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IDENTIFICACIÓN PRECOZ DEL ICTUS ISQUÉMICO RELACIONADO CON ATEROMATOSIS INTRACRANEAL E IMPLICACIONES EN EL TRATAMIENTO ENDOVASCULAR

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A Cris, por lo que queda por venir

ACRÓNIMOS Y ABREVIACIONES

(por orden alfabético)

ACA, Arteria Cerebral Anterior

ACM, Arteria Cerebral Media

AcT, del inglés, *Intravenous Tenecteplase Compared With Alteplase for Acute Ischaemic Stroke in Canada*

ACI, Arteria Carótida Interna

ANGEL-ASPECT, del inglés, *Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core*

ASPECTS, del inglés, *Alberta Stroke Programme Early CT Score*

ATTEST-2, del inglés, *Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis-2*

ATTENTION, del inglés, *Endovascular Treatment for Acute Basilar-Artery Occlusion*

AUC, del inglés, *Area Under the Curve*

BAOCHE, del inglés, *Basilar Artery Occlusion Chinese Endovascular*

BASIS, del inglés, *Balloon Angioplasty vs Medical Management for Intracranial Artery Stenosis*

BASICS, del inglés, *Basilar Artery International Cooperation Study*

BEST, del inglés, *Basilar Artery Occlusion Endovascular Intervention versus Standard Medical Treatment*

CAPTIVA, del inglés, *Comparison of Anticoagulation and Antiplatelet Therapies for Intracranial Vascular Atherostenosis*

CASSIS, del inglés, *China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis*

DAWN, del inglés, *DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo*

DEFUSE-3, del inglés, *Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke*

DISCOUNT, del inglés, *Evaluation of Mechanical Thrombectomy in Acute Ischemic Stroke Related to a Distal Arterial Occlusion*

DISTAL, del inglés, *Endovascular Therapy Plus Best Medical Treatment Versus BMT Alone for Medium Vessel Occlusion Stroke*

DISTALS, del inglés, *Distal Ischemic Stroke Treatment With Adjustable Low-Profile Stentriever*

DUSK, del inglés, *Endovascular versus medical management in Distal Medium Vessel Occlusion Stroke*

DWI, del inglés, *Diffusion-Weighted Imaging*

ENDLOW, del inglés, *Endovascular Therapy for Low NIHSS Ischemic Strokes*

ESCAPE, del inglés, *The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Time*

ESCAPE-MeVO, del inglés, *Endovascular Treatment to Improve Outcomes for Medium Vessel Occlusions*

EXTEND, del inglés, *Extending the Time for Thrombolysis in Emergency Neurological Deficits*

EXTEND-IA, del inglés, *Extending the Time for Thrombolysis in Emergency Neurological Deficits - IntraArterial*

FDA, del inglés, *Food and Drug Administration*

FLAIR, del inglés, *Fluid-Attenuated Inversion Recovery*

FRONTIER-AP, del inglés, *Clinical Outcome and Safety of Endovascular Versus Standard Medical Therapy for Stroke With Medium Sized Vessel Occlusion*

HDL, lipoproteína de alta densidad

HERMES, del inglés, *Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials*

HIR, Ratio de Intensidad de Hipoperfusión

ICAD, del inglés, *Intracranial Atherosclerotic Disease*

ICARUS, del inglés, *IntraCranial Atherosclerosis Related Large-vessel Occlusion Treated With Urgent Stenting*

ICAS-LVO, del inglés, *Intracranial Atherosclerosis-related Large Vessel Occlusion*

IMS-III, del inglés, *Interventional Management of Stroke III*

LASTE, del inglés, *Large Stroke Therapy Evaluation*

LDL, lipoproteína de baja densidad

MAGNA, del inglés, *MechanicAl thrombectomy for larGe braiN infArctions*

MERCI, del inglés, *Mechanical Embolus Removal in Cerebral Ischemia*

MOSTE, del inglés, *Minor Stroke Therapy Evaluation*

MR CLEAN, del inglés, *Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands*

MR RESCUE, del inglés, *Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy*

mRS, del inglés*, modified Rankin Scale*

NIHSS, del inglés, *National Institutes of Health Stroke Scale*

NINDS tPA, del inglés, *National Institute of Neurological Disorders and Stroke tissue-type plasminogen activator trial*

OCSP, del inglés, *Oxfordshire Community Stroke Project*

OR, del inglés, *Odds ratio*

OGV, Oclusión de Gran Vaso

PAI1, inhibidor del activador del Plasminógeno 1

PROACT, del inglés, *Prolyse in Acute Cerebral Thromboembolism*

ReSET, del inglés, *Rescue Stenting for Failed Endovascular Thrombectomy in Acute Ischemic Stroke*

RESCUE-ICAS, del inglés, *Registry of Emergent Large Vessel Occlusion due to Intracranial Atherosclerosis*

RESCUE-Japan LIMIT, del inglés, *Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core* Trial

REVASCAT, del inglés, *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*

RIC, Rango Intercuartílico

rtPA, del inglés, *Recombinant Tissue-Type Plasminogen Activator*

SAIL, del inglés, *Stent retriever Assisted Lysis*

SAMMPRIS, del inglés, *Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis*

SELECT2, del inglés, *Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke*

sLOX1, receptor soluble tipo lectina similar a la LDL oxidada-1

SR, del inglés, *Stent Retriever*

SWIFT-PRIME, del inglés, *Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment*

TC, Tomografía Computarizada

TEMPO-2, del inglés, *Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion*

TESLA, del inglés, *The Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke*

TEV, Tratamiento Endovascular

TH, Transformación Hemorrágica

THRACE, del francés, *THRombectomie des Artères CErebrales*

TICI, del inglés, *Thrombolysis In Cerebral Infarction*

TM, Trombectomía Mecánica

TNK, Tenecteplasa

TOAST, del inglés, *Trial of ORG 10172 in Acute Stroke Treatment*

TRACE-2, del inglés, *Tenecteplase Versus Alteplase in Acute Ischemic Cerebrovascular Events-2*

TENSION, del inglés, *The Efficacy and Safety of Thrombectomy in Stroke with extended lesion and extended time window*

VAST, del inglés, *Vertebral Artery Stenting Trial*

VISSIT, del inglés, *Vitesse Intra-cranial Stent Study for Ischemic Stroke Therapy*

WASID, del inglés, *Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis*

WEAVE, del inglés, *Wingspan Stent System Post Market Surveillance*

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RESUMEN

Introducción:

Actualmente el tratamiento endovascular es el tratamiento de elección en el ictus isquémico con oclusión de gran vaso. Sin embargo, la estrategia terapéutica óptima en pacientes que presentan una estenosis intracraneal subyacente (ICAS-LVO) es incierta, dado que es una de las causas más comunes de recanalización fallida y se presenta como un desafío.

Por este motivo, la identificación precoz preprocedimiento de esta etiología podría permitir realizar un tratamiento endovascular (TEV) individualizado a la fisiopatología diana, anticipando el uso de maniobras de rescate mecánicas y farmacológicas con el objetivo de optimizar el resultado angiográfico y el pronóstico clínico de este subgrupo de pacientes.

Objetivos:

Identificar biomarcadores clínicos y radiológicos de ICAS-LVO disponibles antes del TEV y evaluar su capacidad predictiva, así como su implicación en la estrategia terapéutica endovascular.

Métodos:

En primer lugar, se realizaron dos estudios retrospectivos a partir de una base de datos prospectiva del Hospital Universitari Vall d'Hebron de pacientes consecutivos con un ictus isquémico tratados mediante trombectomía mecánica entre 2020 y 2022. Se analizaron aquellas variables que se asocian al diagnóstico de ICAS-LVO y pueden ser identificadas antes del TEV de forma sencilla. Mediante el análisis estadístico se evaluó su capacidad predictiva y pronóstica.

En un segundo lugar, se realizó un estudio retrospectivo de dos centros europeos en el que se incluyeron aquellos pacientes tratados con la técnica SAIL (Stent retriever AssIsted Lysis) con tirofiban debido a sospecha de ICAS-LVO y/o recanalización fallida. Se analizó su pronóstico angiográfico, así como su seguridad mediante la tasa de mortalidad y transformación hemorrágica sintomática.

El análisis estadístico se realizó aplicando modelos de regresión logística y/o ordinal según la naturaleza de la variable dependiente.

Resultados:

En nuestra cohorte, la ausencia de fibrilación auricular (Odds Ratio [OR] 9,33, IC95% 1,11-78,42; p=0.040), una menor ratio de intensidad de hipoperfusión (HIR [Tmax>10s/Tmax>6s], OR 0,69, IC95% 0,50-0,95; p=0,025), la calcificación arterial intracraneal sintomática (OR 4,15, IC95% 1,64-26,42; p=0,006), una oclusión más proximal (ICA, MCA-M1: OR 4,00, IC95% 1,23-13,03; p=0,021) y el tabaquismo (OR 2,91, IC95% 1,08-7,90; p=0,035) se asociaron con el diagnóstico de ICAS-LVO. Este modelo clínico-radiológico mostró una buena capacidad predictiva para identificar ICAS-LVO (AUC=0,88, IC95% 0,83-0,94; p<0,001).

Además, las IAC emergieron como predictor independiente de recanalización fallida (OR 11,89; IC 95% 3,94-35,91; P<0,001), necesidad de procedimientos de rescate (OR 12,38; IC 95% 2,22-69,09; P=0,004) y mal pronóstico funcional (mRS≥3; OR 3,51 IC95% 1,02-12,00; P=0,046).

En 44 pacientes que se presentaron con ICAS-LVO y/o recanalización fallida se realizó la técnica *Stent retriever AssIsted Lysis* (SAIL) con tirofiban. Se logró una tasa de reperfusión exitosa sostenida del 79.5% independientemente de la vía de administración de tirofiban (IV-SAIL 80% vs IA-SAIL 78.9%; p=0.932). Únicamente hubo la necesidad de realizar rescate con angioplastia y/o stent en 15 pacientes (34,1%: IA-SAIL 21,1% vs IV-SAIL 44.0%; p=0,112). La tasa de transformación hemorrágica sintomática fue del 6.8%. No hubo diferencias significativas a nivel de reperfusión exitosa, seguridad ni pronóstico clínico desfavorable según la vía de administración del tirofiban.

Conclusiones:

La combinación de características basales clínico-radiológicas (ausencia de fibrilación auricular, hábito tabáquico, localización proximal de la oclusión, menor ratio de intensidad de hipo-perfusión y la presencia de calcificaciones arteriales intracraneales sintomáticas) es útil para identificar pre-procedimiento un caso de ICAS-LVO.

Esta estrategia podría permitir anticipar la necesidad de procedimientos de rescate (como la angioplastia y/o el stent intracraneal), así como realizar un procedimiento individualizado y dirigido a la fisiopatología subyacente. En estos casos, la técnica *SAIL* es útil para inducir la recanalización exitosa con el objetivo de evitar y/o preparar la colocación definitiva de un stent intracraneal.

ABSTRACT

Background:

Endovascular treatment (EVT) has become the standard of care for patients presenting with ischemic stroke due to a large-vessel occlusion (LVO). However, the optimal therapeutic strategy for patients with Intracranial Atherosclerosis-related Large Vessel Occlusion (ICAS-LVO) remains uncertain, as it can be challenging and is one of the most common causes of failed recanalization.

Early identification of this etiology before the procedure could lead to individualize EVT strategy and target the underlying pathophysiology. This approach may anticipate the use of mechanical and pharmacological rescue maneuvers to optimize angiographic outcomes and clinical prognosis in this subgroup of patients.

Aim:

To identify clinical and radiological biomarkers of ICAS-LVO available prior to EVT and evaluate their predictive capacity as well as their implications for endovascular therapeutic strategies.

Methods:

First, two retrospective studies were conducted using a prospective database from the Hospital Universitari Vall d'Hebron, which included consecutive patients with ischemic stroke treated with mechanical thrombectomy between 2020 and 2022. Variables associated with the diagnosis of ICAS-LVO and easily identifiable prior to EVT were analyzed. Statistical analysis was performed to evaluate their predictive and prognostic capabilities.

Second, a retrospective study of two European comprehensive stroke centers was conducted, including patients treated with the Stent Retriever Assisted Lysis (SAIL) technique using tirofiban due to suspected ICAS-LVO and/or failed recanalization. Angiographic outcomes and safety were analyzed, with particular focus on mortality rates and symptomatic hemorrhagic transformation.

Statistical analysis was performed using logistic and/or ordinal regression models depending on the nature of the outcome variable.

Results:

In our cohort, the absence of atrial fibrillation (OR 9.33, 95% CI 1.11-78.42; p=0.040), lower hypoperfusion intensity ratio (HIR [Tmax>10s/Tmax>6s], OR 0.69, 95% CI 0.50-0.95; p=0.025), symptomatic intracranial arterial calcification (sIAC, OR 4.15, 95% CI 1.64-26.42; p=0.006), more proximal occlusions (ICA, MCA-M1: OR 4.00, 95% CI 1.23-13.03; p=0.021), and smoking (OR 2.91, 95% CI 1.08-7.90; p=0.035) were associated with the diagnosis of ICAS-LVO. This clinico-radiological model showed good predictive capability for identifying ICAS-LVO (AUC=0.88, 95% CI 0.83-0.94; p<0.001).

Furthermore, symptomatic intracranial arterial calcifications emerged as an independent predictor of failed recanalization (OR 11.89; 95% CI 3.94-35.91; P<0.001), the need for rescue procedures (OR 12.38; 95% CI 2.22-69.09; P=0.004), and poor functional outcomes (mRS≥3; OR 3.51, 95% CI 1.02-12.00; P=0.046).

In 44 patients presenting with ICAS-LVO and/or failed recanalization, the Stent Retriever Assisted Lysis (SAIL) technique with tirofiban was performed. A sustained successful reperfusion rate of 79.5% was achieved, regardless of the administration route of tirofiban (IV-SAIL 80% vs IA-SAIL 78.9%, p=0.932). Rescue procedures, which included angioplasty and/or intracranial stenting, were required in only 15 patients (34.1%: IA-SAIL 21.1% vs IV-SAIL 44.0%; p=0.112). The rate of symptomatic hemorrhagic transformation was 6.8%. No significant differences were observed in terms of successful reperfusion, safety, or unfavorable clinical prognosis between the tirofiban administration routes.

Conclusions:

The combination of baseline clinico-radiological biomarkers (absence of atrial fibrillation, smoking, proximal occlusion location, lower hypoperfusion intensity ratio, and the presence of symptomatic intracranial arterial calcification) is useful for pre-procedural identification of ICAS-LVO.

This strategy could anticipate the need for rescue procedures (such as angioplasty and/or stenting) and lead to a tailored, pathophysiology-driven approach. In these cases, the SAIL technique is effective in achieving successful recanalization, potentially avoiding and/or preparing for definitive intracranial stent placement.

1. INTRODUCCIÓN

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1.1. Generalidades del ictus

El término ictus, del latín "golpe o ataque", se define clásicamente como aquel síndrome clínico caracterizado por la aparición brusca de una afectación neurológica atribuida a un daño neurológico focal, agudo y de origen vascular. Se incluyen el infarto cerebral, la hemorragia intracerebral y la hemorragia subaracnoidea[1].

Con el desarrollo y el uso estandarizado de las técnicas de imagen en el diagnóstico médico del ictus, actualmente se describe como un episodio de disfunción neurológica de topografía cerebral, espinal o retiniana de duración mayor a 24 horas y/o evidencia de infarto cerebral/hemorragia en tomografía computarizada (TC) o resonancia magnética (RM) cerebral[2].

1.1.1. Epidemiología

A pesar de los recientes avances en su manejo (tanto en el ámbito terapéutico como preventivo), el ictus persiste como uno de los principales problemas de salud independientemente de la ubicación geográfica o la etnia.

En 2019, la tasa de incidencia global ajustada por edad fue de 150,8/100.000 habitantes, mientras que la de prevalencia y mortalidad fueron de 1240,3/100.000 y 4,66/100.000 habitantes, respectivamente[3].

Globalmente, el ictus es la segunda causa de mortalidad tras la cardiopatía isquémica[3]. En España, representa la segunda causa de mortalidad (5.3%), siendo la tercera en hombres tras la cardiopatía isquémica y la patología tumoral; y la segunda en mujeres tras la demencia[4].

Además, durante las últimas 3 décadas, los años de vida ajustados por discapacidad relacionados con el ictus han aumentado de forma significativa (de 91,5 millones en 1990 a 125 millones en 2019) debido al envejecimiento, al aumento de la población y al aumento de la exposición a factores de riesgo como un índice de masa corporal elevado, contaminación ambiental, hipertensión arterial sistólica, consumo de alcohol, sedentarismo, insuficiencia renal y aumento de la temperatura ambiente[3, 5].

Un estudio reciente estima que, en el año 2047, en Europa, la incidencia crecerá un 3% y la prevalencia un 27% debido al envejecimiento de la población y a la reducción de la mortalidad[6].

Según la naturaleza de la lesión subyacente al ictus, se clasifica como:

- **Isquémico**: se produce una interrupción permanente o transitoria del flujo sanguíneo cerebral, habitualmente arterial.
- **Hemorrágico**: se produce una extravasación de sangre a nivel intracraneal secundaria a la rotura de un vaso sanguíneo arterial o venoso. Se incluyen el hematoma intraparenquimatoso, la hemorragia intraventricular y subaracnoidea.

El último reporte de "The Global Burden of Diseases, Injuries, and Risk Factors Study" describe a nivel global la siguiente distribución de casos incidentes de ictus: isquémico (62.4%), hemorragia intracerebral (27.9%) y hemorragia subaracnoidea (9.7%). Dicha distribución se modifica según la economía, siendo la hemorragia intracerebral más incidente en países con ingresos medios/bajos (29,5% frente a 15,8%) y la hemorragia subaracnoidea en países con ingresos altos (19,7% frente a 7,9%)[3].

Debido a que la presente tesis doctoral se focaliza en el ictus isquémico relacionado con la ateromatosis intracraneal (ICAD), de aquí en adelante nos centraremos en el ictus isquémico.

1.1.2. Etiopatogenia del ictus isquémico

A nivel biológico, el ictus isquémico está causado por la interrupción del flujo sanguíneo cerebral secundaria a una oclusión vascular que conlleva isquemia focal en el territorio del parénquima cerebral irrigado por dicho vaso sanguíneo. Si la isquemia es prolongada, se producen procesos de inflamación y citotoxicidad, que conllevan necrosis tisular y daño neuronal irreversible y, por tanto, al infarto cerebral[7, 8].

La etiopatogenia del ictus isquémico es heterogénea debido a que la oclusión vascular se puede producir por múltiples causas. Habitualmente, se utiliza el sistema de clasificación TOAST (Trial of ORG 10172 in Acute Stroke Treatment) para agrupar los distintos subtipos etiológicos del ictus isquémico[9-11]:

- **Cardioembólico** (20%): causado por un embolismo proveniente de la cavidad cardíaca. La causa más frecuente es arrítmica (fibrilación o *flutter* auricular), estructural (acinesia apical, miocardiopatía dilatada) y/o valvular (trombosis valvular, estenosis mitral significativa).
- **Aterotrombótico** (25%): causado por la estenosis (>50%) u oclusión de la

arteria carótida, vertebral o de la circulación intracraneal de presumible origen ateromatoso.

- **Lacunar** (25%): causado por la oclusión de una arteria perforante que irriga un territorio cerebral pequeño (<2cm) de origen microangiopático (lipohialinosis).

- **Causa infrecuente** (5%): engloba aquellas etiologías raras de ictus isquémico. Se incluyen vasculopatías no ateroscleróticas, estado protrombótico y de hipercoagulabilidad, disección arterial, trombosis venosa cerebral y alteraciones metabólicas, entre otras.

- **Etiología indeterminada** (25%): se incluyen aquellos ictus isquémicos en los que no se ha logrado completar el estudio y aquellos en los que tras un estudio exhaustivo presentan más de una causa probable o son de causa desconocida.

1.2. Diagnóstico en fase aguda

1.2.1. Clínica

El diagnóstico inicial del ictus es clínico y se basa en la exploración neurológica y la cronología de aparición de la sintomatología.

Con el objetivo de establecer la severidad del ictus con fiabilidad intra e inter-explorador, se usa la escala NIHSS (National Institutes of Health Stroke Scale), que mediante 15 ítems y hasta un máximo de 42 puntos, estratifica el deterioro neurológico del paciente[12, 13].

Además, la clasificación Oxfordshire Community Stroke Project (OCSP) permite la identificación precoz de la topografía vascular cerebral afecta mediante criterios únicamente clínicos[14].

Con el desarrollo del tratamiento endovascular, la escala NIHSS y la clasificación OCSP son de gran utilidad para predecir la necesidad del tratamiento.

1.2.2. Neuroimagen

Los biomarcadores de neuroimagen mediante TC y/o RM son una herramienta indispensable en el proceso diagnóstico del ictus isquémico. Por una parte, la neuroimagen permite descartar la presencia de una hemorragia intracraneal y situaciones clínicas que simulan la presentación clínica de un ictus (*mimics*), Por otra parte, permite objetivar signos precoces de isquemia cerebral y la oclusión vascular, siendo de gran utilidad para la selección de pacientes candidatos a tratamiento de reperfusión.

1.2.3. Tomografía computarizada

La TC es el estudio de elección en la mayoría de centros debido a su disponibilidad y su rapidez de adquisición, lo que permite disponer de un diagnóstico preciso en el menor tiempo posible.

Existen distintas técnicas de TC para obtener una imagen cerebral completa: tanto del parénquima cerebral, como de la circulación arterial intracraneal y la perfusión tisular[15].

La TC craneal sin contraste permite la visualización del parénquima cerebral. Durante las primeras horas de evolución de un ictus se producen cambios radiológicos que sugieren isquemia precoz. Entre ellos se incluyen la pérdida del ribete insular, la pérdida de diferenciación cortico-subcortical, la atenuación del parénquima cerebral afecto y el borramiento de los surcos corticales[16].

Para la interpretación de los signos isquémicos precoces de forma estandarizada en el territorio de la arteria cerebral media (ACM) se desarrolló el Alberta Stroke Programme Early CT Score (ASPECTS)[17]. Se evalúan 10 regiones cerebrales con la sustracción de 1 punto por cada región afecta, siendo 10 la puntuación máxima en la que no se objetivan cambios isquémicos (Figura 1). Paralelamente, se ha desarrollado y validado la escala pcASPECTS para la evaluación del territorio de la circulación posterior[18].

Además, se pueden objetivar biomarcadores sugestivos de oclusión arterial (hiperdensidad en la localización de la oclusión o *dot sign)* y/o de la etiología subyacente (calcificaciones arteriales intracraneales)[19-23].

La angiografía por TC (angioTC) se utiliza para localizar la oclusión, estenosis u otras anomalías vasculares tanto de los troncos supraaórticos como de la circulación intracraneal de forma no invasiva. Precisa de la administración de contraste yodado[15, 24]. Además, se puede realizar un estudio multifásico con el que se logra una mayor detección de oclusión arterial, una caracterización más precisa del grado de colateralidad y una mayor fiabilidad interevaluadores[25-27].

Por último, el estudio de TC perfusión permite valorar la viabilidad del tejido cerebral isquémico (identificación del área de penumbra) y la hemodinámica cerebral mediante la adquisición repetida de imágenes tras la administración del contraste yodado. Se obtienen mapas cuantitativos según el tiempo de pase del contraste y la concentración alcanzada, que se correlacionan de forma directa con la perfusión cerebral[15].

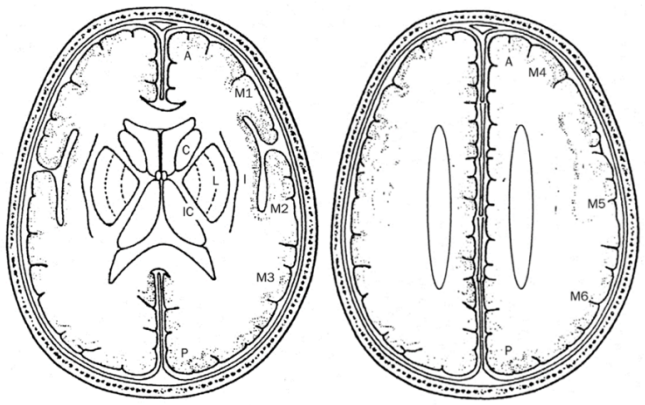

Figura 1. Áreas del parénquima cerebral valoradas en la escala ASPECTS.

Las áreas M1-6 representan el territorio cortical de la ACM. Mientras que el territorio profundo está representado por L (núcleo lenticular), I (ínsula), IC (cápsula interna) y C (caudado).

Adaptada de Barber PA, et al[17]

Según las guías clínicas actuales se recomienda realizar el estudio de imagen en un tiempo <20 minutos desde la llegada del paciente al hospital. Además, se recomienda la administración del tratamiento trombolítico (en los casos en los que se encuentra indicado) tras la realización inicial del TC craneal sin contraste[28].

1.2.4. Resonancia magnética

La RM es más sensible que el TC para la detección de isquemia cerebral en fases más precoces, así como de lesiones de pequeño tamaño y en territorio vertebrobasilar[29].

Sin embargo, tiene una disponibilidad limitada debido a su mayor coste, su mayor duración de exploración y su contraindicación de uso en los pacientes con cuerpos extraños metálicos o dispositivos implantables de primera generación.

Para la evaluación de la penumbra isquémica se usa el *mismatch* Fluid-Attenuated Inversion Recovery - Diffusion-weighted imaging (FLAIR-DWI). Esto es debido a que la secuencia DWI puede detectar isquemia durante los primeros minutos, mientras que las alteraciones isquémicas aparecen a las 6-7 horas en la secuencia FLAIR. En la secuencia DWI, el edema citotóxico y la pérdida de canales de aquoporina-4 que suceden durante los primeros instantes de un ictus isquémico producen una restricción de la difusión de agua en el tejido cerebral afecto, generando una señal hiperintensa en dicha secuencia.

La RM, además, proporciona información sobre la etiología subyacente: lesiones multiterritoriales o corticales sugieren un origen cardioembólico y lesiones en territorio frontera sugieren un origen aterotrombótico por estenosis e hipoperfusión distal.

En casos seleccionados (alergia grave al contraste yodado) puede realizarse un estudio con gadolinio para la evaluación de la circulación intracraneal y la detección de oclusión (angiografía por RM, angioRM), así como estudios de perfusión cerebral (RM perfusión) con la obtención de mapas cuantitativos similares a los obtenidos en el estudio TC perfusión.

Sin embargo, su mayor duración de adquisición y su escasa disponibilidad en fase aguda, relegan su uso en la mayoría de los centros al estudio etiológico una vez pasada la fase hiperaguda del ictus.

1.3. Tratamiento hiperagudo del ictus isquémico

El objetivo del tratamiento del ictus isquémico en fase hiperaguda consiste en obtener la recanalización de la arteria ocluida en el menor tiempo posible, ya que la magnitud del beneficio clínico depende directamente del tiempo en el que se restablece la circulación cerebral[30].

Actualmente, existen dos tratamientos no excluyentes que se consideran el estándar de tratamiento: el tratamiento trombolítico intravenoso y el tratamiento endovascular (TEV)[28, 31, 32].

El tratamiento endovascular es un procedimiento mínimamente invasivo en el que a través de un conjunto de catéteres y dispositivos endovasculares se accede hasta la oclusión arterial y se realizan distintas maniobras mecánicas y/o farmacológicas para la extracción o lisis del trombo.

