1.16	0.33	4.11
5+6	UKO/WTW	0.772	0.88	0.37	2.11	0.791	1.15	0.41	3.18
	LP>6h/WTW	0.138	2.26	0.77	6.61	0.184	2.15	0.69	6.67
Cumulative ordinal OR	UKO/WTW	0.680	1,09	0,73	1,63	0.504	1,17	0,74	1,83
In favor of the WTW group	LP>6h/WTW	0.042	1,68	1,02	2,77	0.067	1,65	0,97	2,81
Good Outcome mRS 3 months	UKO/WTW	0.241	0.76	0.48	1.20	0.264	0.74	0.43	1.26
	LP>6h/WTW	0.106	0.62	0.35	1.11	0.096	0.58	0.31	1.10
Mortality at 3months	UKO/WTW	0.787	0.92	0.49	1.72	0.916	0.96	0.48	1.93
	LP>6h/WTW	0.130	1.68	0.86	3.29	0.282	1.51	0.71	3.20

Table 13. Univariate and adjusted relative effect by ordinal logistic regression.

*Adjusted by age, mRS baseline and Intravenous tPA.

OR: Odds ration, UKO: Unknown onset, WTW: within the window, KO-LP: late presenters OR: Odds Ratio mRS: modified Rankin Scale

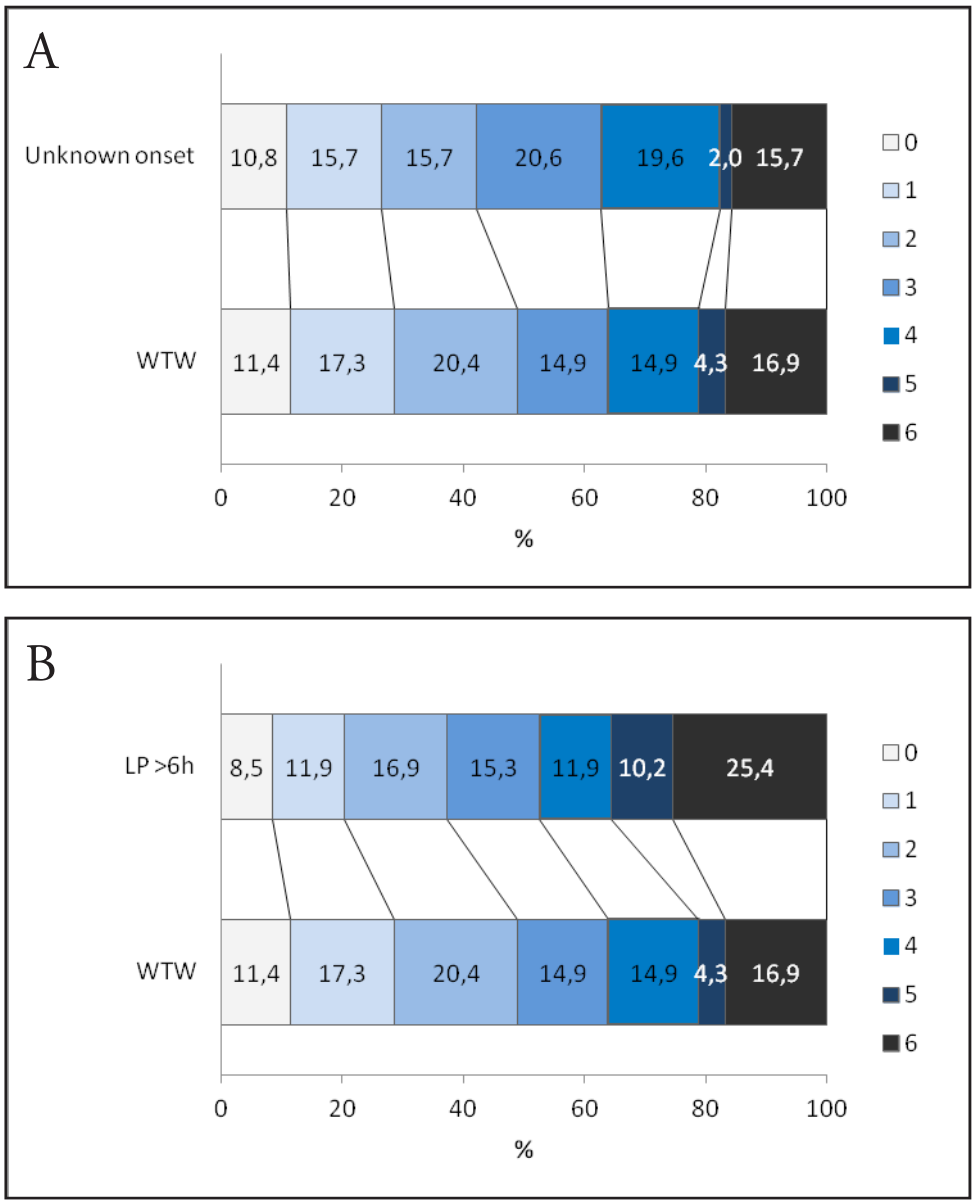

Figure 4. Distribution of mRS score at 3 months in each group.

A: Unknown onset compared to within the window. B: Known onset-late presenting compared to within the window.

UKO Unknown onset, WTW: within the window. KO-LP: late presenters. OR: Odds Ratio mRS: modified Rankin Scale.

4. SECONDARY OBJETIVES

4.1. Predictors of outcome

We aimed to investigate the main predictors of favorable outcome in the three groups of patients. The groups were first collapsed in an overall group because we did not find significant differences in outcome between groups. In a further analysis, we examined the predictive capability of the models obtained in the whole sample in the separate subgroups.

Table 14 shows univariate analysis of the baseline or periprocedural potential predictors of good functional outcome and mortality. As previously described, older age, poorer prior functional capacity, history of hypertension, and diabetes, current treatment with oral anticoagulants, increased blood glucose, higher stroke severity, longer procedural duration, ICH, either any or SICH, and absence of recanalization were significantly associated with lower probability of good outcome and a higher probability of mortality.

	Good outcome				Mortality at 3 months			
	p	OR	95% C.I.for OR		p	OR	95% C.I.for OR	
			Lower	Upper			Lower	Upper
Age (years)	<0.001	0.96	0.95	0.98	0,000	1,05	1,02	1,08
Sex (M vs F)	0.477	1.15	0.78	1.70	0,900	0,97	0,59	1,60
Site	0,858							
ACI		1			0,065			
M1 ACM	0,663	1,33	0,37	4,86	0,622	1,69	0,21	13,79
M2 ACM	0,568	1,50	0,37	6,03	0,569	1,89	0,21	17,14
Tandem	0,828	1,17	0,29	4,67	0,969	1,05	0,11	10,07
TICA	0,924	1,07	0,28	4,05	0,244	3,52	0,42	29,20
Intravenous tPA	0,034	0,66	0,45	0,97	0,565	1,16	0,70	1,92
Time from on set to arrival mins with LSN	0,330	1,00	1,00	1,00	0,605	1,00	1,00	1,00
Time from on set to arrival mins withoutLSN	0,427	1,00	1,00	1,00	0,105	1,00	1,00	1,00
mRS baseline	0,006	0,62	0,44	0,87	0,030	1,52	1,04	2,22
Smoking habit	0,048	1,60	1,00	2,56	0,122	0,58	0,29	1,16
Hypertension	0,005	0,56	0,38	0,84	0,700	1,11	0,66	1,86
Diabetes	0,001	0,44	0,27	0,72	0,083	1,63	0,94	2,85
Dyslipidemia	0,727	0,93	0,63	1,38	0,828	0,95	0,57	1,57
Atrial fibrillation	0,150	0,75	0,51	1,11	0,181	1,41	0,85	2,34
CAD	0,146	0,67	0,40	1,15	0,201	1,50	0,80	2,81
Prior stroke	0,161	0,60	0,29	1,23	0,917	0,95	0,38	2,38
Prior antiplatelet therapy	0,409	0,83	0,54	1,29	0,094	1,58	0,93	2,70
Prior anticoagulants	0,028	0,56	0,34	0,94	0,041	1,84	1,02	3,31
Prior NACOs	0,880	0,89	0,20	4,03	0,807	0,77	0,09	6,47
Statins	0,517	0,87	0,58	1,32	0,463	1,22	0,72	2,06
Systolic BP (mmHg)	0,044	0,99	0,98	1,00	0,024	1,01	1,00	1,03
Diastolic BP (mmHg)	0,146	0,99	0,98	1,00	0,399	1,01	0,99	1,03
Body temperature	0,636	1,12	0,70	1,79	0,383	0,76	0,41	1,41
Blood glucose (mg/dl)	0,000	0,99	0,99	1,00	0,000	1,01	1,00	1,01
Advanced neuroimaging	0,640	0,90	0,59	1,39	0,326	0,73	0,40	1,36
Onset to first NI (mins includes LSN)	0,220	1,00	1,00	1,00	0,914	1,00	1,00	1,00
Onset to NI (mins no LSN)	0,374	1,00	1,00	1,00	0,779	1,00	1,00	1,00
ini_ima2	0,110	1,00	1,00	1,00	0,422	1,00	1,00	1,00
ICH								
No	0,000				0,000			
PH2	0,002	0,04	0,01	0,31	0,000	8,67	3,41	22,03
Resto	0,000	0,41	0,26	0,64	0,078	1,66	0,95	2,91
ICH	0,000	0,34	0,22	0,52	0,002	2,25	1,35	3,75
SICH	0,001	0,04	0,01	0,29	0,000	5,54	2,51	12,22
puerta_aguja	0,413	0,99	0,98	1,01	0,478	0,99	0,97	1,01
ini_gp	0,160	1,00	1,00	1,00	0,821	1,00	1,00	1,00
puerta_gp	0,991	1,00	1,00	1,00	0,701	1,00	1,00	1,00
dur_proc	0,000	0,99	0,98	0,99	0,010	1,01	1,00	1,01
dur_isqu	0,064	1,00	1,00	1,00	0,906	1,00	1,00	1,00
Onset to recanalization mins without LSN	0,060	1,00	1,00	1,00	0,286	1,00	1,00	1,00
Treatment modality	0,120	3,45	0,72	16,44	0,316	0,49	0,12	1,96
ExtracranialICAtreatment	0,527	0,84	0,49	1,43	0,112	0,51	0,22	1,17
Recanalization	0,000	8,03	3,87	16,64	0,000	0,26	0,15	0,45
NIHSS at baseline	0,000	0,90	0,87	0,94	0,001	1,09	1,04	1,15
NIHSSat7dayordischarge	0,000	0,72	0,67	0,77	0,000	1,17	1,11	1,23
ASPECTS =>8	0,133	0,54	0,24	1,21	0,515	0,70	0,24	2,07
Pinture to puncture (mins)	0,977	1,00	1,00	1,00	0,243	1,00	1,00	1,01