1.4. Tratamiento trombolítico

El primer uso documentado del tratamiento trombolítico intravenoso en el ictus es del año 1958[33]. No obstante, el cambio en el paradigma del tratamiento del ictus sucedió en 1992, cuando se publicaron dos estudios pilotos[34, 35] sobre el uso precoz del activador tisular del plasminógeno recombinante (alteplasa o rtPA), y en 1995, cuando se publicó el primer ensayo clínco aleatorizado (National Institute of Neurological Disorders and Stroke tissue-type plasminogen activator - NINDS tPA trial[36]) que demostró que su administración a dosis de 0.9mg/kg durante las primeras 3 horas de evolución mejoraba el pronóstico clínico a los 90 días a pesar de una mayor tasa de transformación hemorrágica (TH). Los resultados de este ensayo clínico motivaron la aprobación del rtPA durante las primeras 3 horas por parte de la *Food and Drug Administration* (FDA) en Estados Unidos.

De forma paralela, a nivel europeo, se realizaron 3 ensayos clínicos en la ventana 0-6 horas (ECASS[37], ECASS II[38], ATLANTIS[39]) que pese a ser técnicamente neutros en el objetivo primario, sugerían una clara tendencia a favor del tratamiento trombolítico.

Finalmente, tras el estudio observacional SITS-MOST[40] (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) se aprobó en Europa en 2007 el uso del rtPA administrado en las primeras 3 horas desde el inicio de los síntomas. Posteriormente, el ECASS III[41] y un meta-análisis con datos individuales de participantes[42] confirmó el beneficio clínico del tratamiento intravenoso con rtPA durante las primeras 4,5 horas (modified Rankin Scale [mRS] score 0-1 41.8% vs. 34.8%) y estableció el aumento del riesgo de mortalidad con el retraso del tratamiento.

En paralelo al desarrollo del TEV, se han realizado diversos ensayos clínicos para ampliar la ventana terapéutica del rtPA. Entre ellos, el WAKE-UP[43] (Efficacy and Safety of MRI- Based Thrombolysis in Wake-Up Stroke) en 2018 mediante la evaluación del *mismatch* DWI-FLAIR durante las primeras 24 horas desde el inicio del ictus; y el EXTEND[44] (Extending the Time for Thrombolysis in Emergency Neurological Deficits) en 2019 mediante la evaluación de mismatch en TC/RM perfusión hasta las 9 horas de evolución. Debido a ello, en el año 2021, se actualizaron las guías europeas del tratamiento trombolítico intravenoso[31].

La tenecteplasa (TNK), fármaco modificado genéticamente con mayor resistencia al inhibidor del activador del plasminógeno 1, mayor especificidad por la fibrina y vida media más larga; ha sido estudiada como alternativa a la alteplasa debido a su mayor facilidad de administración (bolus único) y menor coste[45].

Recientemente, los ensayos clínicos AcT[46] (Intravenous Tenecteplase Compared With Alteplase for Acute Ischaemic Stroke in Canada), TRACE-2[47] (Tenecteplase Versus Alteplase in Acute Ischemic Cerebrovascular Events-2), y ATTEST-2[48] (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis-2) han confirmado la no inferioridad de la TNK frente a rtPA en el ictus isquémico de menos de 4,5 horas de evolución a dosis de 0.25mg/kg en términos de eficacia y seguridad. No obstante, dosis superiores (0.4mg/kg) conllevan un peor pronóstico con mayor tasa de TH y muerte[49].

Las guías europeas del año 2023 recomiendan el uso alternativo de TNK 0.25mg/kg frente a rtPA. Asimismo, se recomienda el uso preferente de TNK frente

a rtPA en pacientes con oclusión de gran vaso candidatos a TEV[50].

Sin embargo, como limitaciones, el tratamiento trombolítico presenta contra-indicaciones importantes (cirugía reciente, tumor cerebral, antecedente de hemorragia grave, etc.) y su uso en ventana ampliada requiere de imagen avanzada, lo que limita su disponibilidad. Además, la tasa de reca-nalización en oclusión proximal es baja (10,9% en la arteria carótida interna - ACI, 21,6% en ACM segmento M1), aumentando en oclusiones más distales (42.5% en ACM-M3, arteria cerebral anterior - ACA, y poste-rior - ACP)[51] sin llegar a superar el 50%.

Aunque en la mayoría de escenarios el tratamiento trombolítico es seguro y eficaz, recientemente se ha descrito en el estudio TEMPO-2[52] (Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion) la ausencia de beneficio y posible aumento del riesgo de muerte del tratamiento con TNK en pacientes que presentan un ictus minor no discapacitante con oclusión intracraneal.

1.5. Tratamiento endovascular

El TEV es actualmente el tratamiento de elección en el ictus isquémico con oclusión de gran vaso (OGV)[28, 32].

Si bien los primeros estudios del TEV en el ictus isquémico se inician a partir del año 1999, no fue hasta el año 2015 cuando se estableció la eficacia de dicha modalidad de tratamiento. Su evolución en los últimos 10 años ha permitido expandir la población de pacientes candidatos a TEV, y, por tanto, que se benefician clínicamente de su realización.

Habitualmente la recanalización exitosa se ha definido como una puntuación en la escala eTICI[53] (extended Thrombolysis in Cerebral Infarction, tabla 3) ≥ 2b. No obstante, diversos estudios sugieren considerar la recanalización completa (puntuación eTICI≥2c) como objetivo de la TM debido a que se ha asociado a una mayor probabilidad de obtener un beneficio funcional[54].

1.5.1. Desarrollo cronológico inicial

Los primeros estudios del TEV se enfocaron en la administración intraarterial de fármacos trombolíticos. En 1998 y 1999, en los estudios PROACT[55] y PROACT II[56], se evaluó la eficacia de prourokinasa intra-arterial frente a placebo en pacientes con menos de 6 horas de evolución y oclusión en el segmento ACM-M1. A pesar de objetivar un aumento en la tasa de recanalización y de independencia funcional a los 90 días, no se logró su aprobación y

tampoco su uso estandarizado en la práctica clínica real.

A partir de los años 2000, se desarrollaron dispositivos endovasculares específicos con el objetivo de atrapar y extraer el trombo de forma mecánica. El primer dispositivo autorizado por la FDA fue el MERCI Retriever® (Mechanical Embolus Removal in Cerebral Ischemia) en el año 2004 debido a los resultados de dos estudios no aleatorizados en los que se observó una tasa de recanalización del 46-57%, una tasa de buen pronóstico neurológico (mRS 0-2) del 36-46% y una tasa de complicaciones clínicamente significativas del 5,5-7,1%[57, 58]. Posteriormente, se desarrollaron dispositivos de segunda generación con el objetivo de extraer el trombo mediante aspiración. En el año 2008, se autorizó el principal dispositivo de aspiración llamado Penumbra System®.

Sin embargo, los dispositivos SR que supusieron el primer cambio de paradigma en el ictus isquémico fueron los de tercera generación:

- Solitaire Flow Restoration Device®: frente al TEV realizado con el MERCI Retriever, logró una mayor tasa de recanalización (61% vs 24%), de independencia funcional (58% vs 33%) y menor mortalidad (17% vs 38%)[59].
- Trevo Retriever®: también frente al MERCI Retriever, mostró una mayor tasa de recanalización (86% vs 60%) y de independencia funcional (40% vs 22%)[60].

1.5.2. Ensayos clínicos en circulación anterior

En el contexto de los resultados de los estudios previos, en el año 2013 se publicaron 3 ensayos clínicos que evaluaron la eficacia y seguridad del TEV frente al tratamiento trombolítico con resultados negativos. Fueron el IMS-III[61] (Interventional Management of Stroke III), SYNTHESIS Expansion[62] y MR RESCUE[63] (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy).

A pesar de la controversia y decepción que generaron estos 3 estudios en la comunidad científica, en el análisis crítico de su metodología se observaron distintas deficiencias que permitieron un mejor diseño de los estudios aleatorizados posteriores.

Por una parte, en la gran mayoría de pacientes se usaron técnicas y dispositivos de segunda generación que lograron una tasa de recanalización inferior a la esperada (27-44%).

Por otra parte, los criterios de inclusión tanto radiológicos como clínicos, así como el retraso terapéutico y la inclusión de centros con escasa experiencia, diluyeron el efecto del tratamiento endovascular.

En 2015 y 2016, se publicaron los 6 ensayos clínicos que cambiaron de forma definitiva el paradigma del TEV en el manejo hiperagudo del ictus isquémico: MR CLEAN[64] (Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands), ESCAPE[65] (The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times), EXTEND-IA[66] (Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial), SWIFT-PRIME[67] (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment), REVASCAT (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)[68] y THRACE[69] (THRombectomie des Artères CErebrales). Sus características se encuentran resumidas en la Tabla 1.

Tabla 1. Comparación de las principales características y resultados de los seis ensayos clínicos que establecieron la eficacia del tratamiento endovascular en el ictus isquémico de circulación anterior.

Nombre del estudio	Tamaño muestral	Tiempo de evolución	Criterios de inclusión	mRS 0-2 90 días	TH sintomática	Mortalidad
MR CLEAN	500	6h	Edad ≥ 18 años NIHSS ≥ 2	32,6% vs 19,1%	7,7% vs 6,4%	21% vs 22%
ESCAPE	315	12h	Edad ≥ 18 años NIHSS ≥ 2 ASPECTS 6-10	53% vs 29,3%	3,6% vs 2,7%	10,4 vs 19%
EXTEND-IA	70	6h	Edad ≥ 18 años TC perfusión	71% vs 40%	0% vs 6%	9% vs 20%
SWIFT-PRIME	196	4,5h	Edad 18-80 años NIHSS 8-30 ASPECTS 6-10	60% vs 35%	0% vs 3%	9% vs 12%
REVASCAT	206	8h	Edad 18-80 años NIHSS ≥ 6 ASPECTS 7-10	43,7% vs 28,2%	1,9% vs 1,9%	18,4% vs 15,5%
THRACE	414	5h	Edad 18-80 años NIHSS 10-25	53% vs 42%	2% vs 2%	12% vs 13%

mRS, modified Rankin Scale; TH, Transformación hemorrágica; NIHSS, National Institute of Health Stroke Scale.

El metaanálisis HERMES[70] (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials), que incluyó los 5 primeros ensayos clínicos, confirmó la eficacia del TEV en el ictus isquémico con oclusión proximal de circulación anterior y ventana temporal precoz, independientemente de las características del paciente y la geografía del mismo. El TEV se asoció a una mayor tasa de independencia funcional (46% vs 26,5%) con un número de pacientes necesario a tratar para reducir al menos en un nivel de puntuación de la mRS de 2,6.

Una vez establecida la eficacia del TEV en pacientes con menos de 6 horas de evolución, los ensayos clínicos DAWN[71] (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) y DEFUSE-3[72] (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) publicados en 2018 ampliaron la ventana terapéutica hasta las 24 horas mediante la selección de pacientes basada en el TC/RM perfusión y la presencia de penumbra isquémica.

Todo esto conllevó la modificación de las guías de práctica clínica[28, 32] (tanto de la American Heart Association como de la European Stroke Organisation), estableciendo el TEV como tratamiento de elección (recomendación clase I, nivel de evidencia A) en pacientes con un ictus isquémico con OGV (ACI terminal, ACM-M1) de circulación anterior que cumplen los siguientes criterios: mRS 0-1, NIHSS≥6, edad≥18, ASPECTS≥6 y se presenten en la ventana precoz (0-6h) o en la ventana extendida (6-24h) si cumplen los criterios de selección descritos en los ensayos:

- **DAWN** (6-24h): discordancia clínico-radiológica mediante la edad, la puntuación NIHSS y el volumen de isquemia cerebral medido de forma automatizada con un software de TC/RM perfusión.
- **DEFUSE-3** (6-16h): núcleo isquémico (core)<70ml, volumen de tejido salvable>15ml y ratio>1,8 mediante TC/RM perfusión.

1.5.3. Ensayos clínicos en circulación posterior

Pese a que el ictus isquémico secundario a una oclusión de la arteria basilar representa aproximadamente un 10% de todos los ictus con OGV y conlleva un pronóstico infausto[73], los ensayos clínicos previos no incluían este subgrupo de pacientes. En la mayoría de centros, debido al beneficio del TEV en OGV de circulación anterior y con la recomendación de

consenso de expertos, se utilizaban los criterios de selección de pacientes de los ensayos clínicos previamente mencionados para la trombectomía en pacientes con oclusión de la arteria basilar.

Por este motivo, se llevaron a cabo dos ensayos clínicos en 2020 (BEST[74] - Basilar Artery Occlusion Endovascular Intervention versus Standard Medical Treatment) y 2021 (BASICS[75] - Basilar Artery International Cooperation Study).

No obstante, ninguno de los dos estudios fue capaz de mostrar un beneficio clínico (puntuación mRS 0-3 a los 90 días) de la trombectomía frente al tratamiento estándar, probablemente debido a un lento reclutamiento y a una elevada tasa de cruce entre ambas ramas de tratamiento.

En el año 2022 se publican los ensayos clínicos ATTENTION[76] (Endovascular Treatment for Acute Basilar-Artery Occlusion) y BAOCHE[77] (Basilar Artery Occlusion Chinese Endovascular) que demuestran una mayor tasa de buen pronóstico clínico del TEV (mRS 0-3 46-46,4% vs 22,8-24,3%) a pesar de un aumento de las complicaciones y de transformación hemorrágica.

Finalmente, sumando la evidencia de un metaanálisis de los 4 ensayos clínicos[78], se recomienda (clase I, nivel de evidencia B) la trombectomía mecánica (TM) en aquellos pacientes con oclusión de la arteria basilar que se presentan dentro de las primeras 12 horas con una puntuación NIHSS≥6, pc-ASPECTS≥6 y una edad entre 18 y 89 años, siendo razonable además su consideración en pacientes con una evolución hasta 24 horas (clase IIa, nivel de evidencia B)[79]. En agosto de 2024, se incluyó en las guías de práctica clínica europeas ESO-ESMINT únicamente la indicación en ictus severo (NIHSS≥10)[80].

1.5.4. Ensayos clínicos en ictus isquémico de gran volumen

Tradicionalmente, aquellos pacientes con un ictus isquémico de gran volumen (ASPECTS 0-5 y/o núcleo isquémico en TC perfusión >70mL) han sido excluidos como candidatos a la TM debido a la creencia de una eficacia disminuida por la presencia de tejido cerebral inviable y a un potencial efecto dañino debido a un aumento del riesgo hemorrágico. No obstante, en los últimos años, se ha estudiado un potencial beneficio del TEV en estos pacientes debido a la:

- Heterogeneidad del núcleo isquémico: dentro de lo que se presuponía infarto establecido, existen zonas entremezcladas de tejido viable[81]

- Potencial reducción del edema citotóxico mediante el aclaramiento de toxinas y el efecto sobre la inflamación[82].

Entre los años 2022 y 2024 se han publicado hasta 6 ensayos clínicos que confirman la eficacia del TEV en el ictus isquémico de gran volumen durante las primeras 24 horas de evolución.

El primero de ellos fue el RESCUE-Japan LIMIT[83] (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial) y posteriormente surgieron el ANGEL-ASPECT[84] (Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core), SELECT2 (Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke), LASTE[85] (Large Stroke Therapy Evaluation), TENSION[86] (The Efficacy and Safety of Thrombectomy in Stroke with extended lesion and extended time window) y TESLA[87] (The Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke).

El meta-análisis con datos individuales de pacientes MAGNA (MechanicAl thrombectomy for larGe braiN infArctions), todavía pendiente de publicación, presentó los resultados preliminares en los que el TEV frente al tratamiento estándar se asocia a una mayor tasa de independencia funcional (mRS 0-2 23% vs 9%, aRR 2.62 [2.31-2.97], p<0.001) y de deambulación autónoma (mRS 0-3 41% vs 24%, aRR 1.76 [1.30-2.38], p<0.001), sin objetivarse un aumento de la mortalidad (27% vs 28%) ni de la tasa de TH sintomática (1,8% vs 1,6%).

Únicamente en la cohorte de pacientes con núcleo isquémico extendido (>150mL), el TEV no se asoció de forma estadísticamente significativa a un mejor pronóstico.

Sin embargo, los resultados preliminares no incluían los datos de los estudios TENSION, TESLA y LASTE (ensayo clínico con mayor número de paciente con núcleo isquémico >150mL), por lo que este grupo se encuentra infrarrepresentado y el meta-análisis todavía carece de poder estadístico suficiente para detectar diferencias significativas dentro de esta categoría específica[88].

En febrero de 2024 se ha publicado una actualización en la que se recomienda el TEV durante las primeras 24 horas desde el inicio de los síntomas en aquellos pacientes con OGV de circulación anterior que cumplen los criterios de inclusión de los ensayos clínicos RESCUE-Japan LIMIT, ANGEL-ASPECT, SELECT2 y TESLA (clase I, nivel de evidencia A)[89]. Sin embargo, aún no se ha incluido en las guías de práctica clínica[28, 32].

Tabla 2. Comparación de las principales características y resultados de los seis ensayos clínicos que establecieron la eficacia del tratamiento endovascular en el ictus isquémico de circulación anterior de gran volumen.

Nombre del estudio	Tamaño muestral	Tiempo de evolución	Criterios de inclusión	mRS 0-3 90 días	TH sintomática	Mortalidad
RESCUE-Japan LIMIT	203	6h	ASPECTS 3-5 (86.2% RM) ACI, ACM-M1	31% vs 12,7%	9% vs 4,9%	18% vs 23,5%
ANGEL-ASPECT	456	24h	ASPECTS 3-5 y/o Core 70-100mL (TC perfusión) ACI, ACM-M1	47% vs 33,3%	6,1% vs 2,7%	21,7 vs 20%
SELECT2	352	24h	ASPECTS 3-5 y/o Core >50mL (TC perfusión) ACI, ACM-M1	37,9% vs 18,7%	0,6% vs 1,1%	38,4% vs 41,5%
TESLA	300	24h	ASPECTS 2-5 ACI, ACM-M1	30% vs 20%	4,0% vs 1,3%	35,3% vs 33,3%
TENSION	253	12h	ASPECTS 3-5 (17,8% RM) ACI, ACM-M1	31% vs 13%	5% vs 5%	40% vs 51%
LASTE	333	7h	ASPECTS 0-5 (83,6% RM) ACI, ACM-M1, ACM-M2	33,5% vs 12,2%	9,6% vs 5,7%	36,1% vs 55,5%

mRS, modified Rankin Scale; TH, Transformación hemorrágica; ASPECTS, Alberta Stroke Programme in Early CT Score; RM, Resonancia Magnética; ACI, Arteria Carótida Interna; ACM, arteria cerebral media.

1.5.5. Limitaciones

A pesar de que la evidencia del TEV se ha establecido en la mayoría de escenarios clínicos del ictus isquémico y la población tributaria de TM se ha expandido de forma considerable durante los últimos 10 años (Figura 2), todavía quedan situaciones clínicas en las que existen áreas de incerteza sobre la eficacia del tratamiento endovascular:

- **Acceso global a la trombectomía**: no obstante, el principal obstáculo para el TEV es la disponibilidad escasa y la curva de aprendizaje en zonas con menor desarrollo económico. Un estudio realizado en 75 países en 2020 mostró que únicamente un 2,8% del conjunto de ictus isquémico tenían acceso a la TM, con una disparidad de 460 veces entre las regiones de más y menor ingreso económico[90].

Por tanto, se necesitan esfuerzos y cooperación globales que optimicen el sistema de atención del ictus y reduzcan la disparidad de acceso a la TM y otros tratamientos con beneficio clínico establecido.

- **Trombectomía en ictus minor (NIHSS <6)**: aproximadamente un 21-22% de los pacientes se presentan con una puntuación NIHSS <6 y un 25% de ellos presentan una oclusión intra o extracraneal[91].

  Actualmente se están realizando dos ensayos clínicos que analizan la eficacia del TEV en este subgrupo de pacientes: MOSTE (Minor Stroke Therapy Evaluation, NCT03796468) y ENDOLOW (Endovascular Therapy for Low NIHSS Ischemic Strokes, NCT04167527).

- **Trombectomía en oclusiones medias y distales**: aproximadamente un 25-40% de los pacientes con un ictus isquémico presentan una oclusión de un vaso medio (se incluye ACM-M2 no dominante, M3, ACP y ACA)[92]. A pesar de que generalmente presentan una evolución más favorable que aquellos pacientes con una OGV, el pronóstico con el tratamiento médico estándar sigue sin ser óptimo (recanalización del 40% aproximadamente con rtPA)[51]. Diversos estudios retrospectivos multicéntricos no han logrado mostrar diferencias significativas en el pronóstico frente al tratamiento médico[93, 94].

  Por este motivo, durante los últimos años se han iniciado hasta 6 ensayos clínicos para estandarizar y optimizar su manejo terapéutico: ESCAPE-MeVO (Endovascular Treatment to Improve Outcomes for Medium Vessel Occlusions, NCT05151172), DISCOUNT (Evaluation of Mechanical Thrombectomy in Acute Ischemic Stroke Related to a Distal Arterial Occlusion, NCT05030142), DISTAL (DISTAL, Endovascular Therapy Plus Best Medical Treatment Versus BMT Alone for Medium Vessel Occlusion Stroke, NCT05029414), DISTALS (Distal Ischemic Stroke Treatment With Adjustable Low-Profile Stent-triever, NCT05030142), FRONTIER-AP (Clinical Outcome and Safety of Endovascular Versus Standard Medical Therapy for Stroke With Medium Sized Vessel Occlusion, 12621001746820p) y DUSK (endovascular versus medical management in Distal Medium Vessel Occlusion Stroke, NCT05983757).

- **Trombectomía en pacientes con discapacidad previa**: los pacientes con una puntuación mRS>2 han sido clásicamente excluidos de los estudios de TEV. No obstante, aunque excepcionalmente se plantea el tratamiento en pacientes con muy alto grado de discapacidad (mRS 5), existe cierta evidencia de estudios observacionales en los se sugiere que pacientes con mRS 3 podrían beneficiarse de la TM[95]. Se estima que aproximadamente un 30% de los pacientes presentan discapacidad premórbida al ictus[95].

  En este contexto, el ensayo clínico TESTED (Treatment With Endovascular Intervention for Stroke Patients With Existing Disability) se encuentra en la fase inicial de inclusión de pacientes con una puntuación mRS 3-4.

- **Medidas de rescate en pacientes con trombectomía fallida**: a pesar de los avances en las técnicas y dispositivos de TM, así como la mayor experiencia adquirida, en el 10-20% de los casos no se logra una recanalización exitosa (Figura 3)[96, 97].

  En la mayoría de las ocasiones, la causa es una oclusión relacionada con ateromatosis intracraneal. Otras causas del fracaso en la recanalización son dificultades de acceso secundarias a la anatomía vascular y/o alteraciones intracraneales (disección arterial, trombo de consistencia dura, tortuosidad arterial o complicaciones intra-procedimiento como vasoespasmo y perforación).

  En estos casos, durante los últimos años se plantean distintas estrategias de rescate como la realización de angioplastia, la colocación de un stent intracraneal o la administración de fármacos adyuvantes (bien trombolíticos o antiagregantes de administración endovenosa/intra-arterial y efecto rápido como los inhibidores de la proteína GPIIb-IIIa) con resultados prometedores en estudios retrospectivos observacionales[98, 99].

  El registro RESCUE-ICAS (Registry of Emergent Large veSsel oCclUsion duE to IntraCranial AtherosclerosiS, NCT05403593) y el estudio ReSET (Rescue Stenting for Failed Endovascular Thrombectomy in Acute Ischemic Stroke, NCT03993340) aportarán nuevos datos próximamente.

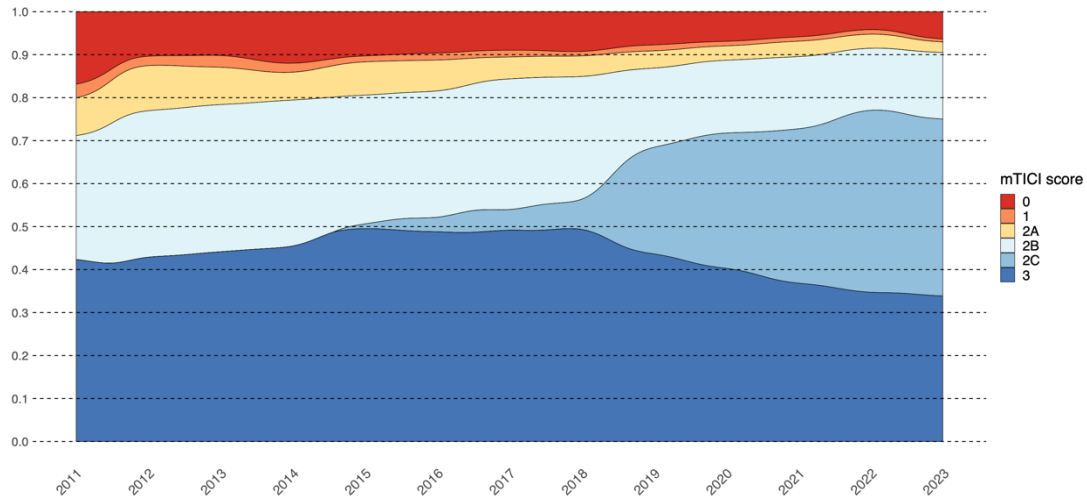

Figura 3. Evolución temporal del resultado angiográfico según la puntuación de la escala modified Thrombolysis in Cerebral Infarction (mTICI)

Datos obtenidos a partir del Registro de Código Ictus de Cataluña (CICAT).

1.6. Ictus isquémico agudo relacionado con ateromatosis intracraneal

La ateromatosis intracraneal (ICAD) es una causa mayor de ictus isquémico, con una prevalencia total del 10-40%.

Su incidencia se modifica según la geografía y etnia (aproximadamente 40% en pacientes asiáticos, 30% en pacientes afroamericanos y 10% en pacientes caucásicos) y según la presencia de factores de riesgo vascular, como el tabaquismo y la edad avanzada[100].

En cuando a su fisiopatología, los mecanismos causales de ictus en contexto de una estenosis intracraneal son múltiples (Figura 4)[101]:

- **Rotura e inestabilidad de la placa ateromatosa**: se produce cuando se fragmenta el endotelio y el material trombogénico queda expuesto en el torrente sanguíneo. La formación del trombo en la superficie intraluminal puede generar una oclusión en el lugar de la estenosis (1) o bien puede producirse una embolización a un territorio distal (2).

- **Crecimiento progresivo de la placa**: la disminución del calibre arterial secundario al crecimiento de la placa y la gravedad de la estenosis puede producir un ictus hemodinámico secundario a hipoperfusión distal (3), que puede empeorar en contexto de hipotensión o hipovolemia, entre otros.

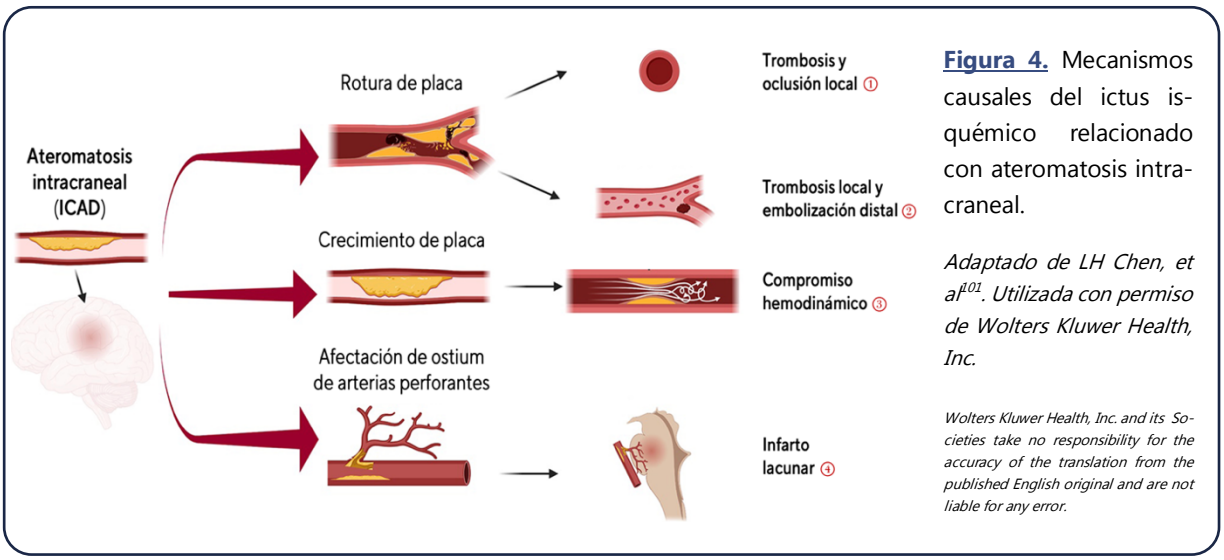

Figura 4. Mecanismos causales del ictus isquémico relacionado con ateromatosis intracraneal.

Adaptado de LH Chen, et al[101]. Utilizada con permiso de Wolters Kluwer Health, Inc.

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- **Afectación del ostium de las arterias perforantes**: el fenómeno de hiperplasia intimal y remodelado vascular que ocurre en la ICAD puede producir una oclusión a nivel del ostium de una arteria perforante, produciendo un ictus con características clínicas y radiológicas de origen lacunar (4).

Centrándonos en aquellos pacientes que presentan una OGV, el ictus relacionado con ateromatosis intracraneal (ICAS-LVO) se presenta con una incidencia estimada entre el 8-10% en Estados Unidos y Europa, con un claro predominio en Asia donde puede alcanzar el 40-48%.

1.6.1. Diagnóstico de ICAS-LVO

En el momento actual, el diagnóstico de ICAS-LVO requiere la presencia de una estenosis intracraneal >50% de presumible origen aterosclerótico y/o la documentación de un compromiso hemodinámico secundario a una reducción significativa del flujo anterógrado en el territorio distal evaluadas tras lograr la recanalización del vaso inicialmente afecto[100, 102, 103].

Debido a que existen otras causas de estenosis intracraneal, como un trombo parcialmente recanalizado, disección arterial intracraneal, vasculitis infecciosa o inflamatoria, vasoespasmo o el síndrome de vasoconstricción cerebral reversible, el diagnóstico de ICAS-LVO puede requerir un estudio diagnóstico completo con el estudio de fuentes embólicas y resultar complejo en la práctica clínica habitual, especialmente durante la fase hiperaguda.

Por tanto, el diagnóstico depende mayoritariamente de las características de neuroimagen y se puede diferenciar en 3 fases: pre-procedimiento, intraprocedimiento y en fase subaguda.

- **Pre-procedimiento**: no existe una definición estandarizada debido a que en la fase hiperaguda en la mayoría de ocasiones no se puede objetivar la estenosis debido a la oclusión del mismo segmento arterial. No obstante, durante los últimos años, con el desarrollo de las técnicas de imagen y su uso para guiar el tratamiento endovascular, se han estudiado distintas características que permiten sospechar una estenosis subyacente. Por ejemplo, se sugiere que los parámetros automatizados de TC perfusión asociados con un buen estado de la circulación colateral, así como las calcificaciones arteriales intracraneales, están asociadas con ICAS-LVO[104-106].

- **Intra-procedimiento**: la arteriografía por sustracción digital es la técnica *gold standard* para la visualización de la luz vascular. Por tanto, durante la TM se pueden objetivar distintos signos sugestivos de ICAS-LVO, como la oclusión del tronco arterial proximal (*truncal occlusion)* o la morfología cónica (*tapered)* o tipo jet de la oclusión (figura 5)[107-110].

  Además, una vez lograda la recanalización, se puede establecer el diagnóstico si se cumple alguno de los siguientes criterios: (1) estenosis residual fija >50%, (2) evidencia de hipoperfusión distal, y/o (3) estenosis<50% con tendencia a la reoclusión[111].

- **Fase subaguda**: en aquellos pacientes no sometidos a TM o con recanalización fallida, el diagnóstico se ha de realizar una vez finalizado el procedimiento. La RM con imagen de alta resolución de pared vascular emerge como una de las pruebas diagnósticas más útiles en esta fase, mostrando la estenosis intracraneal subyacente como un engrosamiento intramural con realce post-contraste heterogéneo y excéntrico, que se relaciona con la histopatología de la aterosclerosis.

  En el año 2022, las guías de la sociedad europea de ictus sugirieron una serie de características de apoyo al diagnóstico de ICAS-LVO: (1) ausencia de fibrilación auricular, (2) ausencia de signo de la arteria hiperdensa en TC o susceptibilidad en RM, (3) infarto en territorio frontera, (4) oclusión en el tronco proximal de la arteria diana, (5) estenosis residual con el SR desplegado o tras 3 pases, y (6) reoclusión precoz[102].

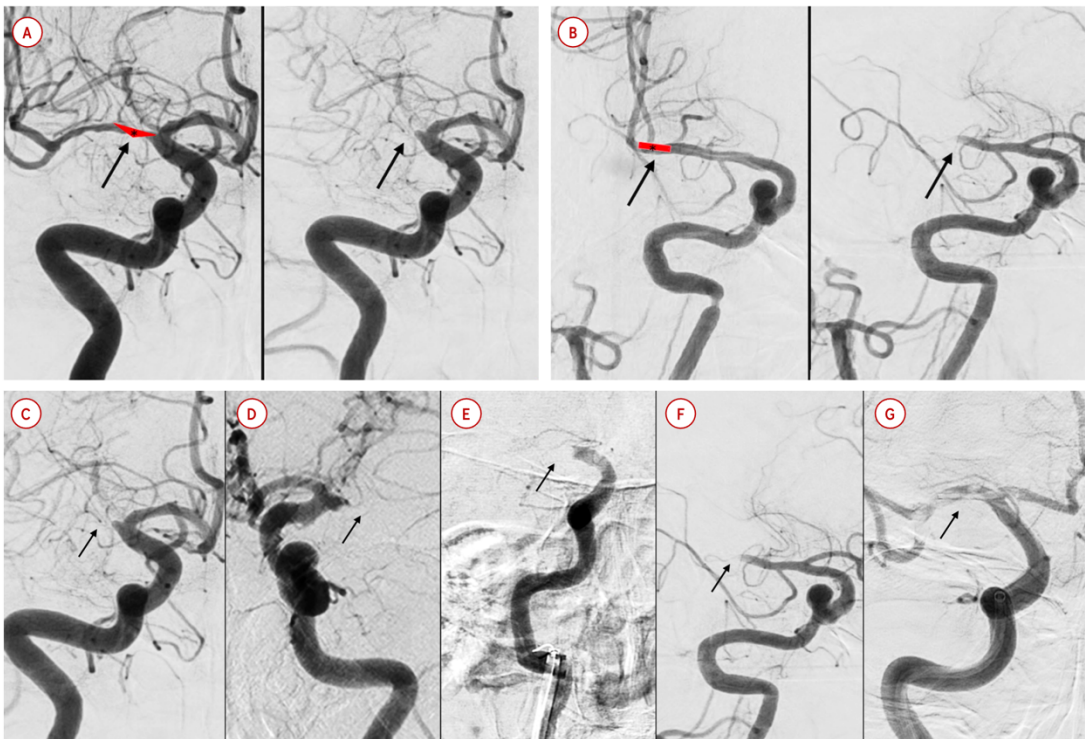

Figura 5. Características angiográficas relacionadas con el patrón de oclusión: (A) oclusión en el tronco proximal de la ACM *(truncal)*, (B) oclusión en la bifurcación de la ACM *(branching)*, (C y D) oclusión con morfología cónica *(tapered)*, (E) oclusión con morfología en menisco *(meniscus)*, (F) oclusión en forma de corte abrubto *(cutoff)*, y (G) oclusión en raíl *(tramtrack)*. La oclusión en el tronco proximal y con morfología cónica son sugestivas de ICAS-LVO.

Adaptado de Yoshimoto[110]. Utilizada bajo licencia open-access y CC Attribution License, ©2023-Yoshimoto

1.6.2. Particularidades del tratamiento endovascular

En la era del TEV como tratamiento de elección del ictus isquémico, la estrategia óptima de la TM para aquellos pacientes que se presentan con ICAS-LVO es incierta. Se considera que este subgrupo de pacientes se beneficia del tratamiento endovascular según los resultados de los ensayos clínicos previamente mencionados, sin embargo, no se han realizado estudios aleatorizados específicos en pacientes con ICAS-LVO debido a su incidencia menor.

Como particularidad, se estima que ICAS-LVO es la causa más frecuente de TM fallida (22-70%) y se ha asociado con un tiempo de procedimiento más prolongado y con una mayor tasa de complicaciones[97]. La TM fallida ocurre aproximadamente en el 19-26% de los casos de ICAS-LVO, mientras que únicamente en el 4-16% de las oclusiones de origen embólico[112]. Además, la tasa de reoclusión intraprocedimiento (36,9% vs 2,7%), la necesidad de angioplastia (9,0% vs 1.3%) o de stent intracraneal (37,8% vs 2,6%) son más elevadas en los pacientes con ICAS-LVO[113].

Todo ello hace que el TEV en casos de estenosis intracraneal subyacente sea más complejo y se presente en la actualidad como un desafío.

Por tanto, en la actualidad no existe un consenso sobre cuál debería ser la primera técnica a realizar cuando la sospecha de ICAS-LVO es elevada. Un estudio sugiere que en estos casos la TM con uso de SR es más eficaz que con el uso de aspiración distal (77.6% vs 43,5%)[114]. No obstante, la evidencia es escasa y se limita a series de casos de corte observacional y retrospectiva.

Debido a la tasa de fracaso en la recanalización, de reoclusión elevada y la probable estenosis residual se realizan múltiples tratamientos de rescate entre los que se encuentran la angioplastia, la colocación de un *stent* intracraneal, la administración de fármacos antiagregantes (inhibidores de la gliporoteína IIa-IIIb), o la combinación de estas técnicas con una evidencia basada en estudios observacionales[112].

Las guías de práctica clínica europeas recomiendan la angioplastia y el stent intracraneal como medidas de rescate, sin especificar el momento idóneo ni el tratamiento adyuvante farmacológico necesario para lograr un mejor resultado angiográfico y clínico.

1.6.3. Pronóstico clínico de ICAS-LVO

El pronóstico clínico tras el TEV en aquellos pacientes con ICAS-LVO ha sido escasamente estudiado debido a la ausencia de ensayos clínicos dirigidos a este subgrupo de pacientes en fase hiperaguda. Sin embargo, la evidencia actual sugiere que los pacientes con ICAS-LVO presentan peor pronóstico a los 3 meses que aquellos de etiología embólica, especialmente en el caso de afectación vertebrobasilar[106, 115].

Además, debido a la progresión natural de la ateromatosis intracraneal, el riesgo de recurrencia de ictus es mucho más elevado. La tasa de recurrencia varía según el grado de estenosis residual, siendo del 10-30% anual en el caso de que la estenosis sea >70% y aproximadamente del 10% en casos de estenosis de menor entidad, a pesar de un tratamiento médico intensivo[116, 117].

En cuanto al tratamiento médico de prevención secundaria, se recomienda la administración de doble antiagregación (usualmente Aspirina y clopidogrel) durante 90 días, además de estatinas de alta potencia con el objetivo de LDL<70mg/dL (ezetimiba y/o inhibidores PCSK9 en caso de intolerancia o LDL superior al umbral), cese del hábito tabáquico, ejercicio físico y control estricto del resto de factores de riesgo vascular como la hipertensión o la

diabetes mellitus. El ensayo clínico WASID[118] (Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis) que evaluó en el año 2005 el uso de warfarina vs Aspirina en la prevención secundaria de un ictus relacionado con ICAD, objetivó un aumento de la mortalidad y de las complicaciones hemorrágicas en los pacientes tratados con warfarina. Actualmente, el estudio CAPTIVA (Comparison of Anticoagulation and Antiplatelet Therapies for Intracranial Vascular Atherostenosis) en fase de inclusión de participantes, evaluará el uso de ticagrelor y el de rivaroxaban añadidos a la Aspirina como opción terapéutica alternativa al clopidogrel.

En cuanto al tratamiento invasivo, no se recomienda el bypass extra-intracraneal debido a las complicaciones periquirúrgicas y a la ausencia de disminución del riesgo de recurrencia. El tratamiento endovascular ha sido evaluado en distintas ocasiones:

- **SAMMPRIS**[119] (Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis, 2011): fue el primer ensayo clínico en evaluar el stenting intracraneal frente a la doble antiagregación y obtuvo un resultado negativo debido a un aumento del riesgo de recurrencia/muerte a los 30 días (14.7% vs 5.8%) y al año (19,7% vs 12,6%). Sin embargo, supuso un cambio de paradigma en el tratamiento médico estándar debido a que fue el primer estudio en el que además de la doble antiagregación, añadió un protocolo intensivo multimodal de corrección de los factores de riesgo vascular, junto con asesoramiento sobre un estilo de vida saludable. La tasa de recurrencia de ictus menor a la esperada en el grupo control conllevó la inclusión de la doble antiagregación durante 90 días en las guías de práctica clínica.

- **VAST**[120] (Vertebral Artery Stenting Trial) y **VISSIT**[121] (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy), en 2015: tampoco objetivaron un beneficio clínico del TEV frente al tratamiento médico con un riesgo de complicaciones del procedimiento demasiado elevado.

- **WEAVE**[122] (Wingspan Stent System Post Market Surveillance): se trata de un estudio de vigilancia postcomercialización publicado en 2019, prospectivo, de un solo grupo y, por tanto, no aleatorizado, ordenado por la FDA para evaluar el riesgo de ictus y/o muerte durante las primeras 72 horas de acuerdo a las instrucciones

de uso del Stent Wingspan (tras la publicación en 2007 y 2008 de dos registros multicéntricos que mostraron un riesgo periprocedimiento del 6,2%[123, 124]). El estudio WEAVE mostró la seguridad del stent Wingspan mediante una tasa de ictus y/o muerte periprocedimiento del 2,6%, inferior al 4% establecido por la FDA. Dichos resultados sugirieron que una mejor selección de pacientes en conjunto con un neurointervencionista experimentado podría resultar en un beneficio clínico en este subgrupo de pacientes.

- **CASSIS**[125] (China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis, 2022): debido a que los ensayos clínicos anteriores se realizaron con dispositivos de primera generación en centros con experiencia variable del operador y sin una selección estricta de pacientes según las características de la estenosis o la presencia de ictus como síntoma guía, durante los años 2014 y 2016 se llevó a cabo este estudio con un diseño más específico y estricto. Como particularidades, se excluyeron aquellos pacientes con un ictus en las 3 semanas previas, así como la presencia de infarto en territorio perforante, además de realizarse en centros de alto volumen de pacientes con una mayor experiencia de los operadores. A pesar de lograr una reducción en la tasa de complicaciones, tampoco demostró un beneficio del stent intracraneal frente al tratamiento médico en pacientes con estenosis intracraneal sintomática (riesgo de recurrencia/muerte a los 30 días 5,1% vs 2,2% y al año 8,0% vs 7,2%).

- **BASIS**[126] (Balloon Angioplasty vs Medical Management for Intracranial Artery Stenosis): a finales de 2024, se publicó el ensayo clínico más reciente en el que se evaluó la angioplastia intracraneal submáxima frente al tratamiento médico. Por primera vez, los resultados mostraron un menor riesgo de un desenlace compuesto (que incluye la ocurrencia de cualquier ictus y/o muerte en los primeros 30 días, así como de un ictus o necesidad de revascularización de la arteria diana en el periodo comprendido entre los 30 días y los 12 meses posteriores) en aquellos pacientes tratados con angioplastia submáxima aosciada a tratamiento médico (4,4% vs 13,5%). Por tanto, la angioplastia podría ser una terapia eficaz en este subgrupo de pacientes, si bien se debe considerar que existe un ligero aumento del riesgo de ictus y/o

muerte durante los primeros 30 días y se necesitan futuros ensayos clínicos que confirmen dichos resultados.

En conclusión, aunque en fase hiperaguda el TEV es el tratamiento de elección, en fase subaguda-crónica, el tratamiento médico ha demostrado ser superior al tratamiento endovascular mediante colocación de un stent intracraneal. Por tanto, actualmente se reserva su uso en casos de compromiso hemodinámico severo o recurrencia a pesar de un adecuado tratamiento médico.

En el futuro, se esperan nuevos ensayos clínicos aleatorizados con una selección estricta de participantes, así como dispositivos (stent farmacoactivo, mayor navegabilidad) y técnicas (p. ej. angioplastia submáxima) de última generación.

2. HIPÓTESIS

2. HIPÓTESIS

En el momento actual no existe una definición estandarizada del ictus isquémico con oclusión de gran vaso relacionada con ateromatosis intracraneal, por lo que habitualmente su diagnóstico se retrasa hasta la finalización del tratamiento endovascular.

La hipótesis de la presente tesis doctoral es que el desarrollo y estudio de biomarcadores clínico-radiológicos evaluables antes del tratamiento endovascular podría permitir la identificación precoz de la ateromatosis intracraneal como etiología subyacente.

A su vez, el diagnóstico preprocedimiento podría permitir realizar un TEV individualizado a la fisiopatología diana de la ateromatosis intracraneal, anticipando el uso de maniobras de rescate mecánicas y farmacológicas con el objetivo de optimizar el resultado angiográfico y el pronóstico clínico de este subgrupo de pacientes.

3. OBJETIVOS

3. OBJETIVOS

El objetivo principal de la presente tesis doctoral es:

- Identificar biomarcadores clínico-radiológicos del ictus isquémico relacionado con ateromatosis intracraneal disponibles antes del TEV y evaluar su capacidad predictiva.

Los objetivos secundaros de la presente tesis doctoral son:

- Estudio de las calcificaciones arteriales intracraneales y su impacto en las tasas de recanalización de la TM, en la necesidad de angioplastia y/o stent intracraneal y en el pronóstico clínico.
- Estudio de parámetros de TC perfusión automatizados para la identifiación precoz y rápida del ictus relacionado con ateromatosis intracraneal.
- Descripción de la técnica Stent Retriever Assisted Lysis (SAIL) con tirofiban como técnica puente antes de la angioplastia y/o stent intracraneal para inducir la reperfusión en pacientes con sospecha de oclusión de gran vaso relacionada con ateromatosis intracraneal y/o oclusiones refractarias.

4. COMPENDIO DE PUBLICACIONES

4. COMPENDIO DE PUBLICACIONES

4.1. Intracranial Artery Calcifications Profile as a Predictor of Recanalization Failure in Endovascular Stroke Treatment

Rodrigo-Gisbert M, Requena M, Rubiera M, Khalife J, Lozano P, De Dios Lascuevas M, García-Tornel Á, Olivé-Gadea M, Piñana C, Rizzo F, Boned S, Muchada M, Rodríguez-Villatoro N, Rodríguez-Luna D, Juega J, Pagola J, Hernández D, Molina CA, Tomasello A, Ribo M.

Intracranial Artery Calcifications Profile as a Predictor of Recanalization Failure in Endovascular Stroke Treatment.

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Stroke

CLINICAL AND POPULATION SCIENCES

Intracranial Artery Calcifications Profile as a Predictor of Recanalization Failure in Endovascular Stroke Treatment

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BACKGROUND: Acute ischemic stroke with large or medium-vessel occlusion associated with intracranial artery calcification (IAC) is an infrequent phenomenon presumably associated with intracranial atherosclerotic disease. We aimed to characterize IAC and its impact on endovascular treatment outcomes.

METHODS: We performed a retrospective cross-sectional study of consecutive patients with stroke treated with thrombectomy from January 2020 to July 2021 in our institution. We described IAC findings (length, density, and location pattern) on baseline noncontrast computed tomography. Patients were divided into 3 groups: IAC related to the occlusion location (symptomatic-IAC group), unrelated to the occlusion (asymptomatic-IAC group), and absence of any IAC (non-IAC group). We analyzed the association between the IAC profile and outcomes using logistic regression models. Intracranial angioplasty and stenting were considered rescue treatments.

RESULTS: Of the 393 patients included, 26 (6.6%) patients presented a symptomatic-IAC, 77 (19.6%) patients an asymptomatic-IAC, and in 290 (73.8%) patients no IAC was observed. The rate of failed recanalization (expanded Thrombolysis in Cerebral Infarction 0-2a) before rescue treatment was higher in symptomatic-IAC (65.4%) than in asymptomatic-IAC (15.6%; $P<0.001$) or non-IAC (13.4%; $P<0.001$). Rescue procedures were more frequently performed in symptomatic-IAC (26.9%) than in asymptomatic-IAC (1.3%; $P<0.001$) and non-IAC (4.1%; $P<0.001$). After adjusting for identifiable clinical and radiological confounders, symptomatic-IAC emerged as an independent predictor of failed recanalization (odds ratio, 11.89 [95% CI, 3.94–35.91]; $P<0.001$), adoption of rescue procedures (odds ratio, 12.38 [95% CI, 2.22–69.09]; $P=0.004$), and poor functional outcome (90-day modified Rankin Scale score ≥3; odds ratio, 3.51 [95% CI, 1.02–12.00]; $P=0.046$).

CONCLUSIONS: The presence of IAC related to the occlusion location is associated with worse angiographic and functional outcomes. Therefore, identification of symptomatic-IAC on baseline imaging may guide optimal endovascular treatment strategy, predicting the need for intracranial stenting and angioplasty.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: computed tomography scan ■ endovascular treatment ■ intracranial artery calcifications ■ intracranial atherosclerotic disease

Acute ischemic stroke with large or medium-vessel occlusion associated with intracranial artery calcification is an infrequent phenomenon that has been associated with different etiologies such as an intracranial atherosclerotic disease and calcified cardiac emboli. A calcified thrombus has been reported in 2.7%–5.9% of patients with an

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For Sources of Funding and Disclosures, see page 437.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early CT Score
IAC	intracranial artery calcification
eTICI	expanded Thrombolysis in Cerebral Infarction
NIHSS	National Institutes of Health Stroke Scale

acute ischemic stroke[1,2] and in 1.3%–1.8% of patients who underwent endovascular treatment (EVT).[3–5]

Although EVT for acute ischemic stroke has been established as the standard of care among patients with large vessel occlusion,[6,7] both intracranial atherosclerotic disease and calcified emboli have been associated with lower recanalization rates. Two recent studies showed that the presence of intracranial artery calcification (IAC) in the symptomatic vessel was associated with significantly worse angiographic outcomes. Despite these findings, symptomatic IAC was not consistently associated with worse functional outcomes and/or mortality.[3,5]

With limited number of studies, the ultimate EVT strategy to achieve best procedural and functional outcomes in patients with an IAC-related acute ischemic stroke remains unclear. We aimed to characterize IAC in acute ischemic stroke patients presenting with a large or medium-vessel occlusion and its impact on EVT procedural results such as recanalization rates, need for intracranial angioplasty and stenting, and clinical outcomes.

METHODS

Anonymized data supporting this study's findings are available for any qualified investigator upon reasonable request to the corresponding author. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statements.[8]

Study Design and Population

We performed a retrospective study based on a prospectively maintained single-center database of patients with an acute ischemic stroke undergoing reperfusion treatments. We selected patients with an intracranial large or medium artery occlusion (intracranial internal carotid, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, intracranial vertebral artery, and/or basilar artery) who received EVT from January 2020 to July 2021. Exclusion criteria were admission after 24 hours from stroke symptoms onset, and the presence of isolated extracranial occlusion. The patient selection process is represented in Figure S1. Chart evaluation of eligible patients was conducted by Dr Rodrigo-Gisbert.

Clinical and Radiological Parameters

Recorded demographic and clinical variables included age, sex, baseline modified Rankin Scale (mRS), medical comorbidities, stroke severity assessed by NIHSS (National Institutes of Health Stroke Scale), ASPECTS (Alberta Stroke Program Early CT Score), workflow times (symptom onset, imaging, and groin puncture), and reperfusion therapies administered. In all cases, first-line EVT was performed with commercially available stent retrievers and aspiration catheters. Rescue procedures (intracranial angioplasty±intracranial stenting) could be adopted according to neurointerventionalist criteria. Recanalization was assessed before and after rescue procedures were adopted. The degree of recanalization was determined prospectively by consensus between the interventionalist and the vascular neurologist immediately after the procedure using the eTICI (expanded Thrombolysis in Cerebral Infarction) score. Patients were considered to achieve successful recanalization if at least 50% of downstream reperfusion was achieved (2TICI≥2B).

The location, length, and density of the IACs with intimal pattern were registered on admission noncontrast computed tomography with a slice thickness ≤1 mm by MR-G and subsequently validated by Drs Ribo and Requena. Definite cases of IAC were included only if consensus was reached by the aforementioned evaluators. All intracranial vessels were visually inspected independently of the occlusion location to identify hyperdense lesions or segments. When hyperdensities were identified, a region of interest was drawn over the vessel and/or thrombus to measure the Hounsfield units (HU); IAC was considered for values>130 HU, analogous to cardiology scoring systems.[9] IAC pattern was differentiated into intimal and medial IAC according to a previously validated score, which assesses thickness (1 point for ≥1.5 mm, 3 for <1.5 mm), circularity (1 point for dot, 2 for <90°, 3 for 90–270°, and 4 for 270–360°), and morphology along the long axis of the artery (1 for irregular/patchy, 4 for continuous, and 0 points for indistinguishable).[10] The score designates an intimal IAC when ranged from 1 to 6 points, and a medial IAC when ranged from 7 to 11 points.

Compagne et al reported that patients with an intimal IAC pattern did not benefit from EVT in contrast to those with a medial IAC pattern.[11] For this reason, we excluded from our analysis patients with a medial IAC calcification pattern as characterized by a thin, continuous, and almost circular calcification (Figure 1). Patients were divided into 3 groups according to the presence of intimal IAC and its association with the acute occlusion: symptomatic-IAC group (s-IAC), where the lesion is associated with the occlusion; asymptomatic-IAC group (a-IAC), where the lesion is not associated with the occlusion; and absence of any IAC group (no-IAC).