Table 14. Univariate analysis of predictors of outcome.

ICA: Internal carotid artery. MCA: middle cerebral artery. TICA:terminal internal carotid artery. CAD, coronary artery disease. mRs: modified Rankin scale. BP: blood pressure. NI: neuroimaging. LSN:last seen normal. ICH: intracranial hemorrhage. SICH: symptomatic intracranial hemorrhage. OTGP: onset to groin puncture. NIHSS: national institutes of health stroke scale. ASPECTS: Alberta Stroke Program Early CT Score. P2P: Pinture to puncture

We built statistical (Table 15) and biological models (Table 16) of predictors of good functional outcome using multivariate analyses. The statistical model was based on variable selection according to statistical significance in the univariate analysis. Hierarchally, predictors of good outcome were age, NiHSS at baseline, recanalization, parenchymal hemorrhage type 2, intravenous tPA and diabetes. This model had discriminatory capability of 0.84 (95%CI 0.78-0.89) (Figure 5).

					95% CI for OR	
	B	**S.E.**	**p**	**OR**	**Lower**	**Upper**
Age years	-0.050	0.011	<0.001	0.95	0.93	0.97
NIHSS at baseline	-0.126	0.026	<0.001	0.88	0.84	0.93
Recanalization	2.971	0.492	<0.001	19.52	7.44	51.19
ICH			<0.001			
PH2 vs No	-3.074	1.069	0.004	0.05	0.01	0.38
Other vs No	-0.954	0.283	0.001	0.39	0.22	0.67
Intravenous tPA	0.783	0.255	0.002	2.19	1.33	3.61
Diabetes (Yes vs No)	-0.784	0.306	0.010	0.46	0.25	0.83
Constant	0.339	1.145	0.767	1.40		

Table 15. Multivariate logistic model for good outcome by statistical significance.

Variables entered: Age years, NIHSS at baseline, ,recanalization, PH2: parenchymal hemorrhage type 2, Intravenous tPA, Smoking habit, Hypertension, Diabetes.

AUC 0.84 (95% CI 0.78-0.89)

Hosmer and Lemeshow Test 0.632

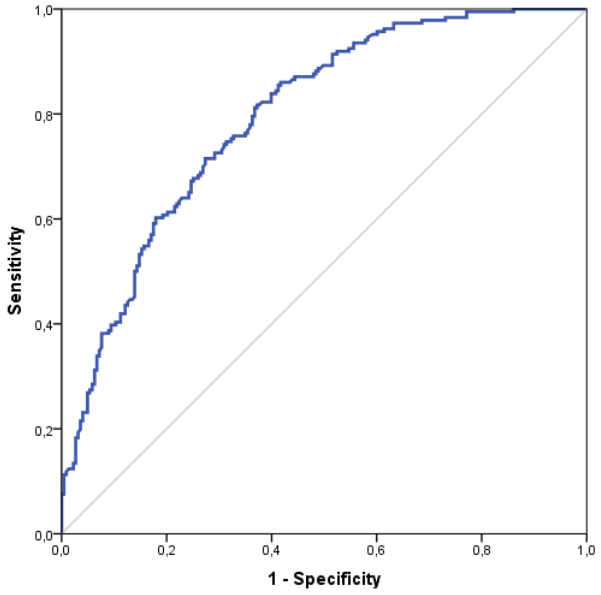

Figure 5. ROC curve. Probability of good outcome statistical model.

The area under the curve (AUC) is AUC 0.84 (95% CI 0.78-0.89).

			95% CI for OR	
Variables	**p**	**OR**	**Lower**	**Upper**
Age years	<0.001	0.95	0.94	0.97
NIHSS at baseline	<0.001	0.89	0.85	0.93
ICH (no/yes)	<0.001	2.81	1.71	4.62
Recanalization	<0.001	16.34	6.53	40.94

Table 16. Multivariate logistic model for good outcome by biological relevance.

Variables entered: Age years, NIHSS at baseline, ICH, ASPECTs, Recanalization.

AUC 0.80 (95% CI 0.75-0.84)

Hosmer and Lemeshow Test 0.972

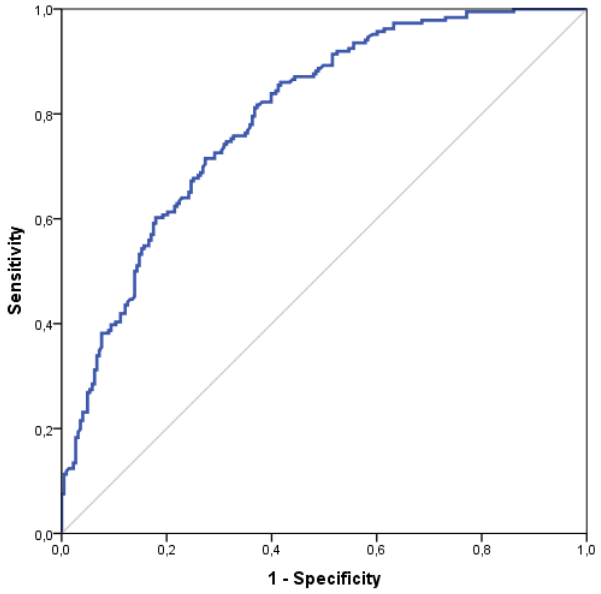

Figure 6. ROC curve. Probability of good outcome biological model.

The area under the curve AUC 0.80 (95% CI 0.75-0.84).

Regarding mortality, older age, PH2, higher systolic BP in mmHg and blood glucose in mg/dl were significantly associated with mortality, while recanalization was significantly associated with a relative reduction of 83% of mortality. The discriminatory capability was 0.80 (95%CI 0.73-0.87) (Figure 7).

					95% CI for OR	
	B	**S.E.**	**p**	**OR**	**Lower**	**Upper**
Age years	0.09	0.03	0.005	1.09	1.03	1.17
Recanalization	-1.77	0.79	0.025	0.17	0.04	0.80
ICH			0.045			
PH2 vs No	2.10	0.89	0.018	8.19	1.43	46.77
Other vs No	0.69	0.53	0.196	2.00	0.70	5.69
Systolic BP (mmHg)	0.02	0.01	0.035	1.02	1.00	1.05
Blood glucose (mg/dl)	0.01	0.00	0.008	1.01	1.00	1.02
Constant	-12.33	3.06	0.000	0.00		

Table 17. Multivariate logistic model for mortality by statistical significance.

AUC 0.80 (95% CI 0.73-0.87)

Hosmer and Lemeshow Test 0.635

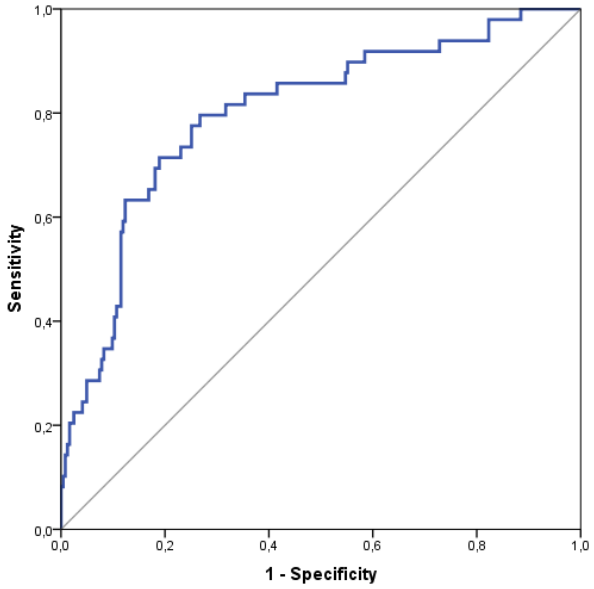

Figure 7. ROC curve. Probability of mortality at 3 months.