The primary clinical outcome was the mRS score at 90 days evaluated through a telephone call by a certified central assessor who was unaware of the IAC findings assignment. CICAT (Codi Ictus de Catalunya) registry is a prospective official mandatory registry of all stroke codes in Catalunya; all included patients are centrally evaluated by trained and certified evaluators (independent from the treating hospitals) who are unaware of potential patient participation in trials or studies. Poor functional outcome was defined as a 90-day mRS score ≥3. All patients were treated according to institutional protocols based on European Stroke Organization guidelines[7] without any investigation or specific treatment performed for the purpose of this study. Data were prospectively recorded in an Institutional database approved

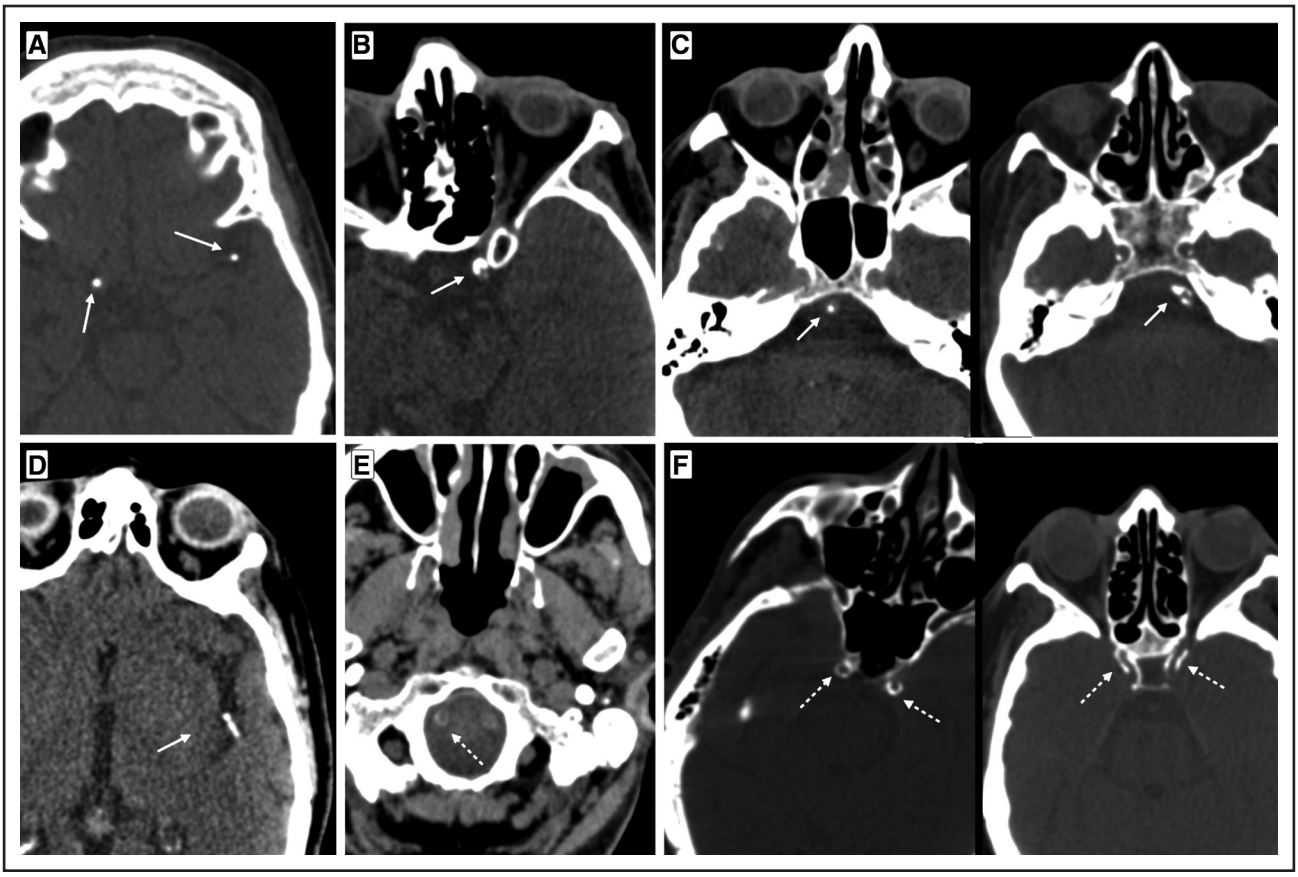

Figure 1. Intracranial artery calcification (IAC).
IAC with intimal pattern (arrows) located in intracranial internal carotid artery (ICA) and M1 segment of right middle cerebral artery (**A**), intracranial ICA (**B**), basilar artery (**C**) and M2 segment of left middle cerebral artery (**D**). We did not consider in our study when an IAC presented medial pattern (dotted arrow), such as right vertebral artery (**E**) and bilateral ICA (**F**).

by the local ethics committee. Because of the retrospective nature of the study, the need for written informed consent was waived.

Statistical Analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assure normality of continuous variables. Categorical variables were presented as absolute values and percentages and continuous variables as median (interquartile range [IQR]) or means (± standard deviation [SD]) as indicated. Statistical significance for intergroup differences was assessed by Pearson χ^2 test or Fisher exact test for categorical variables and by Mann-Whitney *U* test, Student *t* test, or ANOVA/Kruskal Wallis test as appropriate to continuous variables. Multivariable binary logistic regression analyses were modeled to determine the association between symptomatic-IAC and outcomes, including angiographic results (failed recanalization at first pass and before rescue procedures defined as eTICI 0-2a, final eTICI score), need of rescue procedures, and functional disability. The analyses were adjusted using variables that presented a statistically significant association or clinical relevance with the explored outcome (Tables S1–S3).

A *P* value <0.05 was considered statistically significant. All analyses were performed using the IBM SPSS Statistics software, version 25.

RESULTS

From January 2020 to July 2021, a total of 462 patients who presented to our institution with an acute ischemic stroke due to a large or medium-vessel and were treated with EVT were eligible for the study. Of them, we finally included 393 patients who met eligibility criteria. The median age was 77 (IQR, 65–85) years, 48.6% (191 patients) were women, and the median premorbid mRS was 1 (IQR, 0–2). Among evaluated patients, 26 patients were found to have a symptomatic-IAC (s-IAC 6.6%), 77 patients were found to have an asymptomatic-IAC (a-IAC: 19.6%), and 290 were found to have no IAC (no-IAC: 73.8%). Table 1 summarizes the baseline characteristics and demographics according to the presence of IAC.

The anatomic distribution of IAC is also shown in Table 1. Symptomatic-IAC was more frequently found in the intracranial internal carotid (9/26, 34.6%) and posterior circulation arteries (8/26, 30.7%). Fourteen patients with s-IAC (53.8% of s-IAC) presented additional IAC in other locations unrelated to the occlusion. Median s-IAC attenuation and length were 453±250 HUs and 4.83±2.83 mm, respectively. There were no differences

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Table 1. Baseline Characteristics and Demographics

	Symptomatic IAC (n=26)	Asymptomatic IAC (n=77)	No IAC (n=290)	*P* value†
Age (y) [median, IQR]	80 (66–87)	82 (72–88)	72 (63–83)	<0.001
Sex (women) [n, %]	12 (46.2%)	29 (37.7%)	150 (51.7%)	0.087
Risk factors [n, %]				
Former or current smoker	9 (34.6%)	23 (29.9%)	81 (27.9%)	0.901
Hypertension	18 (69.2%)‡	65 (84.4%)‡	190 (65.5%)‡	0.006‡
Diabetes	9 (34.2%)	21 (27.3%)	60 (20.7%)	0.161
Atrial fibrillation	4 (15.4%)	27 (35.1%)	72 (24.8%)	0.083
Ischemic heart disease	5 (19.2%)	17 (22.1%)	41 (14.1%)	0.199
Previous stroke	6 (23.1%)	12 (15.6%)	61 (21.0%)	0.528
Dyslipidemia	11 (42.3%)	43 (55.8%)	120 (41.4%)	0.074
Premorbid mRS [median, IQR]	1 (1–2)‡	1 (1–3)‡	0 (0–2)‡	0.001‡
0	6 (23.1%)	10 (13.0%)	84 (29.0%)	
1	9 (34.6%)	30 (39.0%)	118 (40.7%)	
2	7 (26.9%)	17 (22.1%)	57 (19.7%)	
3–4	1 (3.8%)	20 (26.0%)	31 (8.7%)	
TOAST classification				<0.001‡
Cardioembolic	6 (23.1%)	43 (55.8%)	168 (57.9%)	
Large-vessel atherosclerosis	15 (57.7%)	16 (20.8%)	47 (16.2%)	
Other determined etiology	0 (0%)	4 (5.2%)	22 (7.4%)	
Undetermined etiology	5 (19.2%)	14 (18.2%)	53 (18.2%)	
Baseline NIHSS [median, IQR]	15 (9–22)	16 (10–21)	16 (10–20)	0.923
Tandem occlusion [n, %]	4 (15.4%)	11 (14.3%)	38 (13.1%)	0.924
Occlusion level [n, %]				<0.001‡
Intracranial ICA	9 (34.6%)	9 (11.7%)	46 (15.9%)	
MCA M1	4 (15.4%)	35 (45.5%)	134 (46.2%)	
MCA M2	5 (19.2%)	16 (20.8%)	78 (26.9%)	
MCA M3	0 (0%)	2 (2.6%)	1 (0.3%)	
ACA	0 (0%)	3 (3.9%)	5 (1.7%)	
PCA	0 (0%)	6 (7.8%)	10 (3.4%)	
VA	5 (19.2%)	0 (0%)	4 (1.4%)	
BA	3 (11.5%)	6 (7.8%)	12 (4.1%)	
Wake-up stroke [n, %]	11 (42.3%)	35 (45.5%)	106 (36.6%)	0.359
Onset to groin time [mean±SD]	501.8±368.6	438.8±321.3	416.0±299.2	0.368
ASPECTS [median, IQR] [n, %]	10 (8–10)	10 (8–10)	9 (8–10)	0.558
Intravenous thrombolysis	4 (15.4%)	18 (23.4%)	96 (33.1%)	0.061
Primary endovascular technique [n, %]				<0.001‡
Combined technique*	19/26 (73.1%)‡	69/77 (89.6%)‡	228/290 (78.6%)‡	
ADAPT	1/26 (3.8%)‡	6/77 (7.8%)‡	39/290 (13.4%)‡	
Stent retriever+balloon guide catheter	1/26 (3.8%)‡	2/77 (2.6%)‡	19/290 (6.6%)‡	
Other	5/26 (19.2%)‡	0/77 (0%)‡	4/290 (1.4%)‡	
Number of IAC [mean±SD]	2±1.06	1.62±0.96	...	<0.001
IAC location [n, %]	26	115	...	<0.001
Intracranial ICA	9 (34.6%)	47 (40.9%)		
MCA M1	4 (15.4%)	4 (3.5%)		
MCA M2	5 (19.2%)	1 (0.9%)		
MCA M3	0 (0%)	2 (1.7%)		
ACA	0 (0%)	3 (2.6%)		
PCA	0 (0%)	0 (0%)		
VA	5 (19.2%)	55 (47.8%)		
BA	3 (11.5%)	3 (2.6%)		
Maximal length (mm) [mean±SD]	4.83±2.83	5.37±3.15	...	0.590
Maximal density (HU) [mean±SD]	453±250	541±257	...	0.106
Coexistence of asymptomatic IAC [n, %]	14/26 (53.8%)	...	...	...

ACA indicates anterior cerebral artery; ADAPT, A Direct Aspiration First Pass Technique; ANOVA, analysis of variance; ASPECTS, Alberta Stroke Program Early CT Score; BA, basilar artery; CTP, computed tomography perfusion; IAC, intracranial artery calcifications; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; and VA, vertebral artery.

*Combination of stent retrieval and distal aspiration.

†*P* value indicates differences between the 3 groups: Pearson χ^2 test for categorical variables and ANOVA/Kruskal Wallis test as appropriate to continuous variables. *P*<0.05 was considered statistically significant.

‡Value of statistic, *P*<0.05.

in terms of attenuation and length of the IAC between s-IAC group and a-IAC group. There were no differences in terms of stroke severity, ASPECTS, workflow times, or rate of intravenous thrombolysis between the 3 groups (Table 1).

Angiographic and Clinical Outcomes

The most frequent first-line EVT technique was combination of stent retrieval and distal aspiration (316/393, 80.4%). As compared with patients in non-IAC group, patients in the s-IAC group had longer groin puncture to reperfusion time (64 minutes [IQR, 40–89] versus 38 [IQR, 24–67]; P=0.002). The rate of failed reperfusion without rescue procedures (65.4% versus 15.6% in a-IAC and 13.3% in non-IAC groups, P<0.001) and the use of rescue procedures (26.9% versus 1.3% in a-IAC and 4.1% in non-IAC groups, P<0.001) were higher in the s-IAC patients (Table 2). The presence of s-IAC was not significantly associated with higher number of thrombectomy passes. Detailed information on the angiographic and clinical outcomes is presented in Table 2.

When the IAC intimal pattern was included in the multivariable logistic regression model with potential confounders (such as age, ASPECTS, tandem occlusion, onset to groin time, intravenous thrombolysis, and first-line EVT technique), symptomatic-IAC emerged as an independent predictor of failed recanalization at first pass (eTICI 0–2a 73.1% versus 53.2% in a-IAC and 40.7% in non-IAC; P=0.008; OR, 4.37 [95% CI, 1.47–13.0]), failed recanalization without rescue procedures (eTICI 0–2a 65.4% versus 15.6% in a-IAC and 13.4% in non-IAC, P<0.001; OR, 11.89 [95% CI, 3.94–35.91]) and need of rescue procedures (26.9% versus 1.3% in a-IAC and 3.8% in non-IAC, P=0.004; OR, 12.38 [95% CI, 2.22–69.09]). Preprocedural intravenous thrombolysis was not associated with recanalization rates (Table 3, Figure 2A).

Among patients with s-IAC who underwent rescue procedures, final successful recanalization (TICI 2b-3) was achieved in 71.4% of cases (Figure 2B). Thus, rescue procedures in s-IAC patients resulted in an improvement of recanalization. However, failed recanalization rates were still higher (28.6% versus 14.3% in a-IAC and 10.3% in non-IAC; P=0.189; OR, 3.94 [95% CI, 0.51–30.52]).

The presence of s-IAC was not significantly associated with hemorrhagic complications (Table 2). After adjusting for identifiable confounders in the clinically-targeted multivariable analysis, s-IAC was an independent predictor of 90-day disability (mRS 3–6, 80.8% in s-IAC versus 76.6% in a-IAC and 62.3% in non-IAC, P=0.046; OR, 3.51 [95% CI, 1.02–12.00] comparing with a-IAC and non-IAC groups (Table 3, Figure 3).

DISCUSSION

Our study shows that up to 6% of the patients undergoing EVT for an acute stroke harbor a calcification at the occlusion location that is identifiable on admission CT imaging. The presence of an s-IAC predicted worse procedural and functional outcomes. However, recanalization rates improved with rescue procedures such as intracranial angioplasty and stenting. Preprocedural

Table 2. Angiographic and Clinical Outcomes

	Symptomatic IAC	Asymptomatic IAC		No IAC	
	(n=26)	(n=77)	*P* value*	(n=290)	*P* value*
Angiographic					
Frequency of rescue procedures [n, %] Angioplasty Angioplasty+stenting	7/26 (26.9%) 0/7 7/7	1/77 (1.3%) 0/1 1/1	<0.001†	12/290 (4.1%) 2/12 10/12	<0.001†
Groin to reperfusion time [median, IQR]	64 (40–89)	53 (31–78)	0.118	38 (24–67)	0.002†
Number of passes [median, IQR]	2 (1–3)	2 (1–2)	0.990	2 (1–2)	0.782
First pass eTICI 0–2a [n, %]	19/26 (73.1%)	41/77 (53.2%)	0.076	118/290 (40.7%)	0.001†
eTICI 0–2a without rescue procedures [n, %]	17/26 (65.4%)	12/77 (15.6%)	<0.001†	39/290 (13.3%)	<0.001†
Final eTICI 0–2a	12/26 (46.2%)	11 (14.3%)	<0.001†	30/290 (10.3%)	<0.001†
Clinical					
NIHSS at 24 h [median, IQR]	16 (5–23)	13 (6–20)	0.401	10 (4–18)	0.114
Intracerebral hemorrhage (PH 1–2) [n, %]	2/24 (8.3%)	14/77 (18.2%)	0.346	32/288 (11.1%)	0.500
Symptomatic intracerebral hemorrhage [n, %]	1/24 (4.2%)	1/77 (9.1%)	0.676	22/288 (7.6%)	0.454
90-d mortality [n, %]	11/25 (42.3%)	31/77 (40.3%)	0.854	78/289 (27.0%)	0.097
90-d mRS score 3–6 [n, %]	21/26 (80.8%)	59/77 (76.6%)	0.661	180/289 (62.3%)	0.060†

eTICI indicates expanded Thrombolysis in Cerebral Infarction; IAC, intracranial artery calcifications; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and PH, parenchymal hemorrhage.

*P value indicate differences between the symptomatic-IAC patients and asymptomatic-IAC and non-IAC patients, respectively: Pearson χ^2 test for categorical variables and Mann-Whitney U test or Student t test as appropriate to continuous variables. P<0.05 was considered statistically significant.

†Value of statistic, P<0.05.

Table 3. Multiple Logistic Regression Analyses for Symptomatic IAC as a Poor Prognostic Factor

Angiographic and clinical outcomes	OR	95% CI	*P* value
Failed recanalization at first pass (eTICI 0–2a)	4.37	1.47–13.0	0.008
Failed recanalization without rescue procedures (eTICI 0–2a)	11.89	3.94–35.91	<0.001
Failed final recanalization (eTICI 0–2a)*	3.94	0.51–30.52	0.189
Need of rescue procedures (angioplasty and/or stenting)	12.38	2.22–69.09	0.004
90-d mortality	2.39	0.90–6.36	0.081
90-d mRS score 3–6	3.51	1.02–12.00	0.046

Covariates included in the multivariable analysis were: age, ASPECTS, tandem occlusion, intracranial occlusion location, onset to groin time, thrombolysis, and first-line endovascular technique for angiographic outcomes. Age, premorbid mRS, hypertension, Atrial fibrillation, onset to groin time, NIHSS at onset, number of passes, and intracranial occlusion location for clinical outcomes (see Table S1–S3). eTICI indicates expanded Thrombolysis in Cerebral Infarction; IAC, intracranial artery calcifications; and mRS, modified Rankin Scale.

*OR adjusted to symptomatic-IAC with rescue procedures.

identification of s-IAC could lead to the early consideration of rescue treatments. This becomes important since the conventional tools for mechanical thrombectomy such as aspiration and/or stent retriever alone may not be sufficient in this disease process and the sequelae of recurrent thrombectomy attempts, such as thrombus fragmentation and microvascular impairment could be detrimental leading to worse outcomes.

IAC within the symptomatic vessel has been proposed as a potential and infrequent marker of a worse angiographic outcomes in multiple studies.[1–3,5,12,13] An in-vitro model of calcified occlusions suggested the triple combination of a stent retriever, local aspiration, and flow arrest using a balloon guide catheter as the best first-line approach.[14] However, there is a paucity of data to guide the optimal EVT strategy to achieve the best clinical outcomes in these patients.

Our study shows that acute ischemic stroke associated with IAC is not a rare phenomenon. Symptomatic IAC was observed in up to 6.6% of the patients receiving EVT in our institution, which is slightly higher than previous studies reports.[3,5] However, our study includes both anterior and posterior circulation occlusions and IAC located in medium size intracranial vessels, while previous studies included only patients with an anterior circulation stroke.

Although previous studies have hypothesized an embolic etiology of symptomatic IAC,[1,2] clinical and radiological characteristics of these patients favor an intracranial atherosclerotic disease etiology. Intimal calcification pattern (Figure 1) related to atherosclerotic luminal stenosis can occur in all major cerebral arteries and is a major cause of territorial hypoperfusion and artery-to-artery embolism.[15] No significant correlation between medial calcification and luminal stenosis has been established yet, although it is thought to affect arterial stiffening with consequent compliance deterioration and vasodilation limitation.[16,17] Furthermore, EVT in acute ischemic stroke with underlying intracranial atherosclerotic disease has been described as more complex and technically challenging, with a higher probability of recanalization failure.[18,19] Thus, the presence of intimal IAC on imaging can be considered as an adjunct biomarker in the diagnosis of intracranial atherosclerotic disease in addition to other imaging biomarkers and modalities such as the presence intracranial plaque and perfusion imaging.

In our series, successful recanalization (eTICI≥2b) was achieved with first-line technique in only 26.9% of s-IAC cases, as opposed to 84.4% and 86.6% of a-IAC and non-IAC groups, respectively. Accordingly, s-IAC was associated with the need of endovascular rescue procedures, as intracranial angioplasty and stent deployment, and worse functional outcomes. Despite recanalization rates and the need of rescue procedures between asymptomatic-IAC and non-IAC groups being similar, worse outcomes were observed in asymptomatic-IAC patients. IACs (both symptomatic and asymptomatic) could also be associated with poor prognosis because of higher prevalence of vascular risk factors, older age, arterial wall stiffening, or microvascular impairment.

As previously reported,[3,5] intravenous thrombolysis before EVT did not lead to a higher or lower rate of recanalization. Intracranial stent deployment requires concomitant administration of intravenous antiplatelet therapy, which might increase the risk of intracranial bleeding if intravenous thrombolysis has been administered. Our limited cohort does not allow us to achieve conclusions related to concomitant intravenous thrombolysis administration. Further studies are warranted to assess the safety of intravenous thrombolysis administration where s-IAC seen on initial imaging and where intracranial stenting and peri-procedural antiplatelet therapy are anticipated.

In the case of s-IAC–related occlusions where rescue procedures such as stenting and/or angioplasty were performed, the rate of recanalization rose to values closer to the asymptomatic-IAC group and non-IAC group rates. Early adoption of rescue procedures might lead to successful reperfusion through decreasing the number of thrombectomy attempts. This translates to improved clinical outcomes due to several reasons such as shorter procedural time, decreased arterial wall damage or thrombus fragmentation, and/or microvascular impairment.[20,21]

The feasibility, safety, and efficacy of rescue intracranial stenting after failed thrombectomy in patients with anterior circulation large vessel occlusions had been suggested in 2 retrospective studies[22–24] and is being tested in prospective randomized clinical trials (NCT03955835 and NCT03993340). More studies are needed in order to optimize patient selection for these procedures. The

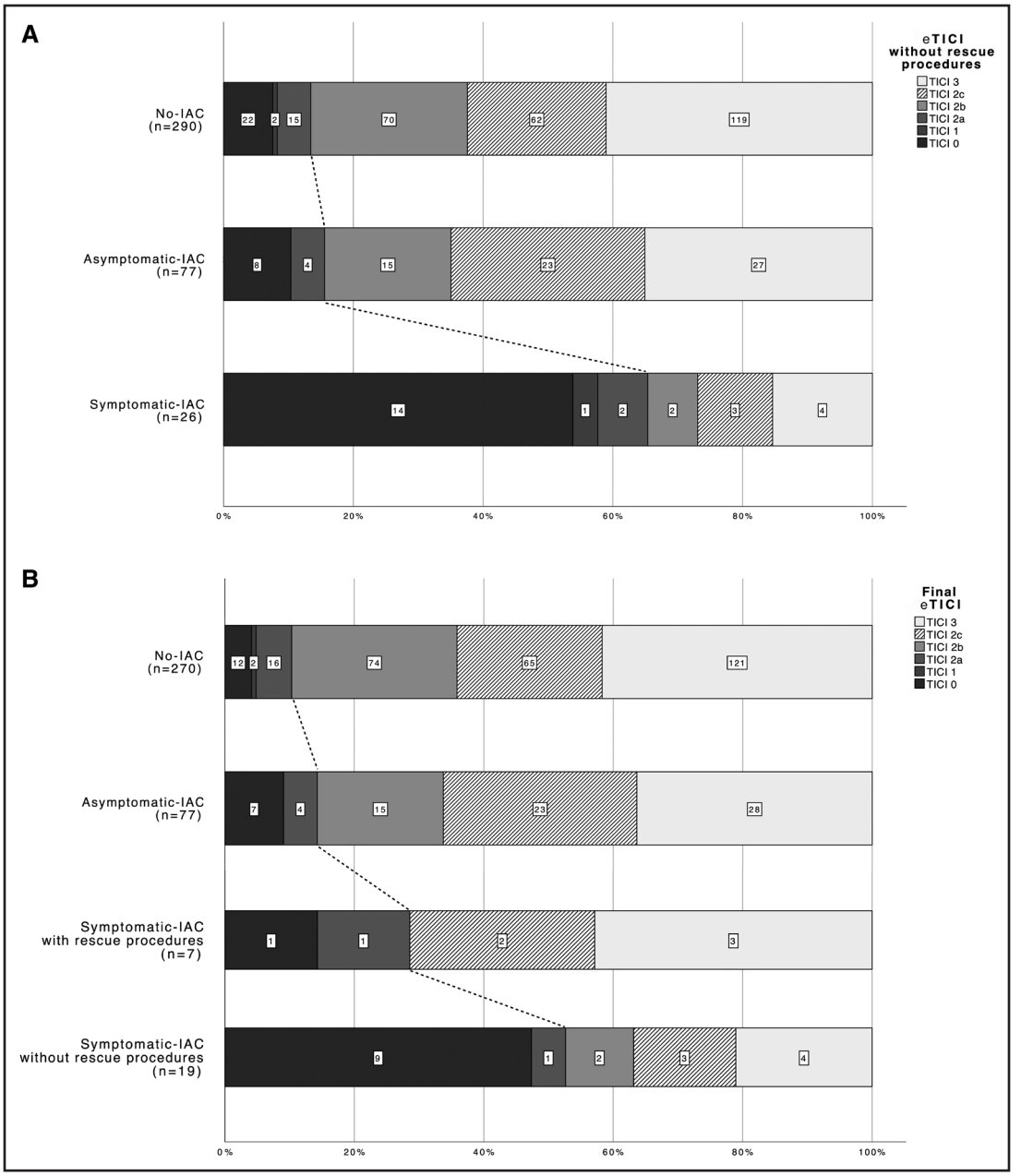

Figure 2. Angiographic outcomes.
A, Angiographic outcomes defined by expanded Thrombolysis in Cerebral Infarction (eTICI) score before rescue treatment. **B**, Final angiographic outcomes after rescue treatment. IAC indicates intracranial artery calcifications.

presence of symptomatic-IAC on initial imaging could be considered for this purpose.

If a symptomatic-IAC–related occlusion is identified on baseline stroke imaging, we suggest that intracranial angioplasty and stent deployment be considered among the first-line treatment options; the strategy might include initial loading of antiplatelet drugs and gentle debulking of the lesion with a stent-retriever to avoid repetition of unsuccessful thrombectomy attempts that could cause endothelial denudation and plaque activation. Further studies are warranted to specifically evaluate the safety and clinical efficacy of primary intracranial stenting in patients with symptomatic-IAC related occlusion.

Limitations

Our study has some limitations. Main limitations include a retrospective analysis, the lack of independent imaging core laboratory adjudication, and the self-reported eTICI evaluation. Additionally, the standard EVT approach in our center is a combined stent retriever and distal aspiration technique, with rare use of balloon guide catheter, followed by as needed rescue procedures at the discretion of

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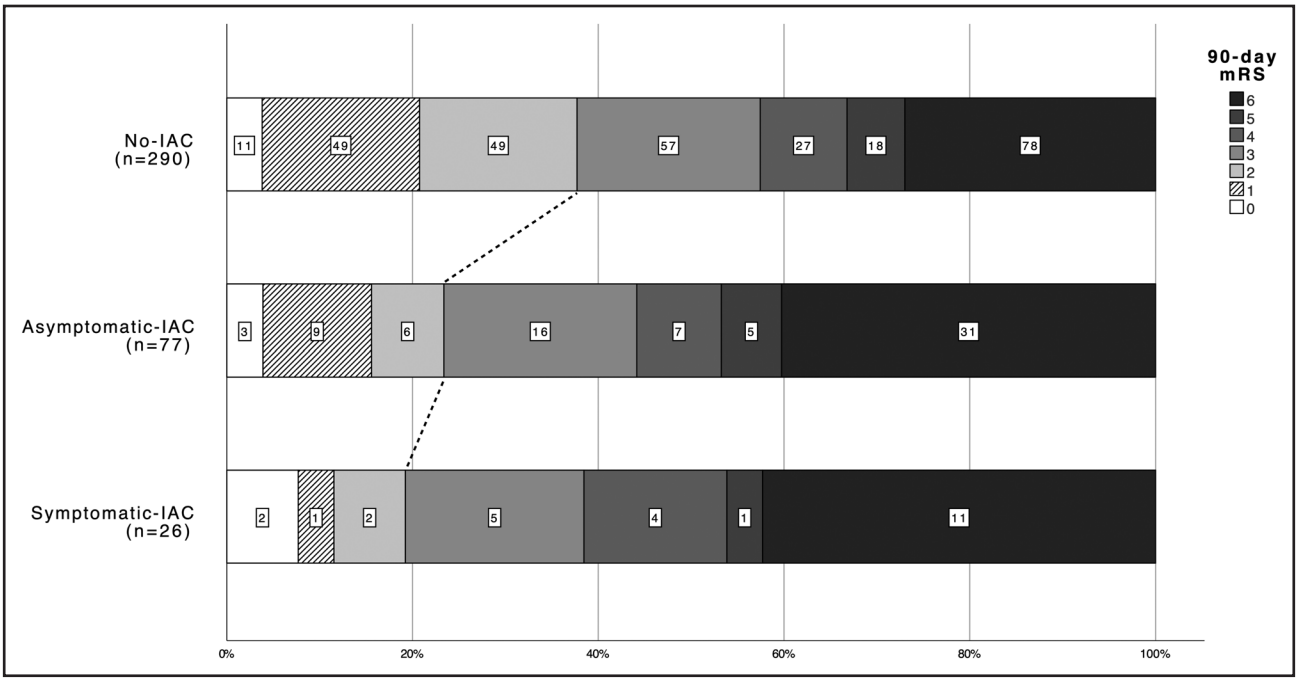

Figure 3. Functional outcome at 90 d.
IAC indicates intracranial artery calcifications; and mRS, modified Rankin Scale.

the treating neurointerventionalists. Different approaches may have led to different angiographic results; however, our overall rate of recanalization is comparable to other prospective series. Finally, our study has been performed in a single center and the results need to be reproduced in multicenter studies to confirm our findings.