The area under the curve (AUC) is 0.80 (95% CI 0.75-0.84).

When both predictive models (good functional outcome and mortality at 3 months) were applied to each subgroup, WTW, UKO and KO-LP, the discriminatory capability was similar in all subgroups. (Table 18).

		Area under curve	SE	p	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
Mortality at 3 months	WTW	0,812	0,042	<0.001	,730	,893
	Unknown onset	0,829	0,072	<0.001	,688	,970
	LP >6h	0,881	0,055	<0.001	,774	,988
Good outcome	WTW	0,844	0,024	<0.001	,798	,891
	Unknown onset	0,870	0,035	<0.001	,801	,938
	LP >6h	0,842	0,053	<0.001	,738	,947

Table 18. Discriminatory capability of the outcome predictors.

As succesful recanalization has been identified as one of the main predictors of favorable outcome in patients treated with mechanical thrombecotmy, we explored the good outcome and mortality rates according to recanalization status by subgroups. As shown in table 19, the rate of mortality and poor outcome was higher in patients who did not recanalize (TICI 0 - 2ª) versus those who recanalize (TICI 2b,3) in alll the subgroups.

		WTW				Unknown onset				LP >6h				Total			
		TICI post				TICI post				TICI post				TICI post			
		0-2a		2b-3		0-2a		2b-3		0-2a		2b-3		0-2a		2b-3	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mortality at 3 months	No	23	60,5%	187	87,0%	18	66,7%	68	90,7%	5	55,6%	39	78,0%	46	62,2%	294	86,5%
	Yes	15	39,5%	28	13,0%	9	33,3%	7	9,3%	4	44,4%	11	22,0%	28	37,8%	46	13,5%
Outcome (mRS at 3 months)	>2	34	89,5%	96	44,7%	24	88,9%	35	46,7%	7	77,8%	30	60,0%	65	87,8%	161	47,4%
	=<2	4	10,5%	119	55,3%	3	11,1%	40	53,3%	2	22,2%	20	40,0%	9	12,2%	179	52,6%

Table 19. Favorable outcome and mortality according to recanalization.

4.2. Effect of the workflow time metrics on outcome

The second secondary aim was to explore the effect of workflow time metrics on functional outcome and mortality in univariate analyses. Time of onset of symptoms in the UKO subgroup was estimated as the LSN time. Figures 8 and 9 show that there were not differences in the median values and IQR for onset to groin puncture time and for picture to puncture (P2P) time between patients alive or dead at 3 months and between those with good or poor outcome. These findings remained in all the studied subgroups.

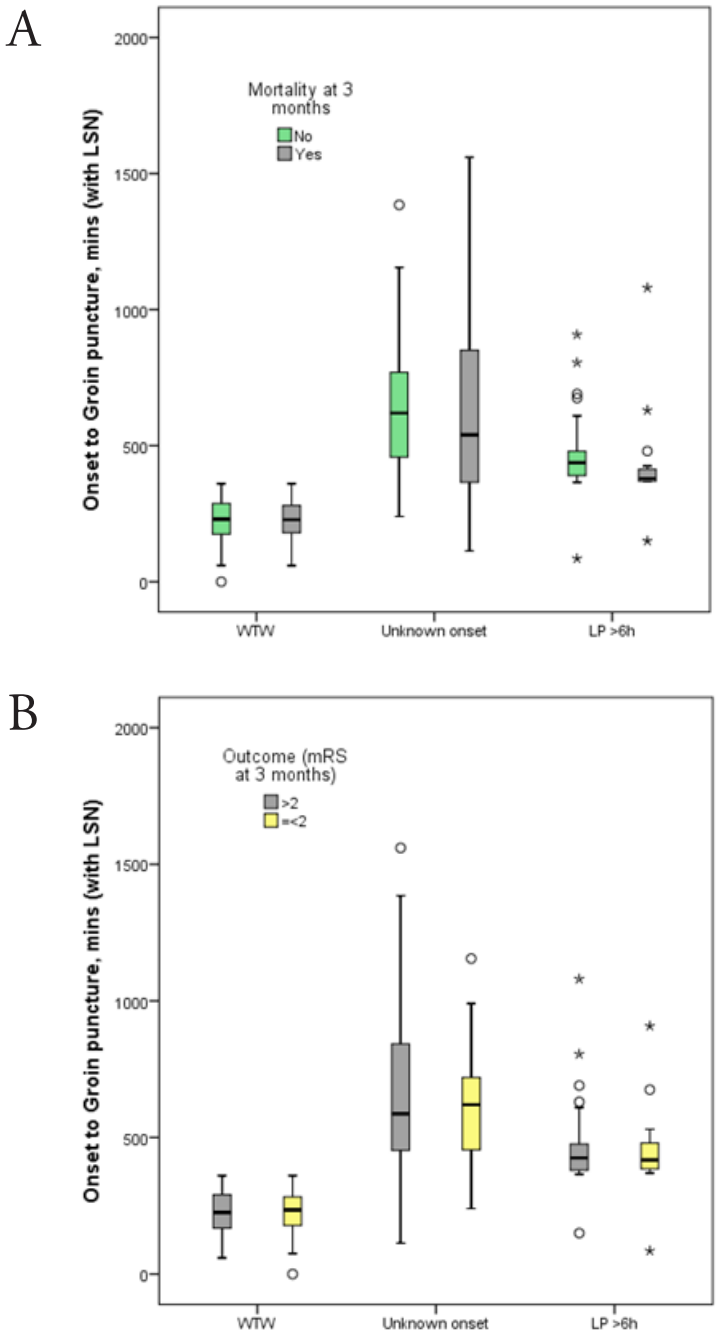

Figure 8. Onset to groin puncture. Association with mortality (A) and outcome (B).

Box plots (median and IQR)

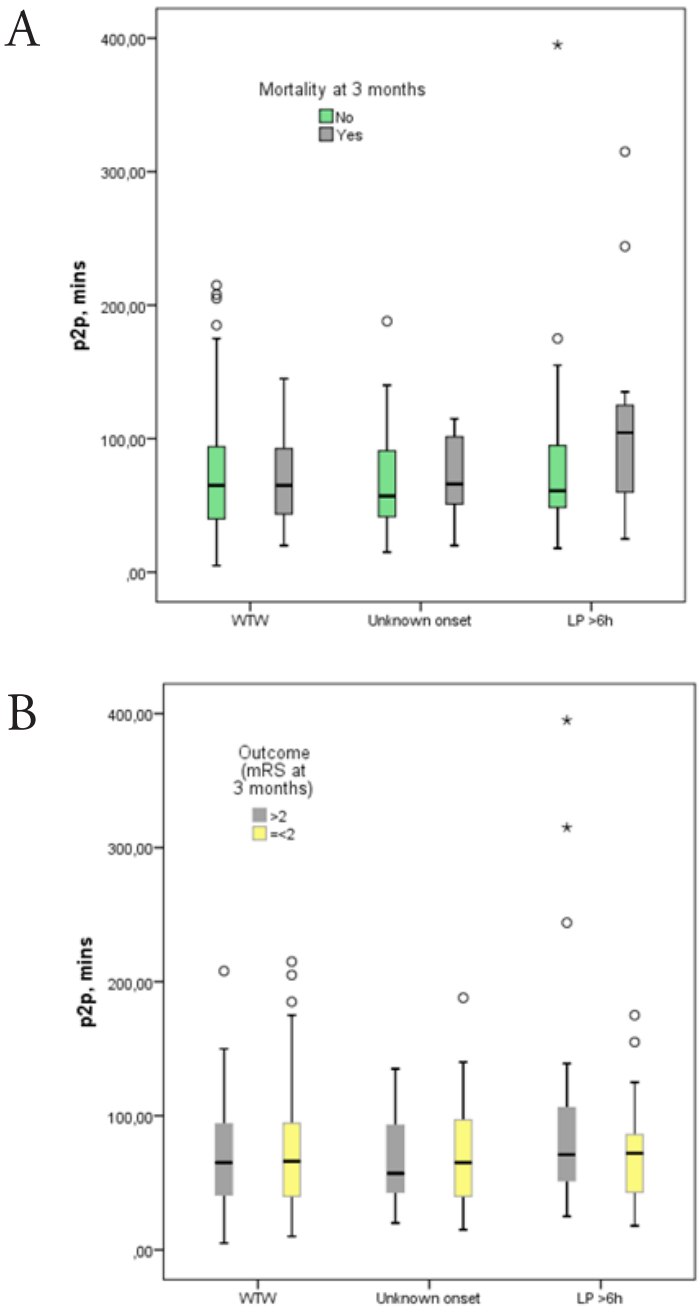

Figure 9. Picture to puncture. Association with mortality (A) and outcome (B).
Box plots (median and IQR).

VI
Discusion

1. BRIEF DISCUSSION OF THE PUBLICATION

The first finding of our study is that the subgroups of patients outside the time window (UKO and KO-LP) were not comparable, confirming that they represent two different populations. Therefore, OTW patients (UKO and KO-LP) could not be pooled and compared face to face with patients within the time window (WTW). Thus each group has been reported separately throughout the whole manuscript and the results have been presented individually comparing each subgroup (UKO and KO-LP) with patients WTW. This is a difference with most of the reports in the literature that present their OTW patients pooled as a group and thus compare them directly with patients treated WTW.

The main finding of the present study is that favorable outcome can be achieve in similar rates in patients beyond the therapeutic time window (UKO and KO-LP) than in patients WTW, in anterior circulation strokes treated with EVT using stentrievers, selected by advanced neuroimaging. This finding confirms the primary hypothesis of this thesis, as well as supports previous reported series on patients beyond the time window treated with EVT, in which the good outcomes were not different to the patients within the window.[140]

A second important finding is that, in our series, the secondary hypothesis that presumed similar safety (SICH and mortality) within and beyond the time window, could be confirmed. This adds to the data of other publications of EVT beyond conventional time windows, in which the SICH rate is not only higher but also sometimes lower than in other patients. However, it is important to mention that, although the rate of SICH did not significantly differ across OTW groups and WTW, hemorrhagic transformation was significantly higher in one of the OTW groups (KO-LP) than in the WTW group. This increase in hemorrhagic infarction or parenchymal hematoma overall in patients outside the window has not been described previously to our knowledge. In fact, some late presenting patients have the unique profile of a better clinical outcome due to their underlying pathophysiology of slow infarct progression. For that reason, our results should be interpreted with caution. First, because of the small sample size of the KO-LP group, second, because our KO-LP group might not have been representative as the reported KO-LP group in the literature have considerably longer time windows, third, because the definition of KO-LP

varies according to the time window beyond six or eight hours, and fourth, because our KO-LP group had a very high rate of treatment with IVT (50%) which notably differs from the reported rates of IVT in late presenting patients, which are often excluded from IVT or report very low rates of IVT.

The third finding of the study is that the times to treatment were significantly longer in UKO and in KO-LP than in WTW, which did not translate in poorer outcomes supporting the tissue clock or physiology based paradigm.[141] Interestingly, the OTGP were much longer in the UKO than in the KO-LP, which reflects the potential confusion of using TSLN as the onset time, which often overestimates the time elapsed from onset. The absence of impact of time to treatment on outcomes has been showed previously in large series[118] as well as in clinical trials[127]. Predictors of favorable outcome in the OTW groups were age, NIHSS, no ICH, recanalization, site of occlusion other than ICA, absence of IVT or diabetes. Predictors of mortality in the OTW groups were age, recanalization, ICH, PH2, systolic blood pressure and hyperglycemia. These latter two have lately been reported and should also be studied further, especially the hemodynamic status in recanalized versus non-recanalized patients.

The last finding was that the rate of favorable outcomes with EVT using ST OTW was not highly superior to those reported in the literature using first generation devices, which is surprising as ST have confirmed to achieve higher and faster recanalization rates translating in better outcomes. Interestingly, although our recanalization rates were higher than in previous series, they did not translate in higher outcomes across OTW subgroups. Our good outcome rates of 42 % in the UKO group are comparable with two reports from Aghaebrahim et al[125] and Jung et al[140] in the pre-ST era, which yielded favorable outcomes in 43% of 78 UKO-WUS and in 37% of 55 UKO-WUS, respectively. However, good outcome rate of 37.3% in 63 KO-LP of our series, and of 35.2% in 128 KO-LP of Jung et al report, was lower than the rate (50%) achieved in the 128 KO-LP of Aghaebrahim et al[125]. Taken together, these findings suggest that the newer recanalization strategies are superior but also that the results of the KO-LP groups may be heterogeneous. It should be noted that the times to treatment were significantly higher in the Aghaebrahims study (1092 minutes) than in the study by Jung (413 minutes) et al in our study (420 minutes).

2. LITERATURE REVIEW AND CONTRIBUTION OF THE STUDY TO THE LITERATURE

2.1. Evidence from randomized controlled trials

There is currently no evidence from randomized controlled trials directly addressing the issue of patients with unknown onset treated with endovascular therapy.

With regard to patients with UKO or late in the time window, the current guidelines establish that: *When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence C) and that additional randomized trial data are needed.*[36]

Those additional randomized trial data will come from the currently ongoing trials addressing this issue, which to our knowledge are the DAWN, POSITIVE, DEFUSE 3 and WASABI, which are described in detail in the section 5.6. The DAWN trial was originally designed in 2008 as a non-controlled study with a time window beyond 8 hours and in the era of the MERCi and Penumbra devices. Back in 2009, the preliminary data from 193 patients was presented as abstract, showing favorable outcomes in 45.7%[142]. In 2011, a study of Jovin et al, reported favorable outcomes in 40% in 169 patients fulfilling DAWN criteria, but using first generation devices.[109] However, the final results were not published and the current study has been revisited with neuroimaging and procedural changes like the use of stentrievers. The DAWN trial is currently enrolling patients OTW and will provide data in UKO onset patients (WUS or nonWUS) as well as in KO that present late.

However, there are already completed randomized trials that have directly addressed this issue:

- The DEFUSE 2 trial demonstrated that patient selection by MRI within 12hours from symptom onset could predict the outcome after endovascular therapy. The patients

with target mismatch that reperfused had much better outcomes than non-target patients. The malignant profile patients had poor outcome despite reperfusion. This study demonstrated that in late presenting patients treated from 6 to 12 hours after onset, the benefit was similar to the early presenting patients, and that if reperfusion was not achieved, the infarct volume increased despite collaterals. But probably, the most important finding of this trial is that the patients with target mismatch benefited from EVT irrespective of the time from symptom onset, which confirms the tissue clock paradigm.

- The MR RESCUE *trial,* however, did not show efficacy selecting patients within 8 hours for mechanical embolectomy based on advanced neuroimaging with MR. It is important to acknowledge that in this trial, first generation devices were used instead or stentrievers. Also, it is worth mentioning that before 2015, when the new guidelines were published based on the five positive RCTs, the time window for endovascular therapy had been traditionally 8 hours, which is the reason why this trial had this time cut-off. Given the current time window, this trial could give some data on the result of EVT in late presenters from 6 to 8 hours, however, given the negative trial and the above mentioned limitations, no conclusions can be drawn as the study failed to prove the hypothesis than penumbral patter selection would yield better outcomes than non penumbral pattern selection or than untreated patients.

- Recent stentriever RCTs information do not yield information on UKO patients as they were excluded. However, some information could be obtained on KO-LP patients. To our knowledge only ESCAPE and REVASCAT had longer windows than 6 hours, with 12 and 8 hours, respectively. In the ESCAPE trial, only 16% of the patients were treated after 6 hours, but even in this small subgroup a trend was seen in favor of EVT when comparing with the control group with OR 1.7 95% CI (0.7-4.0). [143] The subgroup analysis on patients treated beyond 6 hours within REVASCAT has not been published separately. However, a comparison with these studies is not possible to date, because the data of those patients, either unknown or late (6h to 12h in ESCAPE, or 6 to 8h in REVASCAT) has not yet been reported separately. A subanalysis of the REVASCAT trial showed that the association between time to reperfusion and outcome

was primarily driven by the time from imaging to reperfusion and not by the time from symptom onset to imaging, pointing that as long as the imaging is favorable at the time of selection, the patient may benefit from thrombectomy, and that the shorter the imaging to reperfusion time, the better the outcome. This statement is especially true in those patients presenting with high ASPECTS scores on admission neuroimaging, probably reflecting a good collateral flow.[144] Regarding time, it should be noted that MR CLEAN reported that the clinical benefit was time dependent and that there was a marked decline if reperfusion occurred after 6 hours and 19 minutes, so the benefit was not statistically significant. A recent report on the workflow metrics of the ESCAPE trial showed that imaging to reperfusion time was a significant predictor of outcome, however, onset to imaging time was not associated with outcome.[145] Although the time window was different across trials ranging from within 12 hours to within 6hours, the median onset to groin puncture time was <4.5 hours in all trials.[93] Nevertheless, it should be noticed that the time window for KO-LP patients in these trials is considerably shorter than the presumed slow progressors time window and thus, results should be interpreted carefully since these patients are not representative of all KO-LP ones. Conversely, MR clean findings support the importance of time among fast progressors.

2.2. Literature review of non-controlled studies

Before reviewing the literature, it is important to clarify the terms. It should also be noted that when the paper was published, there was not such differentiation between the groups that fall outside the therapeutic window (OTW): UKO - and its subgroups UKO-WUS or UKO-non-WUS - and KO-LP.

2.2.1. Literature on patients treated outside the time window (OTW)

Few case series of endovascular treatment of UKO or treatment with known onset beyond the established time windows (6 hours or 8 hours) have been published to date. (Table 23). Some of

those studies have concluded that the rates of recanalization, SICH mortality and good outcomes are similar to patients with KO, and those results are in line with our data.

However, comparisons among those studies should be done with caution, because definitions and times to treatment differ. Also, some reports include posterior circulation strokes, which might be more resistant to ischemia. Even in papers reporting only anterior circulation strokes, the sites of occlusion may be different. Finally, in other studies, EVT was not performed with stentrievers, so that they are procedurally different, with likely longer procedural times, and thus, maybe worse results.