Conclusions

The presence of IAC related to the occlusion location among patients with an acute ischemic stroke is not infrequent and it is associated with worse angiographic and functional outcomes. Identification of symptomatic-IAC on baseline stroke imaging may help anticipate the optimal endovascular treatment strategy and suggest the need for rescue procedures, such as intracranial stenting and angioplasty.

ARTICLE INFORMATION

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Supplemental Material

Figure S1
Tables S1–S3

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4.2. Clinico-radiological features of intracranial atherosclerosis-related large vessel occlusion prior to endovascular treatment

Rodrigo-Gisbert M, García-Tornel A, Requena M, Vielba-Gómez I, Bashir S, Rubiera M, De Dios Lascuevas M, Olivé-Gadea M, Piñana C, Rizzo F, Muchada M, Rodriguez-Villatoro N, Rodríguez-Luna D, Juega J, Pagola J, Hernández D, Molina CA, Terceño M, Tomasello A, Ribo M.

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Clinico-radiological features of intracranial atherosclerosis-related large vessel occlusion prior to endovascular treatment

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The identification of large vessel occlusion with underlying intracranial atherosclerotic disease (ICAS-LVO) before endovascular treatment (EVT) continues to be a challenge. We aimed to analyze baseline clinical-radiological features associated with ICAS-LVO that could lead to a prompt identification. We performed a retrospective cross-sectional study of consecutive patients with stroke treated with EVT from January 2020 to April 2022. We included anterior LVO involving intracranial internal carotid artery and middle cerebral artery. We analyzed baseline clinical and radiological variables associated with ICAS-LVO and evaluated the diagnostic value of a multivariate logistic regression model to identify ICAS-LVO before EVT. ICAS-LVO was defined as presence of angiographic residual stenosis or a trend to re-occlusion during EVT procedure. A total of 338 patients were included in the study. Of them, 28 patients (8.3%) presented with ICAS-LVO. After adjusting for confounders, absence of atrial fibrillation (OR 9.33, 95% CI 1.11–78.42; $p = 0.040$), lower hypoperfusion intensity ratio (HIR [Tmax > 10 s/ Tmax > 6 s ratio], (OR 0.69, 95% CI 0.50–0.95; $p = 0.025$), symptomatic intracranial artery calcification (IAC, OR .15, 95% CI 1.64–26.42, $p = 0.006$), a more proximal occlusion (ICA, MCA-M1: OR 4.00, 95% CI 1.23–13.03; $p = 0.021$), and smoking (OR 2.91, 95% CI 1.08–7.90; $p = 0.035$) were associated with ICAS-LVO. The clinico-radiological model showed an overall well capability to identify ICAS-LVO (AUC = 0.88, 95% CI 0.83–0.94; $p < 0.001$). In conclusion, a combination of clinical and radiological features available before EVT can help to identify an ICAS-LVO. This approach could be useful to perform a rapid assessment of underlying etiology and suggest specific pathophysiology-based measures. Prospective studies are needed to validate these findings in other populations.

Abbreviations

AIS	Acute Ischemic Stroke
ICAD	Intracranial Atherosclerotic Disease
ICAS-LVO	Intracranial atherosclerosis related large vessel occlusion
EVT	Endovascular treatment
MT	Mechanical thrombectomy
CTP	Computed tomography perfusion
LVO	Large vessel occlusion

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In the era of endovascular treatment (EVT) for acute ischemic stroke with large vessel occlusion (LVO)[1,2], the optimal EVT strategy for the treatment of underlying intracranial atherosclerotic disease (ICAD) remains unclear.

Mechanical thrombectomy (MT) in patients with underlying ICAS-LVO can be challenging and remains the most common cause of failed reperfusion using usual MT strategies. In these cases, MT has been associated with longer procedural time with higher complications rate, and worse angiographic and clinical outcomes[3]. Although there is a paucity of randomized data, rescue MT with balloon angioplasty and/or stenting is often necessary and has proven to be technically feasible and effective[4].

The diagnosis of ICAS-LVO prior to EVT could be useful to optimize patient selection and perform a patient-tailored thrombectomy anticipating rescue treatments such as mechanical or pharmacological interventions. However, the diagnostic performance of clinical and radiological biomarkers to detect underlying ICAD before EVT has not been systematically studied. Previous studies suggest that automated parameters of computed tomography perfusion (CTP) associated with a good collateral status are associated with underlying ICAD[5–9].

For this single center study, we aimed to evaluate a combination of clinical and radiological features available before EVT to help to quickly identify the presence of ICAS-LVO.

Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements, all procedures were conducted in strict adherence to applicable guidelines and regulations[10,11]. The study protocol was reviewed and approved by Vall d'Hebron Hospital Ethics Committee, approval number (PR(AG)434/2023). Because of the retrospective nature of this study, the need for written informed consent was waived by the Vall d'Hebron Hospital Ethics Committee.

Data availability

Anonymized data supporting the current study's findings are available for any qualified investigator upon reasonable request to the corresponding author.

Study design and population

We performed a cross-sectional study based on a prospectively maintained single-center database of patients with an acute ischemic stroke undergoing reperfusion treatments. We included patients with an anterior intracranial LVO (intracranial internal carotid, middle cerebral artery segments M1 and M2) who had baseline non-contrast CT, CT angiography and CT perfusion and underwent EVT from January 2020 to April 2022. Exclusion criteria were admission after 24 h from stroke symptoms onset and the presence of an extracranial occlusion of the internal carotid artery. A flow chart of the included patients and reasons to exclusions is represented in Fig. 1.

Clinical and radiological parameters

Recorded demographic and clinical variables included age, sex, baseline modified Rankin Scale (mRS), medical comorbidities, stroke severity assessed by National Institutes of Health Stroke Scale (NIHSS), admission Alberta Stroke Program Early CT score (ASPECTS), workflow times (symptom onset, imaging, and groin puncture), and reperfusion therapies administered. The degree of reperfusion was determined prospectively by consensus between the interventionalist and the vascular neurologist immediately after the procedure using the expanded Thrombolysis in Cerebral Ischemia (eTICI) score. Patients were considered to achieve successful recanalization if at least 50% of downstream reperfusion was achieved (eTICI ≥ 2B).

A symptomatic intracranial artery calcification (IAC) was defined as the presence of IAC with intimal pattern in the occlusion location or immediately proximal, in direct contact with the occlusion, as previously described[12]. Calcifications were registered on admission non-contrast CT with a slice thickness ≤ 1 mm and were considered for values > 130 HU, analogous to cardiology scoring systems[13]. IAC pattern in LVO was differentiated into intimal and medial IAC according to a previously validated score, which assesses thickness (1 point for ≥ 1.5 mm, 3 for < 1.5 mm), circularity (1 point for dot, 2 for < 90°, 3 for 90°–270°, and 4 for 270°–360°), and morphology along the long axis of the artery (1 for irregular/patchy, 4 for continuous, and 0 points for indistinguishable). Indistinguishable was used to describe dot like calcifications that were too small to assign any morphological characteristics to, and were therefore not categorizable. The score designates an intimal IAC when ranged from 1 to 6 points, and a medial IAC when ranged from 7 to 11 points[14].

Automated CTP parameters were assessed by RAPID® software (iSchemaView, Menlo Park, CA) on baseline neuroimaging study. We included cerebral blood flow (CBF) < 30%, T_{max} > 4 s, T_{max} > 6 s, T_{max} > 10 s, mismatch volume (difference between T_{max} > 6 s and CBF < 30%), hypoperfusion intensity ratio (T_{max} > 10 s/T_{max} > 6 s ratio, HIR), and T_{max} > 4 s/T_{max} > 6 s ratio. HIR was used to determine collateral status as favorable (HIR < 0.25) and unfavorable (HIR > 0.25) based on ROC analysis and previously published thresholds[7,15].

We defined ICAS-LVO by angiographic residual fixed stenosis > 50% after successful reperfusion in the target vessel with distal flow impairment or a trend to re-occlusion during the EVT procedure. The residual stenosis degree was assessed according to the Warfarin Aspirin Symptomatic Intracranial Disease criteria[16]. Re-occlusion was defined as an immediate re-occlusion of the target vessel during EVT procedure after initial revascularization. Stroke mechanism work-up included heart rhythm monitoring for at least 72 h, imaging of both the extracranial and intracranial arteries supplying the area of brain ischemia with CT angiography, precordial echocardiography, and a comprehensive evaluation if rare causes were suspected.

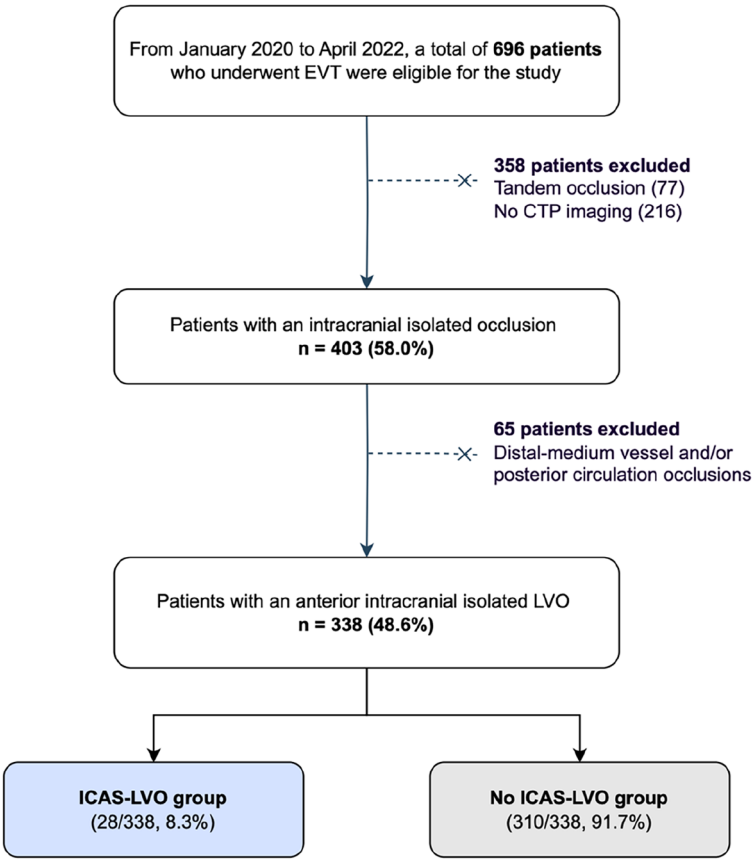

Figure 1. Patient selection flow chart. Footnote: EVT, endovascular treatment; CTP, computed tomography perfusion; LVO, large vessel occlusion; ICAS-LVO, intracranial atherosclerosis related large vessel occlusion.

Statistical analysis

Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assure normality of continuous variables. Categorical variables were presented as absolute values and percentages and continuous variables as median (interquartile range (IQR)) or means (± standard deviation (SD)) as indicated. Statistical significance for intergroup differences was assessed by Pearson $\chi 2$ test or Fisher exact test for categorical variables and by Mann–Whitney U test or Student t-test as appropriate to continuous variables.

A multivariable binary regression model was constructed using the Least Absolute Shrinkage and Selection Operator (LASSO) method to identify a subset of variables independently associated with underlying ICAD. The LASSO method included variables that demonstrated either a statistically significant association or clinical relevance to the explored outcome. The cutoff of HIR with best sensitivity and specificity to predict underlying ICAD was determined through a receiver operating characteristic (ROC) curve, utilizing the Youden's Index. Additionally, a sensitivity analysis was conducted, focusing on patients with successful reperfusion at any time during EVT.

ROC curves were constructed to assess model diagnostic accuracy to detect the presence of underlying ICAD, including independent predictors from the multivariable analysis the following models: (1) radiological variables only, (2) clinical and radiological variable. The diagnostic accuracy of each model was determined based on the area under the ROC curve with a confidence interval (CI) of 95%. Additionally, a comparison between the AUCs of both models was conducted using the DeLong test implemented in R with the *pROC* package.

A p value < 0.05 was considered statistically significant. All analyses were performed using the IBM SPSS Statistics (version 25) software and R (version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Dr Molina reported receiving personal fees from AstraZeneca for consultant services outside the submitted work. Dr Tomasello reported receiving personal fees from Anaconda Biomed, Balt, Medtronic, Perflow, and Stryker outside the submitted work. Dr Ribo reported receiving personal fees from Anaconda Biomed, AptaTargets, Cerenovus, Medtronic, Methinks, Philips, Sanofi, Stryker, Balt, and Rapid AI outside the submitted work; he has a modest ownership of NoraHealth. The other authors report no conflicts. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Results

Baseline characteristics and univariate analysis

From January 2020 to April 2022, a total of 695 patients with an acute ischemic stroke that underwent EVT were eligible for the study. We included 338 patients (48.6%) who met the eligibility criteria, of whom ICAS-LVO was diagnosed in 28 patients (8.3%). The median age was 79 (IQR 66–86) years, 196 patients (58.0%) were women, and the median baseline mRS was 1 (IQR 0–2). In our population, only a single patient of Asian ethnicity was included in the non-ICAD group (1/338, 0.3%).

Patients with ICAS-LVO were younger (70 years [IQR 66–86] vs 80 years [IQR 67–86]), had a higher proportion of former/current history of smoking (57.1% [16/28] vs 23.1% [72/310]), a lower proportion of atrial fibrillation diagnosis (3.6% [1/28] vs 35.5% [110/310]), and a lower median admission NIHSS score (11 [IQR 8–18] vs 16 [IQR 10–20]). CTP-derived perfusion maps showed that patients with ICAS-LVO had a smaller ischemic core volume (median 0 mL [IQR 0–7] vs 6 mL [IQR 0–26]), a higher proportion of $T_{max} > 4$ s/$T_{max} > 6$ s ratio > 2 (53.6% [15/28] vs 33.9% [105/310]), and a lower hypoperfusion intensity ratio (HIR) (median 0.16 [IQR 0–0.37] vs 0.44 [IQR 0.29–0.57]). No significant differences were observed in other baseline characteristics. Table 1 summarizes the baseline characteristics and demographics according to the diagnosis of ICAS-LVO.

Multivariable and ROC analysis

After adjusting for identifiable baseline confounders such as age, baseline NIHSS score, $T_{max} > 4$ s/$T_{max} > 6$ s > 2, and ischemic core (CBF < 30%), the absence of atrial fibrillation (OR 9.33, 95% CI 1.11–78.42; $p = 0.040$), the presence of symptomatic IAC (OR 0.15, 95% CI 1.64–26.42, $p = 0.006$), lower HIR (OR 0.69, 95% CI 0.50–0.95; $p = 0.025$), a proximal occlusion (ICA, MCA-M1: OR 4.00, 95% CI 1.23–13.03; $p = 0.021$) and smoking habit history (OR 2.91, 95% CI 1.08–7.90; $p = 0.035$) were associated with ICAS-LVO (Table 2 and Fig. 2). On CTP imaging, the best cutoff point to identify ICAS-LVO was HIR < 0.25 according to ROC analyses.

The probabilities obtained from a multivariate model which includes variables significantly associated with ICAS-LVO showed an overall well capability to identify a LVO with underlying ICAD. The multivariate model with radiological variables, which includes symptomatic IAC, HIR, and occlusion location (AUC 0.80, 95% CI 0.70–0.90; $p < 0.001$), as well as the model which included clinical variables (history of smoking and atrial

	All patients (n = 338)	ICAS-LVO (n = 28)	No ICAS-LVO (n = 310)	*p* Value
Age (years) [median, IQR]	79 (66–86)	70 (62–77)	80 (67–86)	< 0.001
Sex (female) [n, %]	196 (58.0%)	16 (57.1%)	180 (58.1%)	0.925
Risk factors [n, %] Former or current smoker Hypertension Diabetes mellitus Dyslipidemia Atrial fibrillation Ischemic heart disease Active oncological disease Previous stroke	 88 (26%) 230 (68.0%) 92 (27.2%) 167 (49.4%) 111 (32.8%) 59 (17.5%) 16 (4.7%) 69 (20.4%)	 16 (57.1%) 18 (64.3%) 8 (28.6%) 13 (46.4%) 1 (3.6%) 3 (10.7%) 0 (0%) 6 (21.4%)	 72 (23.3%) 212 (68.4%) 84 (27.1%) 154 (49.7%) 110 (35.5%) 56 (18.1%) 16 (5.2%) 63 (20.3%)	 < 0.001 0.656 0.867 0.742 0.001 0.323 0.678 0.889
Premorbid mRS [median, IQR]	1 (1–2)	1 (0–2)	1 (1–2)	0.413
Baseline NIHSS [median, IQR]	16 (10–20)	11 (8–18)	16 (10–20)	0.024
Occlusion level [n, %] Intracranial ICA MCA M1 MCA M2	 65 (19.2%) 152 (46.2%) 117 (34.6%)	 7 (25%) 15 (53.6%) 6 (21.4%)	 58 (18.7%) 41 (45.5%) 111 (35.8%)	 0.297
Proximal occlusion (Intracranial ICA plus MCA M1) [n, %]	223 (66.0%)	22 (81.5%)	201 (64.6%)	0.076
Wake-up stroke [n, %]	129 (38.2%)	14 (50%)	115 (37.1%)	0.178
Onset to imaging [mean ± SD]	323 ± 287	412 ± 292	315 ± 285	0.098
Onset to groin time [mean ± SD]	393 ± 296	452 ± 299	388 ± 296	0.265
ASPECTS [median, IQR] [n, %]	9 (8–10)	9 (8–10)	9 (8–10)	0.256
Symptomatic IAC [n, %]	19 (5.6%)	6 (21.4%)	13 (4.2%)	0.002
CTP automated parameters				
CBF < 30%	5 (0–24)	0 (0–7)	6 (0–26)	0.004
Mismatch volume	78 (52–116)	75 (37–128)	78 (52–115)	0.078
Tmax > 4 s/Tmax > 6 s	1.78 (1.54–2.27)	2.01 (1.59–2.61)	1.77 (1.52–2.24)	0.909
Tmax > 4 s/Tmax > 6 s > 2	120 (35.5%)	15 (53.6%)	105 (33.9%)	0.037
HIR	0.43 (0.26–0.57)	0.16 (0–0.37)	0.44 (0.29–0.57)	< 0.001
HIR < 0.25	79 (23.4%)	18 (66.7%)	61 (19.7%)	< 0.001

Table 1. Baseline characteristics and demographics. ICAD, intracranial atherosclerotic disease; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; MCA, middle cerebral artery; ASPECTS, Alberta Stroke Program Early CT score; IAC, intracranial artery calcification; CBF, cerebral blood flow; HIR, hypoperfusion intensity ratio.

	Univariate analysis			Multivariate analysis			
	Unadjusted OR	95% CI	*p* Value	LASSO coefficient	OR	95% CI	*p* value
Absence of atrial fibrillation	14.23	1.91–106.28	0.010	2.29	9.89	1.18–82.97	0.035
Proximal occlusion (intracranial ICA, MCA M1)	2.41	0.89–6.54	0.085	1.42	4.12	1.23–13.38	0.018
Former/current smoker	4.08	1.83–9.10	0.001	1.22	3.38	1.28–8.94	0.014
Symptomatic IAC	6.55	2.26–18.98	0.001	1.95	6.99	1.74–28.05	0.006
HIR (0.1 unit increment)	0.63	0.51–0.78	< 0.001	-0.40	0.67	0.53–0.85	0.001
Age (1 unit increment)	0.96	0.94–0.99	0.004	-0.01	0.99	0.96–1.03	0.686
Baseline NIHSS (1 unit increment)	0.93	0.87–0.99	0.022	-0.04	0.96	0.88–1.05	0.407

Table 2. Binary logistic regression model for detecting large vessel occlusion with underlying ICAD. ICA, internal carotid artery; MCA-M1, middle cerebral artery segment M1; IAC, intracranial artery calcification; HIR, hypoperfusion intensity ratio; NIHSS, National Institutes of Health Stroke Scale; CBF, cerebral blood flow.

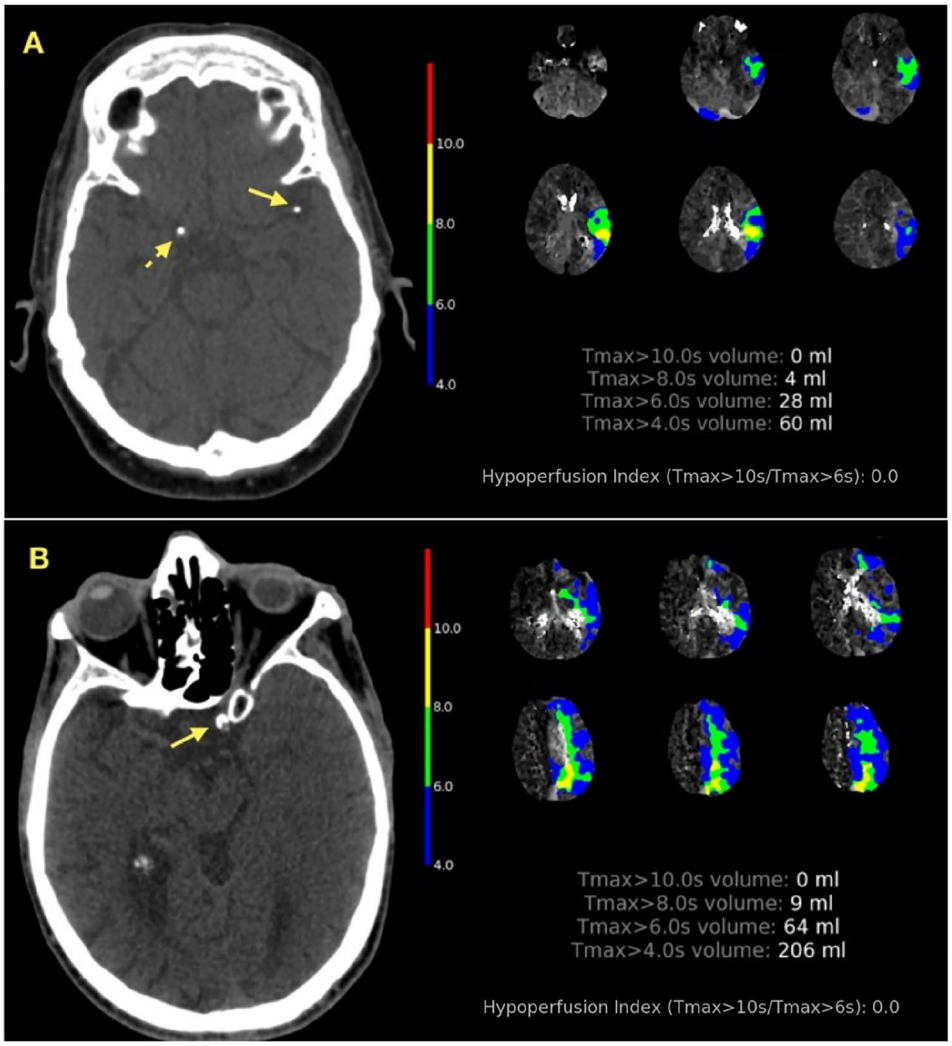

Figure 2. Illustrative cases demonstrating intracranial atherosclerosis-related large vessel occlusions biomarkers. (**A**) Patient with left MCA segment M1 occlusion; and (**B**) patient with left intracranial ICA occlusion. In both cases, axial non-contrast CT with symptomatic intracranial artery calcification in occlusion location (yellow arrow), asymptomatic IAC (dotted arrow, only patient **A**); and CTP automated parameters including HIR < 0.25.

fibrillation) were added to the radiological variables (AUC 0.88, 95% CI 0.83–0.94; $p < 0.001$). The clinico-radiological model significantly improved the predictive capability to identify an ICAS-LVO compared to the radiological model alone (DeLong test: Z = 2.0116, $p = 0.044$). The ROC curves for both evaluations (radiological and comprehensive clinico-radiological models) are represented in Fig. 3.

Sensitivity analysis of patients with successful reperfusion

After excluding patients who did not achieve successful reperfusion at any time during the EVT procedure, we analyze a total of 310 patients. Of them, 25 patients (8.1%) were diagnosed with ICAS-LVO. Lower HIR (0.1-unit increment, OR 0.68, 95% CI 0.53–0.87; $p = 0.002$), a proximal occlusion (OR 5.05, 95% CI 1.36–18.75; $p = 0.016$), presence of symptomatic IAC (OR 5.15, 95% CI 1.12–23.65; $p = 0.035$), smoking history (OR 4.04, 95% CI 1.45–11.29, $p = 0.008$), and absence of atrial fibrillation (OR 9.77, 95% CI 1.17–81.89, $p = 0.036$) persisted as independently associated factors with pre-EVT identification of ICAS-LVO.

Angiographic outcomes

In our cohort, those with an ICAS-LVO exhibited a lower rate of successful reperfusion before the use of rescue treatments (which are defined as intracranial angioplasty + /− intracranial stenting) (eTICI ≥ 2b 21.4% [6/28] vs 89.7% [278/310], $p < 0.001$), a higher rate of rescue treatments (60.7% [17/38] vs 1.6% [5/310], $p < 0.001$) and a lower rate of final successful reperfusion (eTICI ≥ 2b 71.4% [20/38] vs 91.3% [283/310], $p = 0.003$). Complete angiographic outcomes according to the presence of ICAS-LVO are presented in Table S1.

Discussion

Our study provides evidence supporting the hypothesis that the underlying presence of ICAS-LVO can be accurately predicted before EVT using clinical and radiological variables. Specifically, the presence of intracranial artery calcifications, collateral status on admission CTP, occlusion location, and the presence of atrial fibrillation or smoking habit were significantly associated with ICAS-LVO in our cohort of stroke patients treated with thrombectomy. These findings can orient towards an early identification and management of an underlying atherosclerotic lesion, potentially leading to a tailored EVT procedure and improved clinical outcomes.

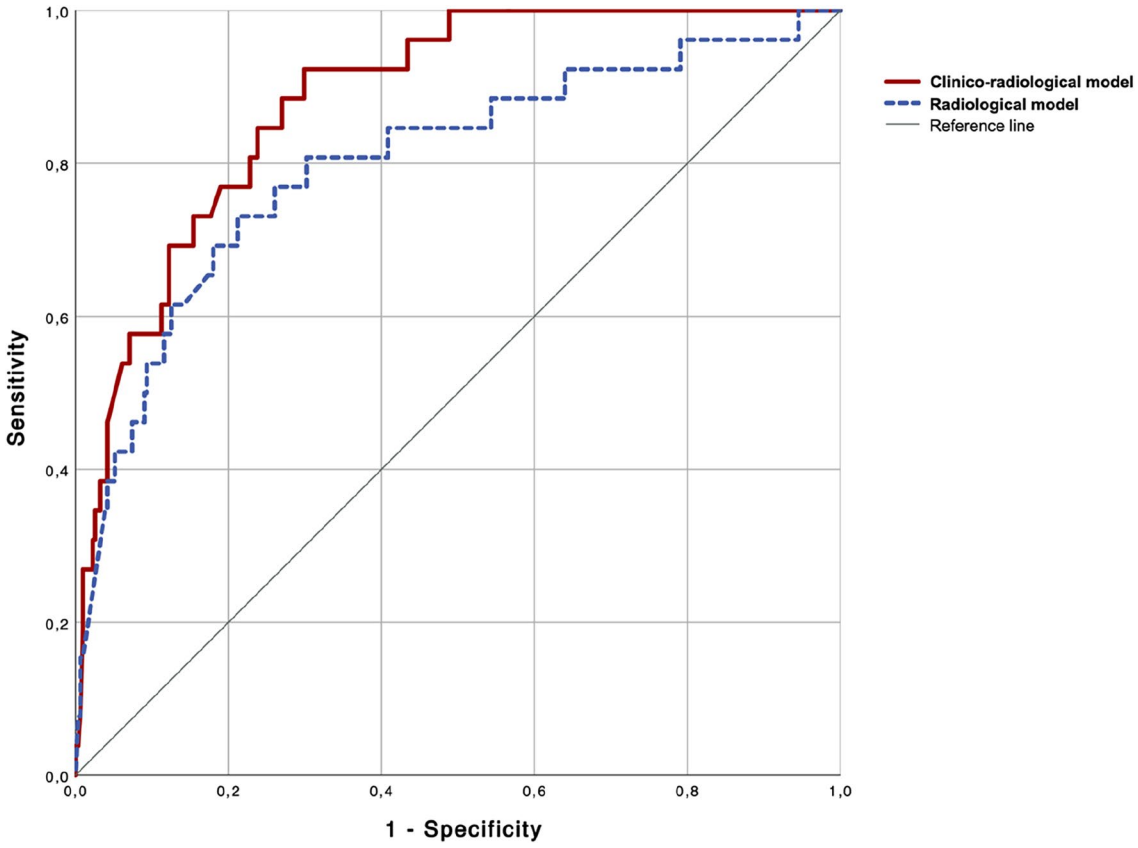

Figure 3. Capability to identify large vessel occlusion with underlying ICAD according to receiver operating characteristic (ROC) analysis. ROC analysis of regression models that include independent predictors of LVO with underlying ICAD in an isolated radiological model including IAC, HIR, and occlusion location (AUC 0.80, 95% CI 0.70–0.90: $p < 0.001$) and a comprehensive clinico-radiological model including smoking and atrial fibrillation in addition to previous radiological features (AUC 0.88, 95% CI 0.83–0.94; $p < 0.001$). Footnote: AUC, area under the curve; IAC, intracranial artery calcifications; HIR, Hypoperfusion intensity ratio.

The potential benefit of EVT is limited by recanalization failure in a portion of stroke patients that ranges 15–30%[17]. Several factors may contribute to recanalization failure, including clot characteristics such as fibrin-rich or calcified clots, anatomical challenges, and atherosclerotic occlusions[12,18,19]. Currently, the diagnosis of ICAD-related occlusion based on The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification requires a full diagnosis work-up, delaying the diagnosis after EVT is performed[20]. Unfortunately, there is no standardized criteria for diagnosing underlying ICAD in acute LVO before EVT[21]. To facilitate a timely detection of the condition, current approaches include applying artificial intelligence technology to analyze CTP maps parameters and/or using information related to recanalization status after the first pass during EVT[22,23].

As showed in our cohort, EVT in ICAS-LVO has been associated with a higher risk of reperfusion failure and remains a therapeutic challenge. Emergent rescue treatments, such as antiplatelet drug adding, angioplasty and/or stent deployment, are often necessary in these cases[4]. A recent cohort analysis with data from the ANGEL-ACT registry has shown that angioplasty and/or stenting is effective and safe in patients with an ICAS-LVO and should be performed at an early stage of the endovascular procedure to increase the chances of success[24]. A diagnostic tool with this clinico-radiological set can optimize patient assessment in order to adopt pathophysiology-based decisions. Implementing upfront the recommended pharmacological and mechanical strategies for ICAD lesions, will avoid extensive activation of the underlying plaque secondary to multiple failed passes with non-specific devices. The EVT strategy often includes an initial loading of antiplatelet drugs and gentle debulking of the lesion with a first thrombectomy attempt, followed by an intracranial angioplasty and eventual stent deployment. Therefore, considering this approach before initiating the procedure or after the first thrombectomy attempt could potentially enhance the detection of those occlusions with a higher odd of no reperfusion, and may also prevent therapeutic inertia using rescue treatments at an early stage.

Multiple studies have analyzed clinical and radiological variables associated with ICAS-LVO[5–7,25]. However, this study combines NNCT findings with CTP-derived parameters and clinical variables to allow an accurate prediction of patients with ICAS-LVO.

In our study, a symptomatic IAC was identified in 21.1% of patients with ICAS-LVO, whereas it was found in only 4.2% of patients with embolic occlusions. This finding has been confirmed in other cohorts of patients with ICAS-LVO, where it is reported in 33% of cases[26]. Hence, symptomatic IAC are associated with unsuccessful reperfusion and could be used as an adjunct biomarker in the diagnosis of intracranial atherosclerotic disease in addition to other imaging features such as the presence intracranial atherosclerotic plaque on MRI or perfusion imaging maps patterns[12]. A preceding study showed that individuals with symptomatic IAC occlusion who underwent rescue procedures (intracranial angioplasty and/or stenting bailout) exhibited similar recanalization rate to that of individuals with non-calcified thrombus[12]. Hence, an early adoption of rescue procedures might lead to improved clinical and angiographic outcomes in patients with an ICAS-LVO in conjunction with IAC.

The hypoperfusion intensity ratio is a reliable indicator of collateral status in acute ischemic stroke, which can be quantitatively and automatically derived from CT perfusion datasets. Although a definitive threshold for defining poor collateral status based on HIR is not well established and may vary between different software programs, Guenego et al. showed that a threshold of HIR < 0.4 was associated with good collaterals on digital substraction angiography[27,28]. A more stringent HIR threshold of < 0.3 has been suggested for excellent collateral status and < 0.22 for predicting underlying ICAD in the anterior circulation LVO[7,15]. Therefore, defining a stricter HIR threshold into the stroke-decision workflow could be beneficial for supporting neurointerventionalists in predicting underlying ICAD etiology or identifying "fast/slow stroke progressors". Hence, our findings are consistent with previously published data and HIR < 0.25 dichotomization could be considered for this purpose. Although other CTP automated parameters, such as $T_{max} > 4$ s/$T_{max} > 6$ s ≥ 2, have been proposed as potential markers for ICAS-LVO; these parameters remain non-validated and shown to be less determinant than HIR in predicting ICAS-LVO in our population[5].

The development of a predictive tool with these patient characteristics could help in the early identification of patients who might benefit from a frontline EVT approach different than the usual stentretriever or direct aspiration techniques, considering treatments such as antiplatelet loading and balloon angioplasty + /− stenting at an early stage (either as a first technique or following a failed first-pass thrombectomy attempt). However, there is no robust evidence available to support an optimal treatment strategy for patients with ICAS-LVO undergoing EVT and prospective studies are needed. The ongoing Registry of Emergent Large veSsel oCclUsion duE to IntraCranial AtherosclerosiS (RESCUE-ICAS, ClinicalTrials.gov Identifier NCT05403593) and The Rescue Stenting for Failed Endovascular Thrombectomy in Acute Ischemic Stroke (ReSET, ClinicalTrials.gov Identifier NCT03993340) will provide an important insight to design randomized controlled trials in this patient population.

Limitations

This study has some limitations due to its inherent retrospective, observational and single-center analysis. Main limitations include the lack of independent imaging core laboratory to assess ICAD diagnosis, and the self-reported eTICI evaluation. Patients with absence of recanalization (eTICI 0) were unable to establish underlying ICAD if alternative etiology was present[29], nonetheless these patients exhibit occlusions with a higher risk of reperfusion failure and would also benefit from an intensive treatment involving mechanical or pharmacological rescue measures. Furthermore, these study findings are confirmed in the sensitivity analysis of patients with successful reperfusion.

Even though ICAD is the most common cause of stenosis/re-occlusion, in some cases it may indicate iatrogenic dissection or focal vasospasm. An artificial intelligence automated tool to detect IAC rapidly is warranted. Another limitation is the lack of a standardize decision tree on the adoption of rescue treatments, that were decided patient by patient according to the interventionalist criteria.

Although the model maintains an adequate predictive capability in our cohort, due to the potential limitations of the study, its predictive ability could be lower in other populations. Hence, the results need to be replicated in multicenter studies and in other to replicate our findings and establish its usefulness in routine clinical practice.

Conclusions

A combination of baseline clinico-radiological characteristics assessed before EVT could help to identify anterior circulation ICAS-LVO in non-Asian populations. Imaging biomarkers such as intracranial artery calcifications, collateral status and occlusion location are associated with ICAS-LVO. This approach could be useful to perform a rapid assessment of the underlying etiology, thus guiding a patient-tailored thrombectomy. Prospective studies are needed to validate these novel findings in other populations.

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Author contributions

M.R-G, A.G-T, M.Re, and M.Ri contributed to the conception and design of the study. M.R-G, A.G-T, M.Re, M.Ru, M.D, M.O-G, C.P, F.R, M.M, N.R-V, D.R-L, J.J, J.P, D.H, C.M, A.T, M.Ri contributed to the acquisition and analysis of data. I.V-G, S.B and M.T. provided an external technical review and assistance in statistical analysis. M.R-G drafted the article and prepared the figures with significant contributions from A.G-T, M.Re, A.T, and M.Ri. All authors reviewed and edited the earlier draft of this article and approved the final version of the same.

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Competing interests

Dr Molina reported receiving personal fees from AstraZeneca for consultant services outside the submitted work. Dr Tomasello reported receiving personal fees from Anaconda Biomed, Balt, Medtronic, Perflow, and Stryker outside the submitted work. Dr Ribo reported receiving personal fees from Anaconda Biomed, AptaTargets, Cerenovus, Medtronic, Methinks, Philips, Sanofi, Stryker, Balt, and Rapid AI outside the submitted work; he has a modest ownership of NoraHealth. The other authors report no conflicts. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Additional information

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4.3. Stent retriever AssIsted Lysis (SAIL) Technique with Tirofiban: A Potential Bailout Alternative to Angioplasty and Stenting

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Stent retriever AssIsted Lysis (SAIL) Technique with Tirofiban: A Potential Bailout Alternative to Angioplasty and Stenting

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Stent Retriever AssIsted Lysis Technique with Tirofiban: A Potential Bailout Alternative to Angioplasty and Stenting

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ABSTRACT

BACKGROUND AND PURPOSE: Angioplasty and stent placement have been described as a bailout technique in individuals with failed thrombectomy. We aimed to investigate Stent retriever AssIsted Lysis (SAIL) with tirofiban before angioplasty and stent placement.

MATERIALS AND METHODS: Patients from 2 comprehensive stroke centers were reviewed (2020–2023). We included patients with failed thrombectomy and/or underlying intracranial stenosis who received SAIL with tirofiban before the intended angioplasty and stent placement. SAIL consisted of deploying a stent retriever through the occluding lesion to create a bypass channel and infuse 10 mL of tirofiban for 10 minutes either intra-arterially or IV. The stent retriever was re-sheathed before retrieval. The primary end points were successful reperfusion (expanded TICI 2b–3) and symptomatic intracerebral hemorrhage. Additional end points included 90-day mRS 0–2 and mortality.

RESULTS: After a median of 3 (interquartile range, 2–4) passes, 44 patients received the SAIL bridging protocol with tirofiban, and later they were considered potential candidates for angioplasty and stent placement bailout (43.2%, intra-arterial SAIL). Post-SAIL successful reperfusion was obtained in 79.5%. A notable residual stenosis (>50%) after successful SAIL was observed in 45.7%. No significant differences were detected according to post-SAIL: successful reperfusion (intra-arterial SAIL, 80.0% versus IV-SAIL, 78.9%; $P = .932$), significant stenosis (33.3% versus 55.0%; $P = .203$), early symptomatic re-occlusion (0% versus 8.0%; $P = .207$), or symptomatic intracerebral hemorrhage (5.3% versus 8.0%; $P = .721$). Rescue angioplasty and stent placement were finally performed in 15 (34.1%) patients (intra-arterial SAIL 21.0% versus IV-SAIL 44%; $P = .112$). At 90 days, mRS 0–2 (intra-arterial SAIL 50.0% versus IV-SAIL 43.5%; $P = .086$) and mortality (26.3% versus 12.0%; $P = .223$) were also similar.

CONCLUSIONS: In patients with stroke in which angioplasty and stent placement are considered, SAIL with tirofiban, either intra-arterial or IV, seems to safely induce sustained recanalization, offering a potential alternative to definitive angioplasty and stent placement.

ABBREVIATIONS: A&S = angioplasty and stenting; eTICI = expanded TICI; EVT = endovascular treatment; IA = intra-arterial; ICAD = intracranial atherosclerotic disease; ICAS-LVO = intracranial atherosclerosis–related large-vessel occlusion; IQR = interquartile range; LVO = large-vessel occlusion; MT = mechanical thrombectomy; SAIL = Stent retriever–AssIsted Lysis; sICH = symptomatic intracerebral hemorrhage; SR = stent retriever

Mechanical thrombectomy (MT) with conventional devices such as stent retrievers (SRs) and aspiration catheters has become the standard of care for patients presenting with ischemic stroke due to a large-vessel occlusion (LVO).[1] However, MT fails to achieve successful reperfusion in approximately 10%–20% of patients. The optimal MT strategy to address occlusions refractory to conventional thrombectomy devices remains unclear. In these cases, an underlying intracranial atherosclerotic disease (ICAD) is usually suspected,[2,3] and repeat thrombectomy attempts may only lead to increased activation of the underlying unstable plaque, decreasing the chances of sustained recanalization at the end of the procedure due to in situ thrombosis and re-occlusion despite final rescue with angioplasty and stent placement.[4,5]

A recent study reported that alternative techniques, beyond SR and aspiration thrombectomy, may be required in up to 70% of patients with an ICAD-related LVO, in contrast to the 7% observed among in individuals with embolic occlusions.[5] Several

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SUMMARY

PREVIOUS LITERATURE: The optimal mechanical thrombectomy strategy to address occlusions refractory to conventional thrombectomy devices remains unclear. Repeated thrombectomy attempts may lead to increased activation of the underlying unstable plaque, in situ thrombosis, and re-occlusion. Several rescue treatments after failed MT have been proposed to achieve successful reperfusion; including balloon angioplasty, intracranial stent placement, or glycoprotein IIb/IIIa inhibitors infusion.

KEY FINDINGS: The Stent retriever AssIsted Lysis (SAIL) is a novel technique in which stent retriever deployment temporarily dilates the lesion creating a bypass channel that ensures arrival of tirofiban to the whole target plaque. The SAIL technique with tirofiban, either intra-arterial or intravenous, seems to safely induce sustained recanalization, potentially avoiding definitive intracranial rescue stent placement.

KNOWLEDGE ADVANCEMENT: The present work provides new clinical insights of the SAIL technique as a potential alternative to traditional bailout when conventional thrombectomy devices fail to recanalize the occluded artery. Further studies are warranted to confirm the efficacy and determine the optimal administration route of tirofiban.

rescue treatments after failed MT have been proposed to achieve successful reperfusion, including balloon angioplasty, intracranial stent placement, or glycoprotein IIb/IIIa inhibitor infusion.[6-9]

Stent retriever AssIsted Lysis (SAIL) with tirofiban is a novel technique in which SR deployment temporarily dilates the lesion creating a bypass channel that ensures arrival of the concomitantly infused drug to the whole target plaque. We aimed to describe the potential benefits of SAIL with tirofiban as a bridging technique before angioplasty and stent placement (A&S) to induce reperfusion in patients with suspected intracranial atherosclerosis–related large-vessel occlusion (ICAS-LVO) and/or refractory occlusions.

MATERIALS AND METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements. All procedures were conducted in strict adherence to applicable guidelines and regulations.[10,11] The study protocol was reviewed and approved by the Vall d'Hebron Hospital Ethics Committee, approval No. PR(AG)434/2023. Because of the retrospective nature of this study, the need for written informed consent was waived.

Data Availability

Anonymized data supporting the findings of the current study are available for any qualified investigator on reasonable request to the corresponding author.

Study Design and Population

We performed a retrospective cross-sectional study based on a prospectively maintained database of patients with an acute ischemic stroke undergoing endovascular reperfusion treatment at 2 European comprehensive stroke centers. We included patients with an intracranial LVO (intracranial ICA, MCA segments M1 and M2, and vertebral and basilar arteries) who underwent endovascular treatment (EVT) from January 2020 to September 2023 and were expected to receive A&S after at least 1 unsuccessful pass of MT (TICI 0–2a) with an SR or direct aspiration and/or presented with an underlying primary or residual angiographic stenosis. All patients received SAIL as a bridging therapy before traditional bailout. Exclusion criteria were admission after 24 hours from stroke-symptom onset and the presence of an isolated extracranial occlusion of the ICA.

EVT

All procedures were performed according to institutional protocols based on European Stroke Organization guidelines.[12] First-line EVT was performed with a commercially available SR and/or aspiration catheters. The reasons to switch to SAIL were the following: 1) incomplete reperfusion (expanded TICI [eTICI] 0-2a) and/or a trend toward re-occlusion, 2) underlying primary or residual stenosis, and 3) persistence of occlusive/subocclusive thrombus. Decisions to perform SAIL, the route of tirofiban administration (intra-arterial versus IV), and adoption of further bailout/rescue techniques (intracranial angioplasty ± intracranial stent placement [A&S]) were made according to neurointerventionalists' criteria. The residual stenosis degree was assessed according to the Warfarin-Aspirin Symptomatic Intracranial Disease Study criteria.[13]

SAIL Technique

SAIL was adopted as bridging before proceeding with definitive A&S, according to neurointerventionalists' criteria after a variable number of failed MT attempts. A microcatheter with a microguidewire was navigated through a distal-access catheter distal to the lesion. An SR was deployed over the occlusion to dilate the lesion and create a temporary bypass channel. Tirofiban infusion was then initiated by either the intra-arterial (IA) route through the distal-access catheter positioned at the proximal end of the SR (IA-SAIL group) or intravenously (IV-SAIL group). The bolus infusion was maintained for 10 minutes, and the standard dose was 10 μg/kg. Once the tirofiban infusion was completed, the SR was gently re-sheathed into the microcatheter before retrieval to avoid friction and reactivation of the underlying plaque. Recanalization was assessed before and after the rescue procedures (angioplasty and/stent placement) were adopted (if performed) during the hyperacute EVT procedure. In most cases, the initial tirofiban administration was followed by a continuous IV infusion (0.15 μg/(kg $\times$ min) during the next 12–24 hours. In Fig 1, an illustrative case of the procedure is presented.

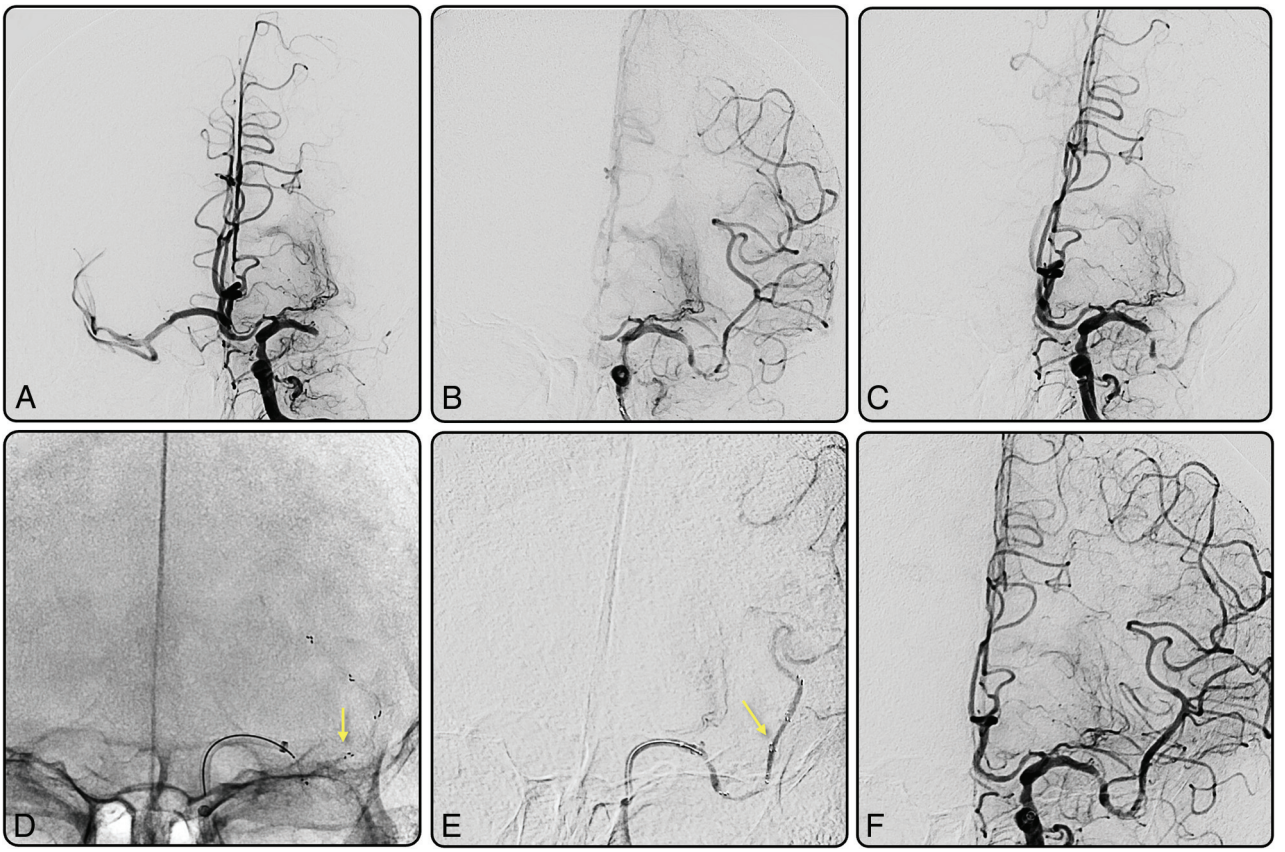

FIG 1. Illustrative case of SAIL with IA tirofiban. *A*, First angiography run shows MCA occlusion (segment M1). After 2 (*B*) and 3 (*C*) attempts of MT with an SR and distal aspiration, there is partial recanalization with a trend to re-occlusion. An SR was deployed over the lesion to create a bypass channel (*D*), and tirofiban was locally infused (*E*) for 10 minutes through a distal-access catheter. An angiogram was obtained to determine the recanalization grade showing successful reperfusion. No re-occlusion was reported at follow-up (*F*). *D*, The *yellow arrow* shows the stent retriever deployed through the occlusive lesion. *E*, The *yellow arrow* shows the created bypass channel and the administration of tirofiban mixed with contrast to ensure the flow.

Clinical and Radiologic Parameters

Recorded demographic and clinical variables included age, sex, baseline mRS, medical comorbidities, stroke severity assessed by NIHSS, admission ASPECTS, workflow times (symptom onset, imaging, and groin puncture), and administered reperfusion therapies.

The degree of reperfusion was determined prospectively by consensus between the interventionalist and the vascular neurologist immediately after the procedure using the eTICI score. Patients were considered to have achieved successful reperfusion if at least 50% of downstream reperfusion was attained (eTICI ≥ 2b50).

Symptomatic intracerebral hemorrhage (sICH), 90-day mRS, and mortality were recorded as clinical and safety outcomes. sICH was defined as any intracranial hemorrhage according to Heidelberg Bleeding Classification that led to neurologic deterioration, as reflected by the NIHSS score worsening of ≥4.[14] Early symptomatic re-occlusion was defined as a neurologic deterioration (NIHSS score worsening of ≥4) associated with re-occlusion of the initially recanalized target artery in the first 24 hours. The degree of recanalization and re-occlusion at 24 hours was assessed by CT/MRA and/or transcranial Doppler according to local center guidelines. At 90 days, functional independence was defined as mRS 0–2.

Statistical Analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assure the normality of continuous variables. Categoric variables were presented as absolute values and percentages, and continuous variables, as median, interquartile range (IQR) or mean (SD) as indicated. Statistical significance for intergroup differences was assessed by the Pearson χ^2 test or the Fisher exact test for categoric variables and the Mann-Whitney *U* test or Student *t* test as appropriate to continuous variables. Multivariable binary logistic regression analyses were modeled to determine the association between the tirofiban route of administration and outcomes. Multivariable analyses were adjusted using variables that presented a statistically significant association or clinical relevance with the explored outcome. Five patients with premorbid mRS 3 were excluded from functional independence analysis.

A P value $< .05$ was considered statistically significant. All analyses were performed using the SPSS Statistics software, Version 25 (IBM).

RESULTS

From a total of 1630 patients who underwent EVT for an intracranial LVO, 44 (2.7%) patients received the SAIL bridging protocol with tirofiban, and later they were considered potential

Table 1: Baseline characteristics and demographics

	All Patients ($n = 44$)	IV Tirofiban ($n = 25$)	IA Tirofiban ($n = 19$)	*P* Value
Age (mean) (yr)	70 (SD, 14)	65 (SD, 15)	77 (SD, 9)	.003
Sex (male) (No. %)	21 (47.7%)	11 (44.0%)	10 (52.6%)	.570
Risk factors (No. %)				
Former or current smoker	9 (20.4%)	4 (16.3%)	5 (26.3%)	.250
Hypertension	30 (68.2%)	14 (56.0%)	16 (84.2%)	.047
Diabetes mellitus	14 (31.8%)	4 (16.0%)	10 (52.6%)	.010
Dyslipidemia	17 (38.6%)	7 (28.9%)	10 (52.6%)	.096
Atrial fibrillation	5 (11.4%)	1 (4.0%)	4 (21.1%)	.077
Ischemic heart disease	8 (18.2%)	3 (12.0%)	5 (26.3%)	.223
Active oncological disease	0 (0%)	0 (0%)	0 (0%)	NA
Previous stroke	3 (6.8%)	1 (4.0%)	2 (10.5%)	.395
Premorbid mRS (median, IQR)	0 (0−1)	0 (0–0)	1 (0−2)	<.001
Baseline NIHSS (median, IQR)	12 (8−17)	11 (7−18)	15 (10−17)	.484
Occlusion level (No. %)				.041
Intracranial ICA	6 (13.6%)	3 (12.0%)	3 (15.8%)	
MCA M1	25 (56.8%)	16 (50.0%)	10 (52.6%)	
MCA M2	7 (15.9%)	1 (4.0%)	6 (31.6%)	
Intracranial VA	1 (2.3%)	1 (4.0%)	0 (0%)	
Basilar artery	5 (11.4%)	5 (20.0%)	0 (0%)	
IV thrombolysis (No. %)	14 (31.8%)	9 (36.0%)	5 (26.3%)	.495
Wake-up stroke (No. %)	12 (27.3%)	5 (20.0%)	7 (36.8%)	.214
Onset to imaging (mean) (min)	300 (SD, 266)	253 (SD, 249)	364 (SD, 284)	.175
Onset-to-groin time (mean) (min)	411 (SD, 302)	412 (SD, 318)	410 (SD, 288)	.980
ASPECTS (median, IQR)	9 (8−10)	9 (8−9)	9 (8−10)	.208
Symptomatic IAC (No. %)	16 (36.4%)	12 (48.0%)	4 (21.1%)	.066
Stroke etiology (No. %)				.082
Cardioembolic	10 (22.7%)	2 (8.0%)	8 (42.1%)	
Atherothrombotic (ICAS-LVO)	27 (61.4%)	18 (72.0%)	9 (47.4%)	
Undetermined	3 (6.8%)	2 (8.0%)	1 (5.3%)	
Dissection	2 (4.5%)	2 (8.0%)	0 (0%)	
Other	2 (4.5%)	1 (4.0%)	1 (5.3%)	

Note:—IAC indicates intracranial artery calcification; NA, not applicable; VA, vertebral artery.

candidates for A&S bailout. Twenty-five patients (56.8%) received IV-SAIL, while 19 patients (43.2%) received IA-SAIL. The mean age was 70 (SD, 14) years, 21 patients (47.7%) were men, and the median premorbid mRS was 0 (IQR, 0−1). The median NIHSS score at admission was 12 (IQR, 8−17). The occlusion locations were as follows: ICA (6, 13.6%), MCA M1 (25, 56.8%), M2 (7, 15.9%), vertebral artery (1, 2.3%), and basilar artery (5, 11.4%). ICAD stroke etiology was confirmed in 27 patients (61.4%).