Author, year	n	NIHSS ss	age	time	imaging	EVT	Recan	SICH	mRS≤2	Occlusion site
Natarajan, 2009[146]	30	13	72	210	CTP CT	MMT	66.7	33.3	20	AC and PC
Natarajan, 2010[147]	135<8h	NA	NA	>480	CTP	MMT	68.9	6.7	40	AC
	33>8h	NA	NA	NA			69.7	15.2	18.2	AC and PC
	21 WUS	NA	NA	NA			81	14.3	42.9	AC
	24 PC	NA	NA	NA			87.5	8.3	37.5	PC
Burkart, 2013[148]	40	18	75.4	151	CTP and CT	MT IAT	65	10	50	AC and PC
Qureshi, 2013[149]	52	13.7	66.4	431.7	CTP/MRI	NA	NA	3	NA	NA
Jovin, 2011 [109]	237	15	63.8	900	CTP, MR	MMT	77.84	8.86	45	AC
Kang, 2012[150]	156 UKO+	12	70	468	No	No	NA	Na	32.7	AC and PC
	83 UKO	14	67.5	276	MR	MMT	50.6	.6	44.6	AC and PC
Jung, 2013[124]	55 WUS	15	61.9	758	MR	MMT	78.2	3.7	37	AC and PC
	22 UKO	18	63.5	NA	MR	MMT	72.7	9.1	38.1	AC and PC
	128 KO>6h	128	61	413	MR	MMT	64.8	3.7	35.2	AC and PC
Aghaebrahim, 2014[151]	78 WUS	15	67	804	MR, CTP	MMT	68	9	43	AC
	128 KO>8h	14	64	1092	MR, CTP	MMT	70	5.5	50	AC
Naragum, 2015[152]	48	19.65	NA	NA	CTP	ST, MMT	72.91	6.25	29	AC and PC
Nogueira,2011[153]	112	15	62.7	1129	CTP, MRP	MERCI	81	14	37.2	AC
Turk, 2013[154]	<7h*	17	68	270	CTP	MMT	71.8	8.7	30-2	AC and PC
	>7h*	15	64	780	CTP	MMT	82.6	5.8	45.5	AC and PC
Millán, 2014[110]	109 KO	18	66.5	351	MR	ST	77.1	10	41.3	AC
	32 UKO	17	64.7	701	MR	ST	65.7	0	50	AC
Present work, 2016	113 UKO	16	67.5	605	MRP, CTP	ST	73.5	2.7	42.2	AC
	63 KO>6h	16.5	68.4	420	MRP, CTP	ST	84.1	9.5	37.3	AC

Table 20. Relevant studies on endovascular therapy for patients outside the time window.

Only studies with 20 patients are included.

OTGP: Onset to groin puncture. CTP: Perfusion CT. MR: Magnetic Resonance. WUS: wake up stroke. UKO: unknown onset, KO: known onset. ST: stentrievers. IAT: Intraarterial Thrombolysis. MMT: Multimodal therapy. MAT: Manual aspiration thrombectomy. AC: anterior circulation, PC: posterior circulation.* Total number of patients was 140. Number of patients in each group was not reported.

Results in these series of OTW strokes cannot be directly compared with the recently published randomized controlled trials that have validated endovascular therapy, and are thus considered the gold standard. However, they globally show similar rates of safety and efficacy outcomes, supporting the notion that EVT may be a safe treatment option for these patients. The largest series published to date in the literature is from the UPMC group with 237 patients treated with

EVT beyond 8 h from time LSN and the study from Jung et al with 205 patients treated with EVT beyond 6 hours from time LSN.

It should be noticed that most of the published series refer to early treatment strategies such as IAT, thrombectomy with first generation retrievers, such as MERCI, stenting, or a combination of all.

More recently dedicated publications have separately reported the response to EVT in each of the specific OTW subgroups: UKO-WUS, UKO-non WUS, and KO-LP.

2.2.2. Literature on Wake up strokes (UKO-WUS)

While there are plenty of papers reporting patients treated with EVT beyond the time window, few report separately the WUS group (Table X). The sample sizes range from 48 and 78 patients, with median OTGP of 540-804 minutes and favorable outcome from 29% to 46%. However, some of these series date from the pre-stentriever era and, in some studies, posterior circulation strokes were included. The RESTORE study treated 83 UKO patients of whom 63 had an UKO-WUS due to LAO. Patients were treated within a median of 9 hours (6.2h-12h) and good outcome was achieved in 46%. SICH occurred in 3.6%, any ICH was not reported.[150] Regarding series of patients with the latest recanalization strategies (ST and/or MAT), Mokin et al reported recanalization rates of 69% and good outcomes in 48%, in 52 patients treated within a mean time of 734 minutes (12.2 hours), in line with our results. There were differences with our study; first, the triaging neuroimaging method was CTP while in our study it was mainly MR; second, the time OTGP was considerably shorter in our series, with a mean difference of approximately 100 minutes; this latter difference was also observed when comparing our study with other published series; and third, Mokin's study included posterior circulation occlusion patients and MAT patients, while these groups were excluded in our study. Longer OTGP time (804 min) was also present in the Aghaebrahim et al study in 78 patients with anterior circulation strokes, showing recanalization in 68% and favorable outcome in 43% of the patients. From our group of 176 patients with UKO, data with regards to wake up stroke were available on 59 patients and

compare similarly with the above mentioned paper, with recanalization rates of 76%, and good outcomes in 48% (data not shown in the results section).

Author, year	n	NIHSS	Age	OTGP	imaging	EVT	Recan	SICH	mRS≤2	Includes PC
Kang, 2012[150]	63	4 (10-17)	67.4	540 (372-720)	MR	MMT	NA	4.8%	46	YES
Jung, 2013[155]	55	15	61.9	758	MR	MMT	78.2	3.7	37	YES
Aghaebrahim, 2014[151]	78	15	67	804	MR, CTP	MAT, ST,	68	9	43	YES
Mokin, 2015[156]	52	NA	NA	NA	CTP	ST, MAT	69	NA	48	YES
Naragum, 2015[152]	48	19.65	NA	NA	CTP	IAT, ST MMT	72.91	6.25	29	YES
Present study, 2016	59	18	67	650	MR	ST	76.3	1.7	48.2	NO

Table 21. Relevant publications on wake up strokes treated with endovascular therapy.

OTGP: Onset to groin puncture. CTP: Perfusion CT. MR: Magnetic Resonance. WUS: wake up stroke. UKO: unknown onset. KO: known onset. ST: stentrievers. IAT: Intraarterial Thrombolysis. MMT: Multimodal therapy. MAT: Manual aspiration thrombectomy. AC: anterior circulation. PC: posterior circulation.

2.2.3. Literature on uknown onset- non wake up strokes (UKO-nonWUS)

The literature on the subset of patients with UKO-nonWUS is very scarce and the sample sizes very small, mainly because until recently these patients had been all equalized according to time LSN and pooled into the same group with the UKO-WUS. According to the largest series on UKO treated with EVT, UKO-nonWUS are less frequent than UKO-WUS. Gralla et al reported on 205 patients OTW from whom 22 (10.7%) were UKO-nonWUS, 55 (27%) were WUS, and the remaining 128 (62.4%) were patients with KO treated beyond 6 hours (KO-LP). In the RESTORE study, 63/83 treated patients with UKO (76%) were WUS and 20/83 (24%) were UKO-non WUS, and they achieved good outcome in 46% and 40% respectively, however the small sample size of the UKO-nonWUS precludes from drawing conclusions. It has been reported that WUS and UKO-nonWUS have different clinical and neuroimaging characteristics. In a series of 276 patients, 104 (36.2%) patients with UKO-nonWUS and 172 (%) WUS, UKO-nonWUS were more severe, had more frequently aphasia or altered level of consciouness, cardioembolic etiology, presented earlier to the hospital and thus more often

received reperfusion therapies than the UKO-WUS. According to time LSN, 4.1% from the WUS group and 50% from the UKO-nonWUS group were eligible for the 4.5 hours IVT window. The rates of EVT were significantly higher (29,8%) in the UKO-nonWUS group than in the UKO-WUS (8.1%). However, there were no significant differences in EVT eligibility between WUS or non WUS, when patients beyond 4.5 hours were analyzed (6 of 43 (14.0%) vs. 19 of 160 (11.9%). Unfortunately, the outcome results were not reported.[157]

2.2.4. Literature on known onset late presenting patients (KO-LP)

One of the particular findings of our study was that late presenting patients had different baseline characteristics and outcomes compared to UKO patients. It is known that late presenters have a unique pathophysiology if they fall into the category of slow progressors, previously described in the introduction. The importance of this group is that these patients are undoubtedly excluded because their onset is known and too late, so there is not doubt like there may be in UKO strokes. However, the paradox is that these patients may benefit even more than earlier faster progressors who present earlier in the time window.

The counter intuitive concept that slow progressors and thus the very late presenters maintaining small infarct core (due to collaterals or other reasons) harbor a much better prognosis needs to be further researched and confirmed in larger studies and widespread. This is crucial, because the time-approach imprinted in the mind of out-hospital and in-hospital personnel automatically excludes this unique subset of patients who would be prone to benefit even more from reperfusion therapies than earlier presenters that in some instances might be fast progressors. At least, KO-LP should be considered for neuroimaging to estimate their infarct core and collaterals and thus establish whether they are fast progressors who already recruited in whom treatment would be dismal or slow progressors, which may dramatically benefit.

Unfortunately for the patients, there are few reports on KO-LP treated with EVT. The two largest series have both 128 patients and cannot be compared directly, due to different time windows (Table 25). In a series of 128 KO-LP defined as beyond 8 hours, the mean time to treatment was 18 hours, with a standard deviation of 33.6 hours, and favorable outcomes were found in

50%, which supports the underlying mechanism of slow progression.[151] Those treatment times radically differ from the times in our study, with a median of 420 minutes (380-476), in which the definition of KO-LP was beyond 6 hours. Another important difference is that usually KO-LP patients are excluded from the use of IVT due to very late onset to door times, whereas 52.4% of KO-LP in our study were treated with IV tPA within the window (in many instances in local hospitals), but presented after 6 hours to EVT. This high treatment rate (is considerably higher than the published articles on late presenters, that report 7% rates of IVT [151] and could explain the increased hemorrhagic rate in KO-LP in our series. Another potential contributor to the hemorrhagic risk could be the lower rate of patient selection by advanced neuroimaging in the KO-LP group than in the UKO group. Although the hemorrhage rate did not translate in higher frequency of symptomatic hemorrhage, it could impact favorable outcomes because we found lower rates in our series (37%) than the expected for late presenters. The second large study, that used the same time window of 6 hours, treated late presenters with median OTGP times of 413 minutes (362-440) and achieved favorable outcomes in 35.6%, These findings mirror our results showing lower rate of EVT success in KO-LP and suggest that patients who show small infarct core close after the window of 6 hours are not representative of late presenters who are slow progressors.

Author, year	n	NIHSS	Age	OTGP	imaging	EVT	Recan	SICH	mRS≤2	Posterior circulation included
Jung, 2013[155]	128	15	61	413 (362-1440)	MR	MMT	64.8	3.7%	35.2	Yes
Aghaebrahim, 2014[151]	128	14	64	1092	MR, CTP	MMT	70	5.5	50	No
Present study	63	17	68.4	420 (380-476)	MR, CTP	ST	84.1	9,5%	37.3%	No

Table 22. Relevant publications on known onset- late presenters.

OTGP: Onset to groin puncture. CTP: Perfusion CT. MR: Magnetic Resonance. WUS: wake up stroke. UKO: unknown onset, KO: known onset. ST: stentrievers. IAT: Intraarterial Thrombolysis. MMT: Multimodal therapy. MAT: Manual aspiration thrombectomy. AC: anterior circulation. PC: posterior circulation.

3. NATURAL HISTORY OF THESE PATIENTS IF LEFT UNTREATED

As treatment in these patients is usually contraindicated, the fate of these untreated patients bearing a large vessel occlusion is ominous, with high mortality and disability rates, which vary according to the occluded vessel. As of today, there are no reported data on the natural history of these specific group of patients (unknown, wake up strokes, or late presenters), neither it is known whether there are specific characteristics that would make them different from untreated stroke patients with stroke due to large vessel occlusion who present early within the time window.

To our knowledge, one of the few studies that can offer some results on the outcome of untreated UKO patients with large vessel occlusion is the RESTORE study.[150] This study compared the outcomes of 83 patients with UKO selected with MRI and treated with reperfusion therapy (68.7% IAT, 20.5% IAT+IVT, 10.8%IVT) with 156 untreated patients with UKO, achieving good outcomes in 44.6% in treated versus 32.7% in untreated patients with SICH rates of 3.6%. Interestingly, this study did not find differences in the subgroups of UKO patients (63 UKO-WUS and 20 UKO-nonWUS) in efficacy and outcomes.

Consequently, given that scarcity of specific studies on the outcome of untreated late presenters or UKO patients, according to site of occlusion, the data to know what would happen to these patients if left untreated is the data from natural history case series according to site of occlusion, or the control arms of the recent randomized controlled trials. However, comparisons should be done cautiously as untreated patients within trials are early presenting while UKO and KO-LP are by definition presenting OTW and likely have a different natural history. Table 26 shows the outcome for a given site of occlusion when the patient is left untreated, which is the case for most UKO or KO-LP strokes and may justify why to treat a patient with a UKO or KO-LP. Even if the outcomes of EVT were worse in OTW than in WTW patients, they would be superior to the rate of good outcomes in untreated patients. Thus the reported rates of 45% of favorable outcomes in large series of patients OTW support the treatment over natural history reports of 19% in the control arms of the MR CLEAN[94], 28.2% in REVASCAT[98] or the 26.5% of good outcome in the HERMES metaanalysis.[91]

STUDY	n	Occlusion sites	Recan	Good Outcome	Poor outcome	Mortality	SICHH
PROACT[29]	59	MCA M1	18	25.4	74.6	27.1	1.9
MELT [30]		MCA		38.6	62.4	3.5	1.8
MR CLEAN[94]	267	ICA, M1,M2, A1, A2	18	19.1	79.9	22.1	6.4
REVASCAT[98]	103	ICA, M1,M2	17	28.2	71.8	15.5	1.9
EXTEND-IA[95]	35	ICA, M1,M2	13	40	60	20	5.7
SWIFT PRIME[158]	98	ICA, M1, M2	17	35.5	44.5	12.4	3.1
ESCAPE[96]	150	ICA, MCA	17	29.3	70.7	19	2.7
HERMES[91]	645	ICA, MCA		26.5	73.5	18.9	4.3

Table 23. Outcomes and safety in the control arms of randomized controlled trials.

MCA: middle cerebral artery. ICA: internal carotid artery. A1: anterior cerebral artery segment. A1, A2: anterior cerebral artery segment A2. SICH: symptomatic intracranial cerebral hemorrhage.

4. STRENGTHS AND LIMITATIONS OF THE STUDY

4.1. Strenghts

There are several strengths in this study. First, it is a homogeneous population with anterior circulation occlusions, which is uncommon in the literature where unclear or unknown or late presenters are reported mixing anterior and posterior circulation cases. It is known that anterior and posterior circulation strokes are different in terms of resistance to ischemia and time windows, which are longer in posterior circulation[159], however this has also been recently questioned.[160,161]

Second, The other strength is that the study is comparative, so that the patients within and beyond the time window are compared while other studies report on patients OTW treated with EVT, without a comparison arm.

Third, our study supports the existing body of literature on pathophysiology based rather than time based patient selection for EVT in stroke patients due to large artery anterior occlusions.

Fourth, our study reports only on patients treated with ST, which have shown superiority regarding recanalization rates and outcomes, and are the currently recommended strategy for EVT.

4.2. Limitations

We acknowledge several limitations in this study. First, the retrospective nature of the study. Second, the absence of information on collateral circulation, which is one of the main determinants to expand the time window and improve outcomes, is an important piece of information lacking. Third, the absence of data on infarct volume, described as pivotal biomarker for patient outcome. Fourth, the small sample size of the UKO group precludes from drawing conclusions that can be generalized, especially if we focus on subset of patients either by site of occlusion, or nature of UKO (WUS or non-WUS) or late presenting stroke. Back at the time when the manuscript was written there was not much specific literature on the subtypes of UKO stroke. Currently, there are ongoing clinical trials specifically aimed to wake up strokes or to late presenting patients (see below). There is controversy to whether the outcomes between these two groups differ. Fifth, there might be a selection bias because of the different neuroimaging method used to select patients. There were a higher proportion of UKO patients studied by advanced neuroimaging than KO-LP patients, which could explain the better outcomes in the first group. Sixth, because our selection criteria are not widely standardized in stroke centers, general application of our results cannot be established. Finally, our study did not differentiate between patients with WUS and patients with UKO-nonWUS. This is important, as some authors have established that the characteristics of UKO-WUS and UKO-nonWUS significantely differ.[157] However, this study also included patients with stroke due to small artery occlusion. Thus, larger studies are warranted to investigate whether there are differences between UKO-WUS due to LAO and UKO-nonWUS due to LAO.

5. ONGOING TRIALS RELATED WITH THE STUDY

There are several trials that could add information to the question of EVT in patients with UKO or KO-LP. A few are specifically designed to primarily study this question (Primary trials) while others are designed to answer other main research question, however, because of their large time window, they could include these patients, and thus are also of interest (Secondary trials). Table 27 Summarizes the trial addressing directly (Primary trials) or indirectly (Secondary trials) the question of patients treated with EVT beyond the window (UKO or KO-LP).

Primary Trials	Secondary Trials
DAWN (8-24h)	FAST COLL (6-12h)
POSITIVE (6-12h)	PROVE-IT (12h)
DEFUSE 3 (6-16h)	NCT02677415** (12h)
WASSABI (*<24h)	BEST (<8h)
ARISE (8-24h)	CRISP (18h)
NCT02737189 (6-24h)	NCT02639806 (<12h)
	ENDOSTROKE (NO TW)
	REDIRECT RECo (8h)
	ANSTROKE (<8h)

Table 24. Ongoing primary and secondary trials on EVT beyond the window.