Table 1 summarizes the baseline characteristics and demographics according to the route of administration of tirofiban.

Angiographic Outcomes

The rate of successful reperfusion (eTICI ≥2b) with conventional MT was 18.2% (8/44). The 8 patients with eTICI ≥2b received SAIL (4 in the IV-SAIL group and 4 in the IA-SAIL group [21.1%, $P = .667$]) because a significant >50% underlying stenosis persisted at the site of occlusion despite successful recanalization. The other main reasons to indicate SAIL with tirofiban were incomplete reperfusion (eTICI 0–2a: 11/44, 25.0%) and immediate re-occlusion (16/44, 36.4%). The median number of failed conventional thrombectomy attempts before adopting SAIL was 3 (IQR, 2−4). The rate of sustained successful reperfusion after the SAIL technique was 79.5% (35/44), regardless of the administration route of tirofiban (IV: 80% versus IA: 78.9%; $P = .932$).

The overall rate of persistent significant stenosis after successful SAIL was 45.7% (16/35) with no differences between IA-SAIL (33.3%, 5/15) and IV-SAIL (55.0%, 11/20; $P = .203$). Rescue A&S was finally performed in 15 patients (overall, 34.1%: IA-SAIL 4/19, 21.1% versus IV-SAIL 11/25, 44.0%; $P = .112$). After rescue A&S, the rate of successful reperfusion increased to 88.6%.

After we adjusted for confounders in a multivariate model (Online Supplemental Data), no differences were observed between IA-SAIL and IV-SAIL regarding successful reperfusion after SAIL (OR, 0.2; 95% CI, 0.0−10.8; $P = .426$) or at the end of the procedure, including A&S bailout (OR, 0.04; 95% CI, 0.0−2.75; $P = .137$).

Two periprocedural major complications were recorded (1 intracranial dissection and 1 perforation); both occurred during A&S bailout. A detailed description of endovascular treatment characteristics is presented in Table 2.

Clinical and Safety Outcomes

Clinical and safety outcomes are shown in Table 3 and the Online Supplemental Data.

At 24 hours, the median NIHSS score was 11 (IQR, 5–18), with no significant differences between IA-SAIL (14 [7−21]) and IV-SAIL (9 [5−15]; $P = .079$). Additionally, 2 patients (8%) in the IV-SAIL group experienced an early symptomatic re-occlusion but none (0%) in the IA-SAIL group ($P = .207$) did.

The sICH rate was 6.8% (IA-SAIL 5.3% versus IV-SAIL 8.0%, $P = .721$). Eleven patients (25.0%) experienced a mild asymptomatic SAH. At 3 months, the mortality rate was 18.2% (IA-SAIL 26.3% versus IV-SAIL 12.0, $P = .223$).

Table 2: Characteristics of endovascular treatment

	All Patients ($n = 44$)	IV Tirofiban ($n = 25$)	IA Tirofiban ($n = 19$)	*P* Value
First-line endovascular technique (No. %)				<.001
ADAPT	17 (38.6%)	15 (60.0%)	2 (10.5%)	
SR alone	4 (9.1%)	4 (16.0%)	0 (0%)	
SR plus distal aspiration	18 (40.9%)	6 (24.0%)	12 (63.2%)	
SAIL technique with tirofiban	5 (11.4%)	0 (0%)	5 (26.3%)	
Angioplasty/stent placement	0 (0%)	0 (0%)	0 (0%)	
No. of passes before SAIL (median, IQR)	3 (2–4)	4 (2–5)	3 (1–3)	.026
Reason for SAIL with tirofiban (No. %)				<.001
Incomplete reperfusion (eTICI 0–2a)	11 (25.0%)	0 (0%)	11 (57.9%)	
Trend to re-occlusion	16 (36.4%)	14 (87.5%)	2 (12.5%)	
Underlying primary or residual stenosis	13 (29.5%)	8 (32.0%)	5 (26.3%)	
Subocclusive thrombus	4 (9.1%)	3 (12.0%)	1 (5.3%)	
eTICI ≥2b after conventional MT (No. %)	8 (18.2%)	4 (16.0%)	4 (21.1%)	.667
eTICI ≥2b after SAIL with tirofiban (No. %)	35 (79.5%)	20 (80.0%)	15 (78.9%)	.932
Significant residual stenosis (>50%) after successful SAIL (No. %)	16/35 (45.7%)	11/20 (55.0%)	5/15 (33.3%)	.203
Intracranial angioplasty and/or stent placement after tirofiban (No. %)	15 (34.1%)	11 (44%)	4 (21.0%)	.112
Angioplasty	9 (20.5%)	7 (28.0%)	2 (10.5%)	
Stent placement	6 (13.6%)	4 (16.0%)	2 (10.5%)	
Final eTICI ≥2b (No. %)	39 (88.6%)	24 (96.0%)	15 (78.9%)	.077
Groin-to-reperfusion time (mean) (min)	100 (SD, 32)	111 (SD, 34)	87 (SD, 24)	.009
Procedural complications (No. %)				.587
Vasospasm target vessel	3 (6.8%)	2 (8.0%)	1 (5.3%)	
Dissection target vessel	1 (2.3%)	1 (4.0%)	0 (0%)	
Perforation	1 (2.3%)	0 (0%)	1 (5.3%)	
Dissection/perforation at tirofiban bailout	0 (0%)	0 (0%)	0 (0%)	
Distal embolism	5 (11.4%)	2 (8.0%)	3 (15.8%)	
New territory embolism	0 (0%)	0 (0%)	0 (0%)	
In-stent thrombosis	0 (0%)	0 (0%)	0 (0%)	
ICA dissection/vasospasm	0 (0%)	0 (0%)	0 (0%)	

Note:—ADAPT indicates A Direct Aspiration First Pass Technique.

Table 3: Safety and clinical outcomes

	All Patients ($n = 44$)	IV Tirofiban ($n = 25$)	IA Tirofiban ($n = 19$)	*P* Value
Early symptomatic vessel re-occlusion (24 hr) (No. %)	2 (4.5%)	2 (8.0%)	0 (0%)	.207
Degree of recanalization at follow-up (No. %)				.010
Complete recanalization/stenosis <50%	22 (68.8%)	13 (56.5%)	9 (100%)	
Stenosis >50%	6 (18.8%)	6 (26.1%)	0 (%)	
Occlusion	4 (12.5%)	4 (17.4%)	0 (0%)	
NIHSS at 24 hr (median, IQR)	11 (5–18)	9 (5–15)	14 (7–21)	.079
NIHSS at discharge (median, IQR)	8 (2–15)	8 (2–14)	9 (4–21)	.256
sICH (No. %)	3 (6.8%)	2 (8.0%)	1 (5.3%)	.721
Postprocedural SAH (No. %)	11 (25.0%)	5 (20.0%)	6 (31.6%)	.380
90-Day mortality (No. %)	9 (18.2%)	3 (12.0%)	5 (26.3%)	.223
90-Day mRS 0–2 (No. %)	18/39 (46.2%)	10/23 (43.5%)	8/16 (50.0%)	.688
90-Day mRS 0–3 (No. %)	26 (59.1%)	16 (64.0%)	10 (52.6%)	.447

Functional independence (mRS 0–2) was achieved in 46.2% of all patients (8/16, IA-SAIL 50.0% versus IV-SAIL, 43.5%, $P = .688$).

A logistic regression model adjusting for potential confounders did not find a significant association between IA-SAIL or IV SAIL with symptomatic intracranial hemorrhage, mortality, or 90- day disability (Online Supplemental Data).

DISCUSSION

Our study shows that SAIL with tirofiban, both IA and IV, is a safe and effective technique for patients with refractory occlusions and/or suspected underlying intracranial stenosis who are candidates for rescue treatment. The use of this technique could potentially avoid the conversion to intracranial angioplasty and stent placement in many cases or confirm the indication in others. As a result, the present work provides new clinical insight about SAIL as a potential alternative to traditional bailout when conventional thrombectomy devices fail to recanalize the occluded artery. Moreover, the adoption of the SAIL technique in patients with failed recanalization could not only improve reperfusion in these patients but also confirm the underlying etiology to optimize secondary prevention treatment.

In this study focused on patients in whom conventional MT did not succeed, the use of bridging SAIL with tirofiban achieved a sustained successful reperfusion in approximately 80% of patients. Additional rescue treatments were required in only

34.1% of these patients. Our sample size is not large enough to describe the superiority of one administration route over the other; the available data suggest that in selected cases, both IV and IA SAIL with tirofiban seem to be similarly safe and effective. The overall rate of sICH (6.6%) and 90-day mortality (18.2%) were comparable with the rates described in large series of unselected patients receiving EVT with conventional devices approved for MT.[15,16]

The administration of tirofiban in ischemic stroke has been described in multiple studies as a safe and potential choice for acute stroke management, both in the presence of LVO and in cases of minor stroke with unplanned EVT.[15,17-20] Recently, the International Stroke Perfusion Imaging Registry (INSPIRE) study reported that IA tirofiban could be associated with an increased risk of bleeding and death.[21] The authors suggested that an IA bolus injection provides a direct contact of tirofiban with the thrombus, with a dramatic increase in the local drug concentration. They hypothesized that this might cause damage to the BBB leading to cerebral hemorrhage. Another study showed that IA tirofiban could decrease the rates of excellent outcome (90-day mRS 0–1) and functional independence (90-day mRS 0–2) in patients with ICAS-LVO undergoing EVT.[22]

To date, there have been no randomized controlled trials investigating the preferred administration route of tirofiban, and all studies have been based on observational data. In our study, the SAIL technique creates a bypass channel across the clot favoring, on one hand, a direct contact of tirofiban through the whole length of the clot and, on the other, a continuous stream and washout that prevents drug stagnation at high concentrations and BBB damage, potentially avoiding a higher risk of hemorrhage and clinical deterioration. Given that the underlying etiology in most patients was probably related to ICAD, SAIL allowed the administered tirofiban to act rapidly at the whole length of the lesion, stabilizing the plaque and locally inhibiting platelet aggregation. Moreover, re-sheathing the SR into the microcatheter before retrieval prevents new denudation and reactivation of the just-stabilized plaque, thereby reducing the risk of re-occlusion.

In our series, the only 2 patients who presented with an early symptomatic re-occlusion were in the IV tirofiban group, suggesting a potentially greater effect of IA administration. The trends toward reduced A&S conversion and higher functional independence rates also suggest the potential benefit of the IA over the IV route of tirofiban administration. However, this potential benefit needs to be weighed against the potential downside of a heightened risk of mortality. Further randomized controlled trials should be developed to confirm this observation and verify the safety of IA tirofiban treatment.

Rescue conversion to angioplasty and stent placement following failed MT had been reported as an effective treatment, leading to high odds of successful reperfusion and 90-day functional independence, independent of the presence of underlying ICAD.[23-25] However, the rate of sICH in patients who underwent rescue A&S ranged from 7% to 10.5%, which is slightly higher than the rate reported with the SAIL technique (6.8%). Mortality was also higher in large observational series of patients with rescue intracranial stent placement after failed thrombectomy (18.5%–29.9% versus 18.2% in SAIL technique).[4,23,26] Hence, certain scenarios can advise against A&S, such as patients with a large infarct core or a history of intracranial hemorrhage or cases in which the lesion originates in arterial segments rich in perforator arteries at high risk of occlusion after angioplasty due to the snowplow effect.[8] The early adoption of SAIL could prevent increasing endothelial damage caused by repetitive MT attempts, offering a potential alternative before the final decision of A&S conversion is made.

Additional studies are warranted to confirm our observation and fine-tune the treatment algorithms describing the optimal steps in which SAIL and A&S should be considered and adopted. The potential negative impact of increasing MT attempts before SAIL, as observed in cases of A&S bailout, should also be investigated.[7]

Limitations

This study has some limitations due to its inherent retrospective and observational nature, in addition to the relatively small sample size of patients included and the absence of a control group of patients who underwent A&S without SAIL bridging therapy. The clot location (including anterior and posterior LVO) and etiology heterogeneity could dilute the potential benefit of the SAIL technique in a specific etiology such as ICAD. Other limitations include the lack of an independent imaging core laboratory to adjudicate recanalization outcomes and the decision to adopt SAIL or traditional bailout with angioplasty and/or stent placement being at the discretion of the treating neurointerventionalist. For these reasons, the study should be considered as a pilot and used to provide preliminary data for the design of future confirmatory studies.

CONCLUSIONS

In patients with stroke undergoing EVT in which intracranial angioplasty and stent placement are considered as bailout after failed mechanical thrombectomy, the SAIL technique with tirofiban, either IA or IV, seems to safely induce sustained recanalization in a substantial number of patients, potentially avoiding definitive stent placement. Further studies are warranted to confirm the efficacy and determine the optimal administration route of tirofiban.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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5. RESUMEN GLOBAL DE RESULTADOS

5. RESUMEN GLOBAL DE RESULTADOS

5.1. Valor de las calcificaciones arteriales intracraneales

En el primer estudio se evaluaron un total de 462 pacientes que se presentaron en nuestro centro con un ictus isquémico asociado a una oclusión de gran o mediano vaso entre enero de 2020 y julio de 2021. Finalmente, se analizaron 393 pacientes y se excluyeron 69 pacientes debido a un tiempo de evolución >24h, oclusión extracraneal aislada o ausencia de TC craneal basal (traslado directo a sala de angiografía).

Se observaron 26 pacientes que presentaban una calcificación arterial intracraneal (IAC, del inglés intracranial artery calcification) sintomática en el lugar de la oclusión (s-IAC: 6.6%), 77 pacientes con una IAC asintomática (a-IAC: 19.6%) y 290 pacientes no presentaban IAC (no-IAC: 73.8%).

Las calcificaciones sintomáticas se localizaron con mayor frecuencia en la ACI terminal (9/26, 34.6%) y la circulación posterior (8/26, 30.7%).

Las s-IAC se asociaron como predictor independiente a la recanalización fallida en el primer pase (eTICI 0–2a 73,1% vs 53,2% en a-IAC y 40,7% en no-IAC), recanalización

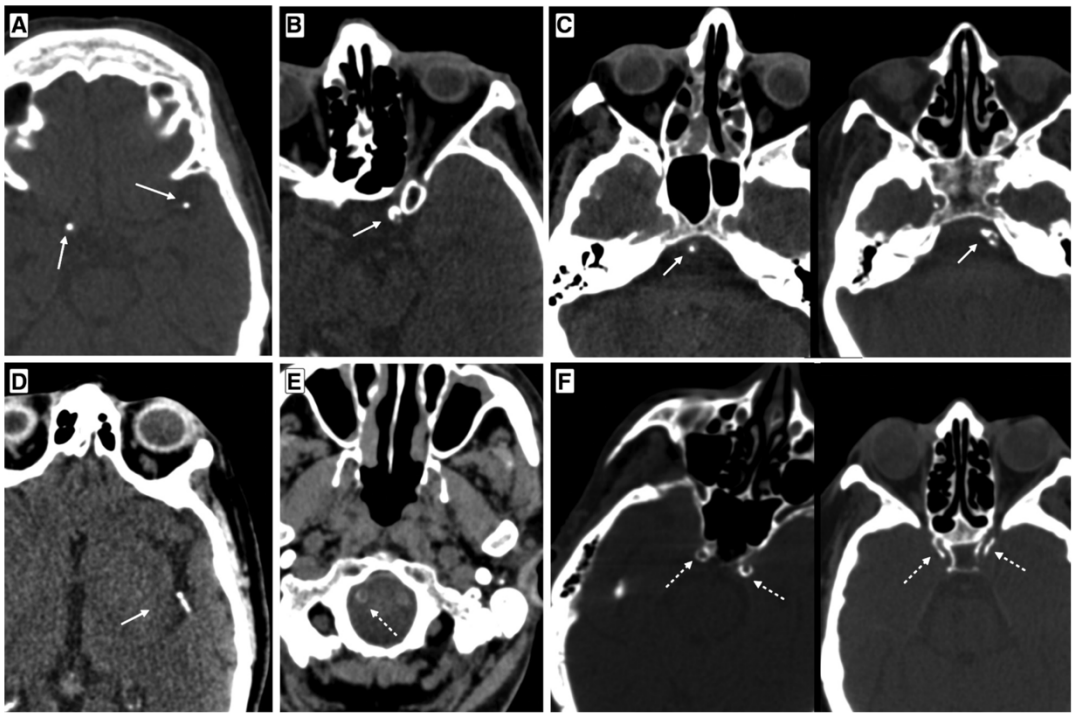

Figura 6. Patrón radiológico de las calcificaciones arteriales intracraneales (IAC).

IAC con un patrón intimal (flechas blancas) localizado en la arteria carótida interna intracraneal (ACI) y en el segmento M1 de la ACM derecha (A), en la ACI intracraneal izquierda (B), en la arteria basilar (C) y en el segmento M2 de la ACM izquierda (D). No consideramos en nuestro estudio los IAC con patrón medial (flecha punteada), como en la arteria vertebral derecha (E) y en ambas ACI (F).

fallida sin procedimientos de rescate (eTICI 0–2a 65,4% vs 15,6% en a-IAC y 13,4% en no-IAC) y la necesidad de realización de angioplastia y/o stenting intracraneal (26,9% vs 1,3% en a-IAC y 3,8% en no-IAC). Los resultados se desglosan en la taba 3.

Además, se observó un peor pronóstico a los 90 días (mRS 3–6 80,8% vs 76,6% en a-IAC and 62,3% en no-IAC) y una tendencia a una mayor mortalidad a los 90 días (42,3% vs 40,3% en a-IAC y 27,0% en no-IAC) - Figura 7.

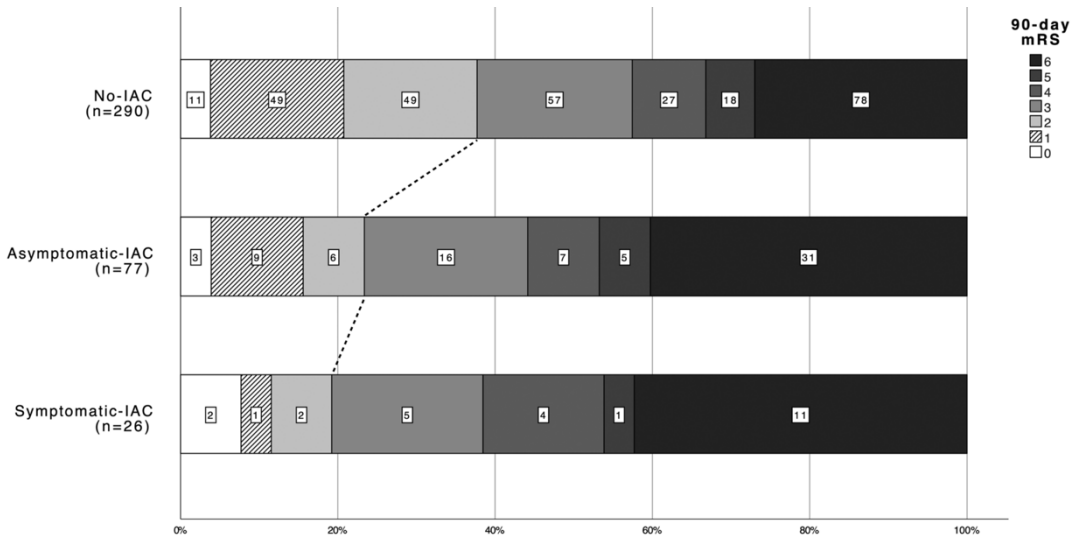

Figura 7. Distribución de la puntuación modified Rankin Scale (mRS) a los 90 días según la presencia y el patrón de calcificaciones arteriales intracraneales (IAC).

Tabla 3. Análisis de regresión logística múltiple para la calcificación arteriales intracraneales sintomáticas como un factor pronóstico desfavorable

Pronóstico angiográfico y clínico	Odds Ratio	IC 95%	P value
Recanalización fallida en el primer pase (eTICI 0-2a)	4,37	1,47-13,0	0,008
Recanalización fallida final sin procedimientos de rescate	11,89	3,94-35,91	<0,001
Recanalización fallida final	3,94	0,51-30,52	0,189
Necesidad de procedimientos de rescate (angioplastia y/o stent intracraneal)	12,38	2,22-69,09	0,004
Mortalidad 90 días	2,39	0,90-6,36	0,081
mRS 3-6 90 días	33	1,02-12,00	0,046

5.2. Biomarcadores clínicos y radiológicos predictores de ICAS-LVO

En el segundo estudio, además de las IAC, se trató de ampliar el estudio y el desarrollo de otros biomarcadores clínicos y radiológicos predictores de ICAS-LVO. Para la homogeneización de la muestra, debido a la posible alteración y artefacto en los valores automatizados de TC perfusión de las oclusiones en tándem y en circulación posterior, se excluyeron dichos pacientes del análisis.

Desde enero de 2020 hasta abril de 2022 se incluyeron 338 pacientes. Entre ellos, la etiología del ictus fue relacionada con ICAD en 28 pacientes (8,3%).

Los pacientes con ICAS-LVO eran más jóvenes (70 años [rango intercuartílico - RIC 62–77] vs 80 años [RIC 67-86]). En cuanto a los factores de riesgo, el tabaquismo era mayor (57,1% vs 23.3%) con una menor prevalencia de fibrilación auricular (3,6% vs 35.5%).

A su ingreso, la puntuación NIHSS en los pacientes con ICAS-LVO era menor (11 [RIC 8-18] vs 16 [RIC 10–20]) y los mapas de TC perfusión mostraron un menor núcleo isquémico (0 mL [RIC 0-7] vs 6 mL [RIC 0-26]) y una menor ratio de intensidad de hipoperfusión (HIR, 0.16 [RIC 0-0.37] vs 0.44 [RIC 0.29-0.57]). Además, tal como ya se había observado en el estudio previo, las IAC sintomáticas fueron más frecuentes en el grupo de ICAS-LVO (21,4 vs 4,2%).

Tras realizar un análisis de regresión y ajustar por posibles variables confusoras la ausencia de fibrilación auricular, el hábito tabáquico, la localización proximal de la oclusión, las IAC y una menor ratio de HIR se asociaron con el diagnóstico de ICAS-LVO (Tabla 4)

5.3. Modelo predictivo de ICAS-LVO

Con los resultados del análisis multivariado, se evaluó la capacidad predictiva para identificar ICAS-LVO (figura 8).

Se realizó un modelo multivariado únicamente con variables radiológicas (IAC sintomática, HIR y localización de la oclusión) que mostró una capacidad predictiva adecuada (Área bajo la curva - AUC 0.80, IC95% 0.70-0.90; $p<0.001$).

Tras añadir además las variables clínicas (hábito tabáquico y fibrilación auricular) el modelo clínico-radiológico mejoró significativamente la capacidad predictiva para identificar ICAS-LVO ((AUC 0.88, IC95% 0.83–0.94; $p<0.001$) en comparación con el modelo radiológico (DeLong test: $Z=2.0116$, $p=0.044$).

Tabla 4. Análisis de regresión logística binaria para la identificación precoz de una oclusión de gran vaso relacionada con ateromatosis intracraneal (ICAS-LVO)

Variable clínico-radiológica asociada a ICAS-LVO	Odds Ratio	IC 95%	P value
Ausencia de fibrilación auricular	9,33	1,11-78,42	0,040
Hábito tabáquico	2,91	1,08-7,90	0,035
Localización proximal (ACI intracraneal, ACM M1)	4,00	1,23-13,03	0,021
Calcificación arterial intracraneal sintomática	7,15	1,64-26,42	0,006
Ratio de intensidad de hipoperfusión (HIR)	0,69	0,50-0,95	0,025
Edad	0,99	0,96-1,02	0,523
Puntuación NIHSS basal	0,96	0,88-1,05	0,401
Nucleo isquémico (CBF <30%)	0,99	0,96-1,03	0,722
Tmax>4/Tmax>6	1,00	0,95-1,05	0,835

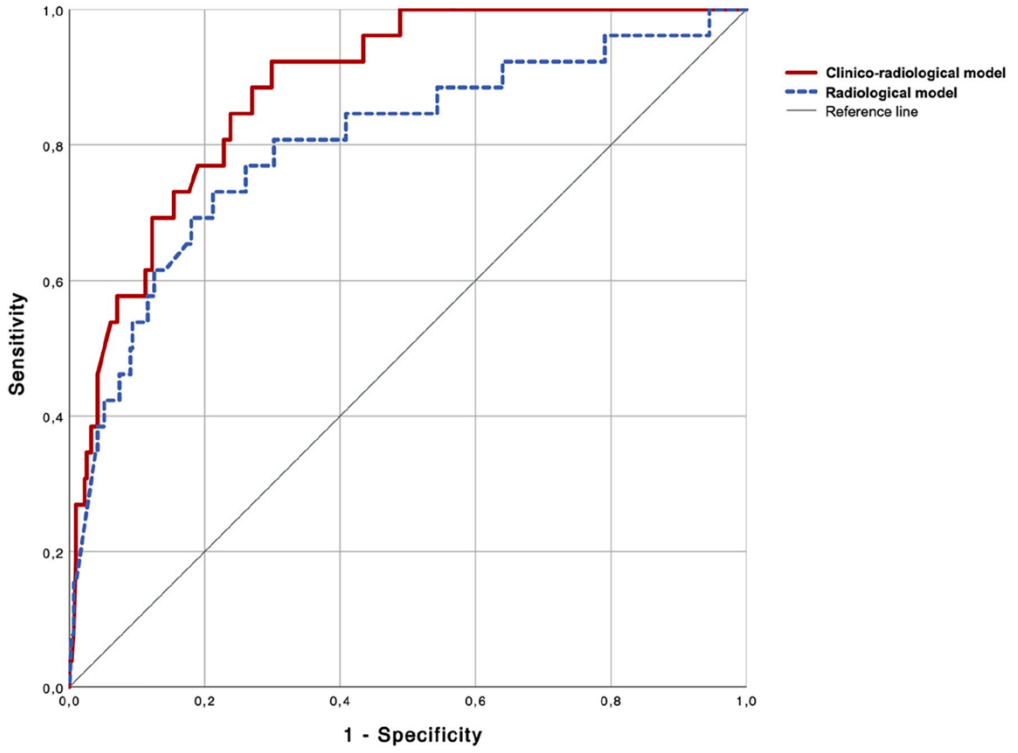

Figura 8. Capacidad predictiva para identificar oclusión de grandes vasos relacionada con ateromatosis intracraneal (ICAS-LVO) según el análisis de la curva característica operativa del receptor (ROC)

5.4. Estrategias de optimización del tratamiento endovascular

En el tercer y último estudio, se realizó un estudio retrospectivo de dos centros europeos para evaluar la técnica SAIL (Stent retriever AssIsted Lysis) con administración de tirofiban en aquellos pacientes con al menos un intento de trombectomía fallida y/o estenosis intracraneal subyacente.