TW: Time window. *UKO-WUS. Note: The acronyms for the study trial are specified below, together with a brief trial overview. When there is no acronym listed, the number or clinical trial (NCT) is used.

5.1. Primary Trials

To our knowledge, there are currently 6 clinical trials addressing the issue of EVT in patients with unknown time of onset, wake up strokes, or late presenting patients. The RESTORE trial was completed and has been described above.

- **The DAWN trial**: Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (NCT02142283) is a prospective randomized trial assigning patients to mechanical thrombectomy with the Trevo stent retriever or to best medical therapy provided the treatment is initiated within 6-24 hours after last seen well and that there is salvageable penumbral tissue with clinical- diffusion mismatch (high NIHSS score with small DWI, CTP-rCBF lesion). Patients should have an ICA and/or MCA-M1occlusion by CTA or MRA, NIHSS ≥10 (assessed within one hour of measuring core infarct volume) and have contraindications or have failed IVT. Neuroimaging inclusion criteria include < 1/3 MCA territory involved, as evidenced by CT or MRI and Clinical Imaging Mismatch (CIM) defined as one of the following on MR-DWI or CTP-rCBF maps: 0-<21 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old), 0-<31 cc core infarct and NIHSS ≥ 10 (and age < 80 years old), 31 cc to <51 cc core infarct and NIHSS ≥ 20 (and age < 80 years old).

- **The POSITIVE trial**: PerfusiOn Imaging Selection of Ischemic STroke PatIents for EndoVascular ThErapy (NCT01852201), randomizes patients to standard of care versus EVT within 6-12 hours of symptom onset, in patients ineligible for IVT, in which penumbral pattern is assessed by MRI or CT. Therefore, patients with UKO within 12 hours will be recruited and also a subset of late presenters provided they can be treated within 12 hours

- **The DEFUSE 3 trial**: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (NCT02586415), aims to identify strokes who can benefit from EVT as much as 6 to 16 hours after stroke onset. Patients with ICA or MCA M1 and a target mismatch profile on CTP/CTA or DWI/PWI will be randomized to EVT with Food and Drug Administration-approved thrombectomy devices versus medical therapy alone. Interestingly, while the DEFUSE 2 did not mention any specifics on patient presentation, DEFUSE 3 specifically states that includes WUS provided they present within 16 hours from LSN. Regarding KO-LP, the limitation is that only patients up to 12 hours will be recruited, which might miss target patients.

- **WASSABI**: Wake up Symptomatic Stroke in Acute Brain Ischemia, (NCT01455935) will treat with EVT patients with Unknown time of onset but less than 24 hours since LSN, with NIHSS 8-22, ASPECTS 7 or more and evidence of penumbra on CTP

- **ARISE**: After 8 Hours Reperfusion in Ischemic Stroke Embolization (NCT02533778), is a prospective pilot study that will recruit patients with onset beyond 8h to 24 wih intracranial vertebral artery, basilar artery, intracranial ICA, ICA terminus bifurcation, MCA M1/M2, or ACA occlusion, with NIHSS ≥ 7 and MRI DWI/PWI or CTA/P, which demonstrates an area of mismatch ≥ 2/3 rd.

- **Basilar Artery Occlusion Chinese Endovascular Trial** (NCT02737189) is a randomized trial of revascularization with solitaire stentriever versus best medical therapy in the treatment of acute ischemic stroke due to basilar artery occlusion presenting within 6-24 hours of symptom onset or LSN, with NIHSS³10 and posterior circulation ASPECTS score ≥6 and Pons-midbrain-index of 0-2.

5.2. Secondary Trials

The trials described onwards include those in which the time window is established beyond 6 hours, and thus, may yield information on wake up or late presenting strokes in which symptom onset is unknown. To hour information, there are at least 9 trials with enlarged time windows (up to 24 hours, or without time window). An outline of each study is presented below:

- **FAST-COLL Study**: MR-based Collateral Imaging to Predict Response to Endovascular Treatment of Stroke (NCT02668627) is a prospective observational trial to evaluate whether MRI-based collateral imaging by Fast Analysis SysTem for COLLaterals,is feasible and can predict the response to endovascular treatment within 6 and 12 hours. It will include patient with NIHSS > 5 and onset LSN to EVT time < 12 hours with ICA, M1 MCA, or M1-MCA equivalent (2 or more M2-MCAs) and ASPECTS 0-5.

- **PROVE IT**: Measuring Collaterals With Multi-phase CT Angiography in Patients With Ischemic Stroke (NCT02184936), is a prospective multi-center hospital-based

cohort study of 500 consecutive patients with acute ischemic stroke presenting within 12 hours of stroke symptom onset with evidence of intracranial occlusion treated with EVT The hypothesis is hypothesize that patients with good and intermediate collaterals on multi-phase CTA achieve good clinical outcome with early recanalization (within 4 hours of baseline imaging); patients with poor collaterals do not do well even with early recanalization.

- **Impact of general versus local anesthesia** on neurological function in patients with acute ischemic stroke undergoing endovascular treatment (NCT02677415) is a randomized single blind study that will include patients with AIS due to anterior circulation LAO and NIHSS ≥10 and within 12 hours from symptom onset who will be randomized to local or general anesthesia.

- **BEST**: Endovascular Interventions versus Standard Medical Treatment (NCT02441556) is a prospective randomized trial for patients with basilar artery occlusion within 8 hours from onset that will be randomized to EVT or best medical therapy

- **CRISP Computed Tomography Perfusion (CTP)** to Predict Response to Recanalization in Ischemic Stroke Project is a prospective multicentric cohort study of 240 consecutive stroke patients who will undergo a CTP scan prior to EVT primary or adjuvant post IVT for hemispheric stroke. Patients require NIHSS ≥5, and begin of EVT within 90 minutes of completion of the CT scan and within 18 hours of symptom onset.

- **General anesthesia for endovascular thrombectomy**; a pilot study (NCT02639806), is a retrospective study comparing patients treated with patients with general anesthesia with sevoflurane versus local anesthesia with lidocaine. Anterior circulation strokes with NIHSS > 5 at the time of treatment and small core proximal occlusion as confirmed by CT angiography (carotid, M1 MCA or M1 MCA equivalent) will be enrolled. The time window is 12 hours from onset or time LSN as long as EVT is initiated within 60 minutes of baseline NCCT.

- **ENDOSTROKE** is an International Multicenter Registry for Mechanical Recanalization Procedures in Acute Stroke (NCT01399762), which will enroll 500 patients with AIS

and MCA M1 or M2, or basilar artery occlusion. No time window or NIHSS range is required.

- **REDIRECT**: RECO Flow Restoration Device Versus Solitaire FR With the Intention for Thrombectomy Study (NCT01983644) is a prospective randomized control trial, that will enroll patients within 8 h from onset to EVT with the Solitaire versus the RECO device.

- **ANSTROKE**: Sedation Versus General Anesthesia for Endovascular Therapy in Acute Stroke - Impact on Neurological Outcome (NCT01872884) is a randomized, single blind study that will include patients with NIHSS scores ≥ 10 (in Right hemisphere) or 14 (in Left hemisphere) depending on the side engagement, and EVT should be started <8 hours after symptom onset.

6. FUTURE RESEARCH QUESTIONS DERIVED FROM THIS STUDY

This study adds evidence to the body of literature supporting the hypothesis of pathophysiology is brain instead of time is brain. This hypothesis has already been shown in the DEFUSE 2 study where patients with comparable time windows displayed highly significant differences in the DWI patterns. Thus, the controversy should not be based on time: *Should we treat patients with unknown onset or not*? The question is: *What makes a patient be a slow progressor or and fast progressor?*, thus shifting the debate of time (known late onset or unknown onset) to the debate of how to predict progression in order to expedite or triage patient treatment. This opens several questions:

- Is there a biomarker to differentiate this subset of patients?

- Is there an imaging surrogate e.g. collaterals to differentiate between slow and fast progressors?

- Once identified the fast progressors, what measures (neuroprotection, hypothermia…) would shift them to slow progressors to buy time until reperfusion therapy is performed? (Jovin, 2014)

- Finally, it may be worth it to find predictors of favorable response to EVT in KO-LP that would make the triage of these patients cost-effective, avoiding the need to transfer all KO-LP patients.