La técnica SAIL es una técnica novedosa en la que se despliega un SR en el sitio de la lesión para crear un canal a lo largo de la estenosis que asegura la llegada de tirofiban y su efecto local. En la figura 9 se encuentra la descripción detallada.

Un total de 44 pacientes fueron tratados con la técnica SAIL antes de realizar un rescate tradicional con angioplastia y/o stent intracraneal. De ellos, 25 pacientes se trataron con tirofiban intravenoso (IV-SAIL 56,8%) y 19 pacientes con tirofiban intraarterial (IA-SAIL 43,2%).

La tasa de reperfusión exitosa (eTICI≥2b) con técnicas de MT convencional (SR, aspiración distal o su combinación) fue del 18.2% (8/44). En estos 8 pacientes, la técnica SAIL se realizó debido a la persistencia de una estenosis fija residual >50%, mientras que en los otros casos fue debido a reperfusión incompleta (eTICI 0-2a: 11/44, 25.0%) y la re-oclusión inmediata (16/44, 36.4%). El número de pases de TM convencional antes de adoptar la técnica SAIL fue de 3 (RIC, 2-4). La tasa de reperfusión exitosa sostenida después de la técnica SAIL fue del 79.5% (35/44) independientemente de la vía de administración de tirofiban (IV-SAIL 80% vs IA-SAIL 78.9%; p=0.932). Únicamente hubo la necesidad de realizar rescate con angioplastia y/o stent en 15 pacientes (34,1%: IA-SAIL 21,1% vs IV-SAIL 44.0%; p=0,112). Tras el rescate, la tasa se reperfusión exitosa se elevó hasta el 88,6%.

En cuanto a la seguridad de la técnica (tabla 5):

- Dos casos de complicaciones mayores (disección intracraneal y perforación). No obstante, ambas complicaciones se produjeron durante el rescate con angioplastia/stent.
- La tasa de TH sintomática fue del 6.8% (IA-SAIL 5,3% vs IV-SAIL 8.0%, p=0,721) y a los 3 meses la mortalidad fue del 18,2% (IA-SAIL 26,3% versus IV-SAIL 12,0%; p=0,223).

No hubo diferencias significativas entre IA-SAIL o IV-SAIL en la tasa de reperfusión exitosa ni en TH sintomática, mortalidad o pronóstico desfavorable a los 90 días.

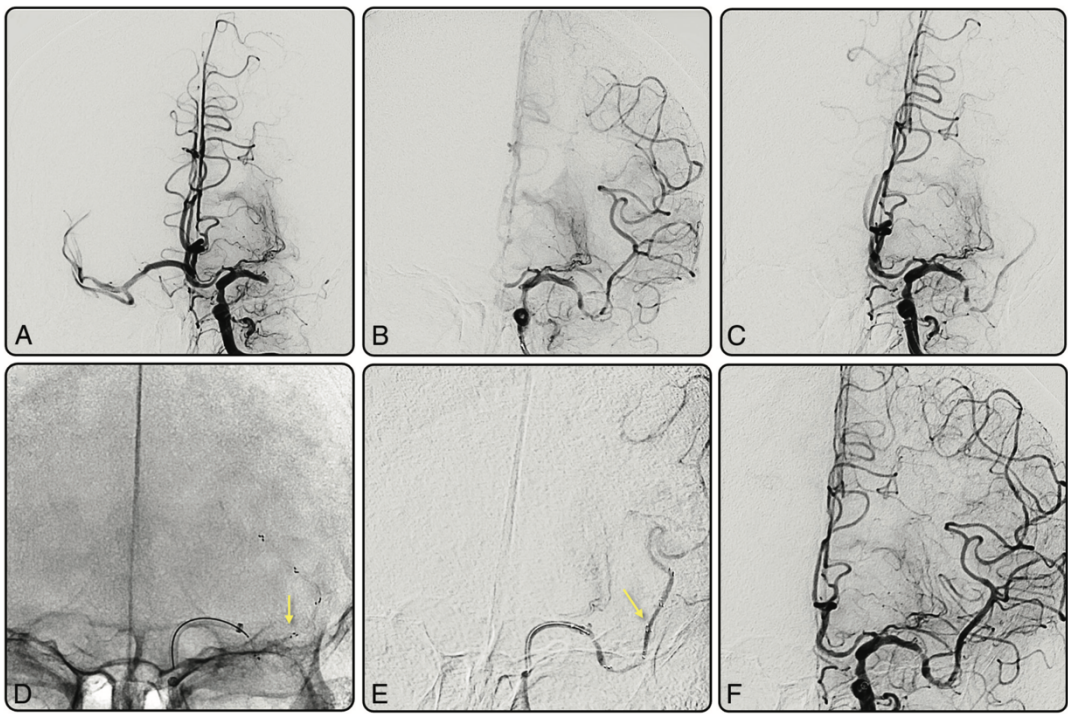

Figura 9. Caso ilustrativo de la técnica Stent retriever AssIsted Lysis con tirofiban intraarterial.

(A) Primera serie angiográfica con oclusión ACM M1 izquierda.
(B y C) Resultado angiográfico tras 2 y 3 pases de trombectomía mecánica con técnica combinada (stent retriever y aspiración distal), respectivamente, con recanalización parcial.
(D) Se despliega un SR sobre la lesión y (E) se infude tirofiban localmente durante 10 minutos a través del catéter de acceso distal.
(F) Serie final que muestra reperfusión exitosa. No se reportó reoclusión en el seguimiento.

Tabla 5. Seguridad y pronóstico clínico de la técnica Stent retriever AssIsted Lysis según la administración de tirofiban intraarterial o intravenoso.

Pronóstico	Todos los pacientes	IV-SAIL (n=25)	IA-SAIL (n=19)	P value
Reoclusión sintomática precoz (<24h)	2 (4,5%)	2 (8,0%)	0 (0%)	0,207
NIHSS a las 24h	11 (5-18)	9 (5-15)	14 (7-21)	0,079
NIHSS al alta	8 (2-15)	8 (2-14)	9 (4-21)	0,256
TH sintomática	3 (6,8%)	7,2 (8,0%)	1 (5,3%)	0,721
Hemorragia subaracnoidea peri-procedimiento	11 (25,0%)	5 (20,0%)	6 (31,6%)	0,380
Mortalidad a los 90 días	9 (18,2%)	3 (12,0%)	5 (26,3%)	0,223
mRS 0-2 a los 90 días	18/39 (46,2%	10/23 (43,5%)	8/16 (50,0%)	0,688
mRS 0-3 a los 90 días	26 (59,1%)	16 (64,0%)	10 (52,6%)	0,447

6. RESUMEN GLOBAL DE DISCUSIÓN

6. RESUMEN GLOBAL DE DISCUSIÓN

6.1. Identificación precoz de ICAS-LVO

Nuestro primer y segundo estudio proporcionan nuevos datos que apoyan la hipótesis de que es posible la identificación precoz y precisa de un ictus isquémico con oclusión de gran vaso relacionada con ateromatosis intracraneal mediante el uso de biomarcadores clínicos y radiológicos. Específicamente, la presencia de calcificaciones arteriales intracraneales en el lugar de la oclusión, el estado de la circulación colateral evaluado mediante el TC perfusión, la localización de la oclusión y el hábito tabáquico así como la ausencia de fibrilación auricular.

Aunque múltiples estudios han analizado de forma aislada las variables asociadas a ICAS-LVO, nuestro estudio combina características clínicas y radiológicas, tanto en TC craneal simple como en TC perfusión.

En cuanto a las IAC, distintos estudios han reportado, aunque con una frecuencia menor, su pronóstico angiográfico desfavorable[127-131]. Nuestro estudio confirma dichos hallazgos y además que no es un fenómeno tan infrecuente (6,6%).

El estado de la circulación colateral se puede evaluar de forma cuantitativa y automatizada mediante la HIR. Sin embargo, no existe un umbral estandarizado que defina un estado de circulación colateral desfavorable, dado que además puede variar según el software de TC perfusión utilizado.

Recientemente, distintos autores han sugerido un umbral de HIR<0,4 para definir buen estado colateral, HIR<0,3 para un estado colateral excelente y HIR <0,22 para predecir ICAS-LVO[132-134]. Por tanto, nuestros resultados son consistentes con la literatura previa y el uso de HIR<0,25 puede ser usado para la identificación precoz de ICAS-LVO.

A pesar de que otros parámetros de TC perfusión como Tmax>4s/Tmax>6s ≥ 2, han sido propuestos como potencial biomarcadores de ICAS-LVO[105], dichos parámetros parecen tener menor valor predictivo que la HIR en nuestra población.

6.2. Implicaciones en el tratamiento endovascular

Por tanto, una herramienta diagnóstica con este conjunto de características clínico-radiológicas podría permitir la optimización de la atención inicial del paciente con ICAS-LVO para adoptar medidas terapéuticas basadas en la fisiopatología de la etiología subyacente (Figura 10).

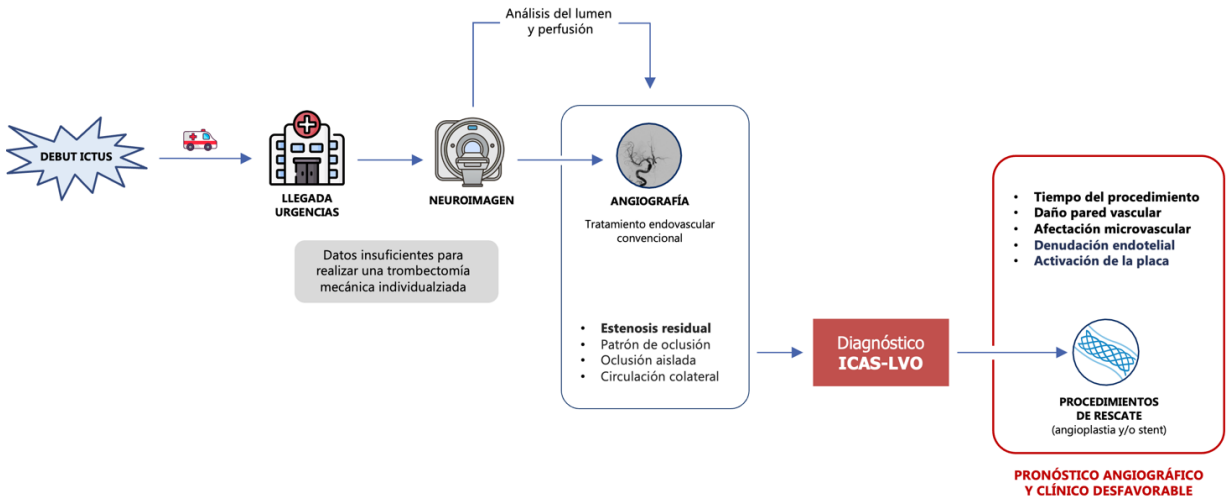

Figura 10. Esquema del flujo de trabajo actual desde la llegada del paciente hasta la realización del tratamiento endovascular.

La implementación de medidas farmacológicas y del TEV de manera precoz en casos de ICAS-LVO podría evitar la activación de la placa ateromatosa, la denudación endotelial, el daño endotelial y la afectación microvascular secundarias a los múltiples intentos de TM fallida con técnicas y dispositivos no específicos. Conllevando todo ello un peor pronóstico clínico para el paciente[135, 136].

Tal como se ha observado en nuestra cohorte, el TEV en pacientes con ICAS-LVO se ha asociado a un mayor riesgo de fracaso en la recanalización y persiste considerándose un desafío clínico. Los procedimientos de rescate, bien farmacológicos o mecánicos, se necesitan con frecuencia para obtener la recanalización y un reciente análisis del registro ANGEL-ACT sugiere que deben realizarse de forma precoz en la primera fase del TEV para aumentar la probabilidad de éxito y buen pronóstico funcional[137, 138].

Sin embargo, en la actualidad aún no existe una evidencia robusta que apoye una estrategia de TM distinta en los pacientes con ICAS-LVO y se necesitan urgentemente estudios prospectivos que se dirijan a este problema clínico. Un estudio in-vitro sugirió que el uso de la triple combinación de SR, aspiración distal y arresto del flujo mediante el uso de catéter guía con balón es la mejor técnica inicial para este subtipo de oclusiones[139].

En este contexto, nuestro tercer estudio sobre la técnica SAIL con tirofiban en pacientes con ICAS-LVO y oclusiones refractarias a la TM con técnica convencional ofrece una nueva perspectiva

como alternativa al rescate tradicional con angioplastia y colocación de stent intracraneal. Además de mejorar la reperfusión en este subgrupo de pacientes, la técnica SAIL también permite confirmar la etiología del ictus isquémico con la visualización de la estenosis intracraneal subyacente gracias a la interacción placa-stent, aportanto así información suficiente para la optimización del tratamiento de prevención secundaria.

Múltiples estudios han descrito la administración de tirofiban en el ictus como una opción segura, tanto en presencia de oclusión arterial como en casos de ictus minor sin tributariedad de TEV[140-142]. Nuestro estudio, además, compara la administración intraarterial e intravenosa de tirofiban, sin objetivar diferencias en la tasa de recanalización exitosa ni de mortalidad o TH sintomática.

Recientemente, el estudio INSPIRE (International Stroke Perfusion Imaging Registry) ha reportado un mayor riesgo de TH sintomática y mortalidad con el uso de tirofiban intraarterial en comparación con el uso endovenoso. Se sugiere que la administración intraarterial genera un gran aumento de la concentración local del fármaco con un posible daño en la barrera hematoencefálica que aumenta el riesgo de hemorragia[143].

En nuestra cohorte, la tasa de TH sintomática (6,6%) y de mortalidad a los 3 meses (18,2%) es similar a las descritas en estudios con gran tamaño muestral en pacientes que reciben un TEV con dispositivos y técnicas convencionales[144]. Como hipótesis, la técnica SAIL, debido al canal creado con el SR, favorece por una parte el efecto local del tirofiban a lo largo de toda la extensión de la lesión y, por otra parte, produce un lavado continuo del fármaco que evita su estancamiento a elevadas concentraciones, eliminando o reduciendo así el mayor riesgo de hemorragia y deterioro neurológico.

Tampoco existen a día de hoy estudios aleatorizados que evalúen la mejor vía de administración de tirofiban.

Por último, aunque la angioplastia y stent intracraneal como medida de rescate ante una TM fallida han sido asociados con una elevada tasa de reperfusión y una mayor probabilidad de independencia funcional a los 90 días independientemente de la presencia de ICAS-LVO[99, 112], existen ciertos escenarios clínicos que desaconsejan su uso. Entre ellos se encuentran los pacientes que se presentan con un ictus isquémico con núcleo isquémico de gran volumen, antecedente de hematoma intraparenquimatoso lobar (debido al aumento del riesgo de TH) o aquellos casos en los que la oclusión/estenosis intracraneal se localiza en segmentos donde se encuentran los

ostiums de las arterias perforantes de los ganglios basales o del tronco del encéfalo (debido al efecto *snowplow*, en el que se produce el desplazamiento forzoso de la placa ateromatosa hasta la oclusión del ostium).

El resgistro RESCUE-ICAS y el estudio ReSET aportarán en los próximos años conocimiento prospectivo y de mayor evidencia científica, que serán útiles para el diseño posterior de ensayos clínicos para la población diana.

Además, próximamente se iniciará el reclutamiento del ensayo clínico ICARUS (IntraCranial Atherosclerosis Related Large-vessel Occlusion Treated With Urgent Stenting, NCT NCT06472336). Será el primero en evaluar de forma aleatorizada el uso de stent intracraneal frente a proseguir la TM convencional tras la ausencia de recanalización en 3 pases.

7. CONCLUSIONES

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En conclusión, en aquellos pacientes con ictus isquémico y oclusión de gran vaso:

1. La presencia de una calcificación arterial intracraneal en la localización de la oclusión no es un hallazgo infrecuente durante la evaluación inicial y se asocia a un peor pronóstico tanto angiográfico como clínico.

2. La combinación de características basales clínico-radiológicas evaluadas antes del procedimiento (ausencia de fibrilación auricular, hábito tabáquico, localización proximal de la oclusión, menor ratio de intensidad de hipoperfusión y la presencia de calcificaciones arteriales intracraneales sintomáticas) es útil para predecir la presencia de ictus isquémico con oclusión de gran vaso relacionada con ateromatosis intracraneal.

3. La identificación precoz de una oclusión con sospecha de ateromatosis intracraneal subyacente permite anticipar la necesidad de procedimientos de rescate, como la angioplastia y/o el stent intracraneal. Sugiriendo así la estrategia óptima, individualizada y dirigida a la fisiopatología del tratamiento endovascular.

4. En aquellos pacientes en los que se considera realizar un procedimiento de rescate con angioplastia y/o stent, la técnica Stent retriever AssIsted Lysis con administración de tirofiban, tanto intraarterial como intravenosa, es útil para inducir la recanalización exitosa con el objetivo de evitar y/o preparar la colocación definitiva de un stent intracraneal.

8. PERSPECTIVAS FUTURAS

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De la presente tesis doctoral se extraen distintas líneas de futuro para la optimización del manejo integral del ictus isquémico relacionado con ateromatosis intracraneal.

Por una parte, el hallazgo de los biomarcadores clínicos y radiológicos como predictores independientes de ICAS-LVO conlleva el posterior desarrollo y automatización. Uno de los principales inconvenientes del modelo explicado previamente es el tiempo de evaluación del conjunto de biomarcadores en una patología claramente tiempo-dependiente como es el ictus.

Durante los próximos años, debido al auge de la inteligencia artificial en el ámbito médico, se tratará de desarrollar una herramienta predictiva validada con artificial que tenga la capacidad de informar de manera precisa y rápida la presencia de una estenosis intracraneal subyacente a la oclusión.

En el caso de que se logre implementar en la práctica clínica dicho algoritmo (figura 11) y se identifique de forma precoz este subgrupo de pacientes, se podrán beneficiar de un tratamiento dirigido precoz.

Además, existen determinados biomarcadores serológicos de ICAS-LVO. Se han descrito, entre otros, una LDL (lipoproteína de baja densidad) elevada y una HDL (lipoproteína de alta densidad) disminuida, aunque se considera poco específico debido a la habitual presencia de factores de riesgo vascular en la mayoría de pacientes con ictus.

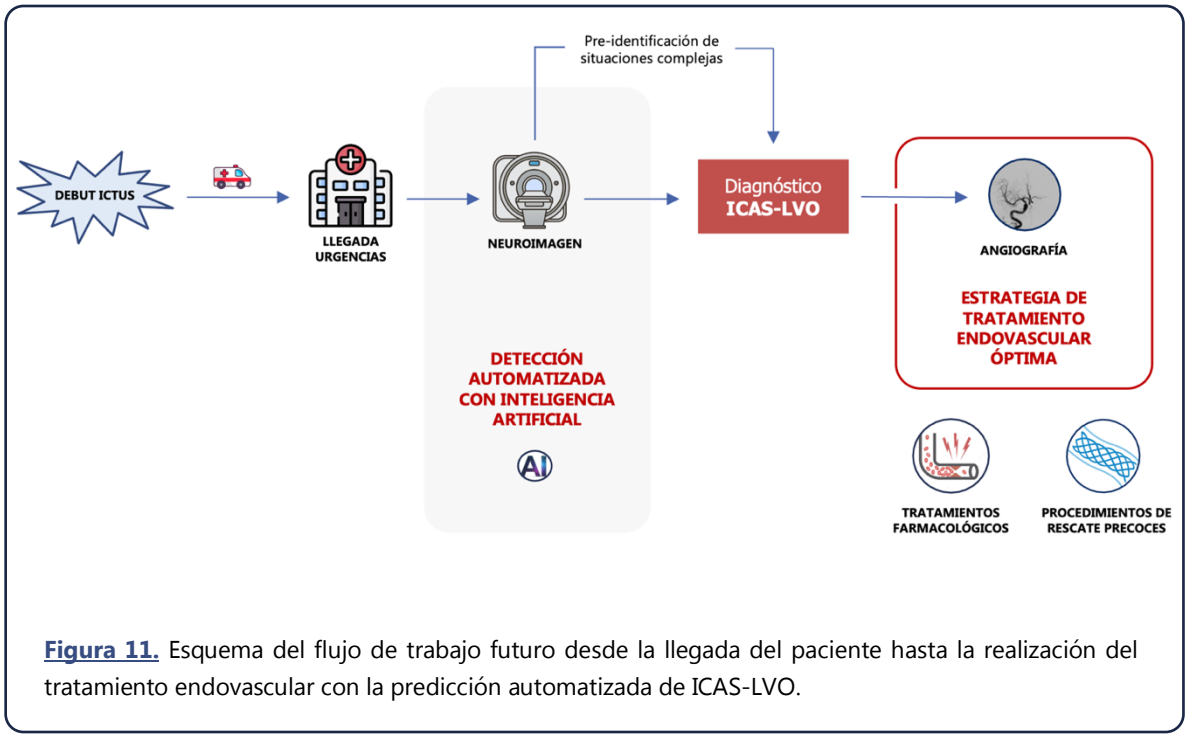

Figura 11. Esquema del flujo de trabajo futuro desde la llegada del paciente hasta la realización del tratamiento endovascular con la predicción automatizada de ICAS-LVO.

Más específicos son el sLOX1 (receptor soluble tipo lectina similar a la LDL oxidada-1) sugestivo de vulnerabilidad de la placa ateromatosa y PAI1 (inhibidor del activador del Plasminógeno 1) de progresión de la ateromatosis[145]. No obstante, no son útiles en fase hiperaguda dado que no se encuentran disponibles. Su desarrollo, así como su correlación con marcadores histológicos del trombo, podría ser útil de cara al uso de un análisis *point-of-care* previo a la trombectomía que informe de la etiología subyacente.

Por otra parte, los resultados de los estudios en curso sobre el uso de tratamientos de rescate en pacientes con fracaso del TEV, permitirán la continua evolución tecnológica de los dispositivos de trombectomía y sus técnicas asociadas. En este sentido, en cuanto a la técnica SAIL, se necesitan datos adicionales para confirmar nuestros hallazgos y establecer en que pacientes la técnica debe ser adoptada. Además, se investigará el posible impacto negativo de un mayor número de pases antes de utilizar la técnica SAIL, tal como se ha observado en los casos de angioplastia. Para todo esto, se diseñará un ensayo clínico aleatorizado para evaluar la técnica SAIL en pacientes con alto riesgo de TM fallida.

En conjunto, un mayor conocimiento sobre la fisiopatología del ictus isquémico relacionado con ateromatosis intracraneal permitirá mejorar el diseño de ensayos clínicos con el objetivo de optimizar tanto el tratamiento hiperagudo como el tratamiento de prevención secundario en este subgrupo de pacientes con mayor riesgo de obtener un pronóstico clínico desfavorable. En primer lugar, una definición estandarizada de ICAS-LVO con marcadores validados de compromiso hemodinámico es de gran necesidad para la selección de pacientes. En segundo lugar, nuevas técnicas como la angioplastia submáxima pueden ser de utilidad en aquellos casos en los que la lesión se encuentre en un territorio rico en arterias perforantes. debido a su menor riesgo de efecto *snowplow*. Por todos estos motivos, el manejo de ICAS-LVO es un aspecto de interés candente en la actualidad científica y sufrirá una evolución constante.

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10. ANEXOS

10. ANEXO

10.1. Escalas

10.1.1. National Institute Health Stroke Scale (NIHSS)

1a. Nivel de conciencia:

0. Alerta
1. Somnolencia
2. Estupor
3. Coma

1b. Preguntas verbales para evaluar nivel de conciencia

0. Ambas respuestas son correctas
1. Una respuesta es correcta
2. Ninguna respuesta correcta

1c. Órdenes motoras para evaluar nivel de conciencia

0. Ambas órdenes realizadas correc tamente
1. Realiza una orden correctamente
2. Ninguna orden correctamente

2. Mirada conjugada (voluntaria o reflejos oculocefálicos)

0. Normal
1. Paresia parcial de la mirada
2. Desviación oculocefálica

3. Campos visuales

0. Sin déficit campimétrico
1. Cuadrantanopsia
2. Hemianopsia homónima
3. Ceguera bilateral

4. Paresia facial

0. Normal
1. Paresia leve (asimetría al sonreír)
2. Paresia total de la musculatura inferior
3. Paresia completa de la musculatura inferior y superior

5. Paresia de extremidades superiores (5a. Izquierdo, 5b. Derecho)

0. Mantiene la posición 10"
1. Claudica en menos de 10"
2. Algún esfuerzo contra gravedad
3. Movimiento en el plano horizontal sin vencer la gravedad
4. Paresia completa

6. Paresia de extremidades inferiores (6a. Izquierda, 6b. Derecha)

0. Mantiene la posición 5"
1. Claudica en menos de 5"
2. Algún esfuerzo contra gravedad
3. Movimiento en el plano horizontal sin vencer la gravedad
4. Paresia completa

7. Ataxia de las extremidades

0. Normal

1. Ataxia apendicular en una extremidad

2. Ataxia apendicular en dos extremidades

8. Sensibilidad

0. Normal

1. Leve o moderada hipoestesia

2. Anestesia

9. Lenguaje

0. Normal

1. Afasia leve o moderada

2. Afasia severa

3. Afasia global o mutismo

10. Disartria

0. Articulación normal

1. Disartria ligera a moderada

2. Disartria severa, ininteligible o anartria

11. Extinción e inatención (negligencia)

0. Normal

1. Inatención/extinción en una modalidad

2. Inatención/extinción en más de una modalidad

10.1.2. modified Rankin Scale (mRS)

- 0, Asintomático: Capacidad funcional normal
- 1, No hay incapacidad significativa: Es capaz de llevar a cabo todas las actividades habituales, a pesar de algunos síntomas.
- 2, Incapacidad leve: Capaz de valerse por sí mismo sin asistencia, pero incapaz de llevar a cabo todas las actividades que anteriormente podía hacer con normalidad.
- 3, Incapacidad moderada: Requiere algo de ayuda, pero es capaz de caminar sin asistencia.
- 4, Incapacidad moderadamente severa: Incapaz de atender las necesidades de su cuerpo sin asistencia, e incapaz de caminar sin asistencia.
- 5, Incapacidad severa: Requiere constante cuidado y atención de enfermeras, postrado, incontinente.
- 6, Muerte.

10.1.3. Expanded Thrombolysis in Cerebral Infarction (eTICI)

- Grado 0: No se observa perfusión (0% de reperfusión).
- Grado 1: Reducción del trombo, pero sin relleno de las ramas arteriales distales.
- Grado 2:
    - Grado 2a: Reperfusión del 1-49% del territorio.
    - Grado 2b50: Reperfusión del 50-66% del territorio.
    - Grado 2b67: Reperfusión del 67-89% del territorio.
    - Grado 2c: Reperfusión extensa del 90-99% del territorio.
- Grado 3: Reperfusión completa (100% del territorio).