Therefore, if neuroimaging and not time is the key to establish whether a patient should be treated or not, paramedics or EMS services should be able to provide a neuroimaging study on-site to avoid unnecessary transfers and/or pursue transfers despite long time elapsed since onset. There are mobile stroke units working, however, some of them with CTA and CTP, which could open a treatment opportunity for many patients. [162–164]

- Another research void that this work shows is the lack of data about the outcome on untreated patients within the three groups beyond the window. Also, given the fact that most patients OTW (UKO or KO-LP) due to large vessel occlusion are currently not given any treatment option, it would be interesting to estimate how many patients per year are not treated and to report the functional outcome, in order to offer data on the natural history of each group. One retrospective study showed that 36% of the patients with UKO could have been treated if time would have not been an exclusion criterion.[165]

- Another controversial question is which neuroimaging tool to use in this type of patients (OTW, UKO or KO-LP): Perfusion CT or MR, CTA with collateral assessment, NNCT, DWI-flair mismatch among others. Moreover, it has been reported that advanced modality imaging delays at least one hour patient treatment without improving patient outcomes, suggesting that non contrast CT with the ASPECTS score might be a valid alternative for triaging and time saving strategy which could lead to better patient outcomes.[166] Gupta el al. did not find any differences between outcomes or SICH of patients selected by CTP or CT, and found a significant delay in time to reperfusion. [167]

- The hypothesis that the outcome of a stroke depends on the occlusion time of the lenticulostriate arteries challenges our results and opens another research line within this work. This hypothesis claims that because these arteries are territory-terminal and thus have no collaterals, their maximum time window is 6 hours, and beyond this time window poor functional outcome as well as hemorrhagic transformation increase. This hypothesis was proved and confirmed by the first carotid intraarterial fibrinolysis publication by Theron et al back in 1989,[168] who described the different types of MCA occlusions according to the involvement of the LSA. This issue has not been addressed directly in large strokes series until very recently, in an article where the involvement of the LSA and the presence of lenticular infarctions were positively correlated[169]. The interest in the involvement of these arteries is the following:

  The degree of leptomeningeal collaterals, largely described as predictor of functional outcome and hemorrhagic transformation as well as directly implied in the extension of the time window in proximal artery occlusions, cannot compensate LSA occlusions. Thus, the ischemic threshold for these occlusions may not be as flexible, and may in fact have a strict time window of 6 hours, as proposed by Kamijyoo et al. [170]This fact opens a topic of further research, that is, whether the outcome of the subgroup of patients with MCA occlusion - treated beyond the time window depends on the patency of LSA.

- The role of parenchymography in prediction of outcomes of strokes due to large vessel occlusion is a further point of interest. Cerebral parenchymography was originally described by Theron as a hemodynamic and physiologic real time assessment of the cerebral circulation by performing a global cerebral angiography from an angiographic run from the aortic arch[171]. The parenchymograpy yields several patterns that focus not only in the arterial but also in the capillary and venous phases. In acute stroke, capillary and venous phases have not been considered of the essence. Regarding venous assessment, the degree of filling of cortical and medullary veins have been proposed as outcome predictors in ischemic stroke as well as perfusion surrogates[172–174]. Regarding capillary assessment, a similar tool to cerebral parenchymography was recently proposed, focusing on the capillary phase and quantifying the filling of the capillaries

in a score.[175] The Capillary Index Score has been lately validated in large stroke cohorts and trials, confirming its accuracy in predicting outcomes[176,177]. This score is similar to that proposed by Theron 20 years earlier with three main differences: 1) Parenchymography yields a more physiologic assessment as it gives a global overview to cerebral perfusion, as both carotid and vertebral arteries simultaneous fill in the brain, thus, there is no need to do a four vessel angiography in the emergency setting which saves time; 2) Parenchymography only offers an anteroposterior view of the brain, thus, to that regard, ICS allows the use of lateral views that may be useful for some stroke localizations; and 3) ICS can be quantified and thus can be generalized and compared.

Thus, the research line that this work offers, is to retrospectively and blindly calculate the ICS score and correlate it with outcomes in both groups with MCA M1 occlusions.

- Because all this work is on anterior circulation, the question of KO-LP, UKO WUS or nonWUS within the posterior circulation remains unanswered. Surprisingly, there are not many large series on posterior circulation subgroups of OTW while it is known that posterior circulation patients present later to the hospital and that they have more tolerance to ischemia. The only series to our knowledge was reported at the international stroke conference with 85 patients with basilar artery occlusion treated without time constraints, with a median Median time from last seen well (TLSW) to groin puncture: 774 min (12.9 hrs) (IQR 5.4h-37.7h) with favorable outcomes achieved in 34% of the patients. Time was not an outcome predictor in uni or multivariate analyses.[178] Probably, the lower incidence of posterior circulation patients is outweighed by the larger rate of patients presenting beyond the conventional time windows. From our total cohort 968 patients, after excluding patients with non documented OTGP or whom had no occlusion or occlusion was not accessible, 753 patients remained, from which 93 (12.3%) had posterior circulation occlusion. When a time window of 8 hours was applied, 27% of the posterior circulation patients were beyond the treatment window. From those patients OTW, 72% were UKO strokes and 28%were KO-LP strokes. Interestingly, the numbers notably shifted when choosing the current time window of 6 hours; in that case 42% of the posterior circulation strokes were OTW, with a distribution of almost half of the patients in each OTW subgroup (48.7 %

UKO and 51.2% KO-LP). These findings suggest that the field of posterior circulation strokes beyond the established time windows might have an important impact because of the higher number of potentially treatable patients and the higher resistance to ischemia.

VII
Conclusions

1. In our series, the outcomes and safety of endovascular therapy with stentrievers to treat strokes due to anterior circulation artery occlusion beyond the therapeutic time window of 6 hours and selected by neuroimaging, was similar to outcomes and safety in patients treated within the therapeutic time window.

2. In our series, the patients beyond the window could not be considered into the same group due to significant differences in baseline and outcome variables. Thus patients beyond the window had to be reported separately in two groups: patients with unknown onset and patients with known onset treated beyond the 6-hour time window.

3. The predictors of good outcome and mortality are similar for patients within and beyond the window, and within the OTW subgroups.

4. Predictors of favorable outcome were younger age, low NIHSS score, recanalization and absence of hemorrhagic transformation.

5. Predictors of mortality were older age, high NIHSS score, lack of recanalization, high systolic blood pressure and blood glucose and absence of hemorrhagic transformation.

6. Time from symptom onset or in hospital time metrics were not predictors of outcome in any of the three groups.

7. Treatment of patients with stroke due to anterior circulation occlusion with endovascular therapy using stentrievers outside the therapeutic window and selected by advanced neuroimaging is justified given the outcomes and safety results and the dismal prognosis of leaving these patients untreated. Ideally these patients should be enrolled in clinical trials aimed to specifically study this topic, however, if for some reason the patient does not qualify, treatment should be carried forward.

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Publications related with this thesis

Millán M, **Aleu A**, Almendrote M, Serena J, Castaño C, Roquer J, Pérez de la Ossa N, Gomis M, Dorado L, López-Cancio E, García-Bermejo P, Hernández-Pérez M, Dávalos A.Safety and effectiveness of endovascular treatment of stroke with unknown time of onset. Cerebrovascular Diseases. Febrero 2014; 37(2):134-40.

Hernández-Pérez M, Pérez de la Ossa N, Aleu A, Millán M, Gomis M, Dorado L, López-Cancio E, Jovin T, Dávalos A.Natural history of acute stroke due to occlusion of the middle cerebral artery and intracranial internal carotid artery.J Neuroimaging. 2014 Jul-Aug;24(4):354-8. doi: 10.1111/jon.12062. Epub 2013 Nov 19

Appendix

1. Modified Rankin Scale

0 = No symptoms at all

1 = No significant disability despite symptoms; able to carry out all usual duties and activities

2 = Slight disability; unable to carry out all previous activities,but able to look after own affairs without assistance

3 = Moderate disability requiring some help, but able to walkwithout assistance

4 = Moderate severe disability; unable to walk without assistanceand unable to attend to own bodily needs without assistance

5 = Severe disability; bedridden, incontinent, and requiring constantnursing care and attention

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2. National Institutes of Health Stroke Scale

Item	Response
1a. Level of consciousness	0 = Alert 1 = Not alert, arousable 2 = Not alert, obtunded 3 = Unresponsive
1b. Questions	0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly
1c. Commands	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task
2. Gaze	0 = Normal 1 = Partial gaze palsy 2 = Total gaze palsy
3. Visual fields	0 = No visual loss 1 = Partial hemianopsia 2 = Complete hemianopsia 3 = Bilateral hemianopsia
4. Facial palsy	0 = Normal 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis
5a. Left motor arm	0 = No drift 1 = Drift before 10 s 2 = Falls before 10 s 3 = No efforta gainstg ravity 4 = No movement
5b. Right motor arm	0 = No drift 1 = Drift before 10 s 2 = Falls before 10 s 3 = No efforta gainstg ravity 4 = No moven1ent
6a. Left motor leg	0 = No drift 1 = Drift before 5 s 2 = Falls before 5 s 3 = No effort against gravity 4 = No movement
6b. Right motor leg	0 = No drift 1 = Drift before 5 s 2 = Falls before 5 s 3 = No effort against gravity 4 = No movement
7. Ataxia	0 = Absent 1 = 1 Limb 2 = 2 Limbs
8. Sensory	0 = Normal 1 = Mild loss 2 = Severe loss
9. Language	0 = Normal 1 = Mild aphasia 2 = Severe aphasia 3 = Mute or global aphasia
10. Dysarthria	0 = Normal 1 = Mild 2 = Severe
11. Extinction/inattention	0 = Normal 1 = Mild 2 = Severe

3. TOAST* Classification of Subtypes of Acute Ischemic Stroke

*Trial of Org 10172 in Acute Stroke Treatment

Large-artery atherosclerosis (embolus/thrombosis)*

Cardioembolism (high-risk/medium-risk)*

Small-vessel occlusion (lacune)*

Stroke of other determined etiology*

Stroke of undetermined etiology

(a) Two or more causes identified

(b) Negative evaluation

(c) Incomplete evaluation

*Possible or probable depending on results of ancillary studies.