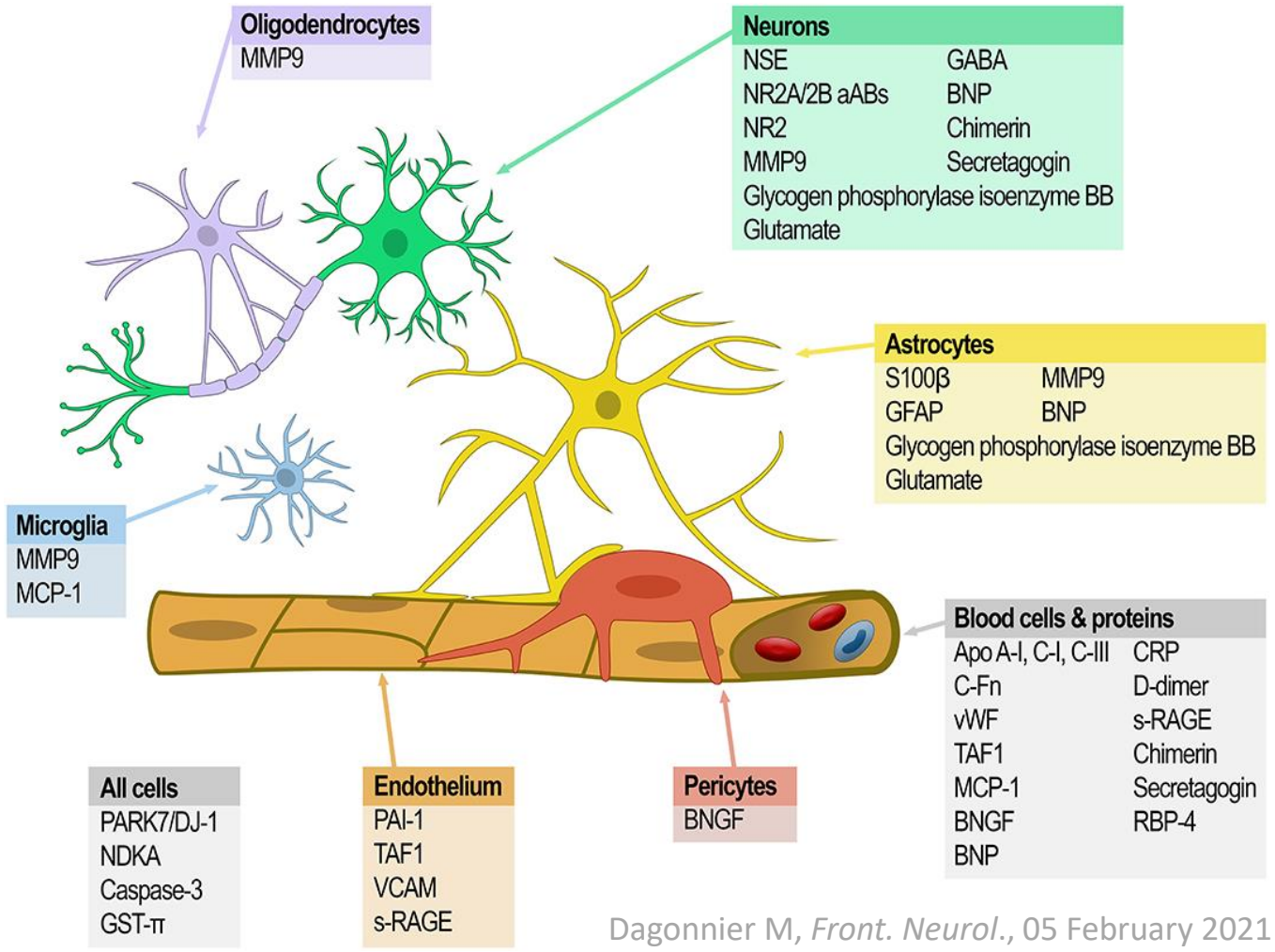
BIOMARKERS FOR IDENTIFICATION OF STROKE AND ITS RECOVERY

Joan Montaner, Anna Rosell

RICORS-ICTUS | Instituto de Salud Carlos III



Dagonnier M, *Front. Neurol.*, 05 February 2021

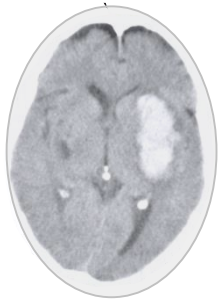
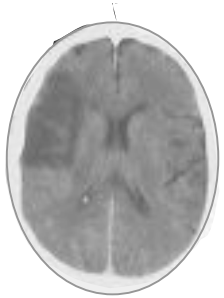
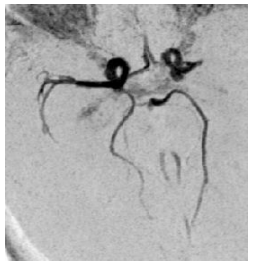
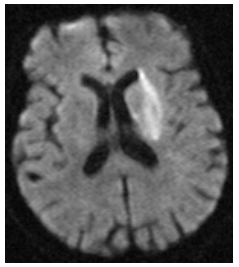
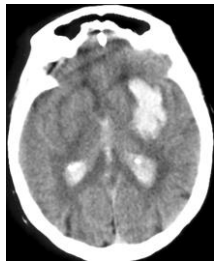
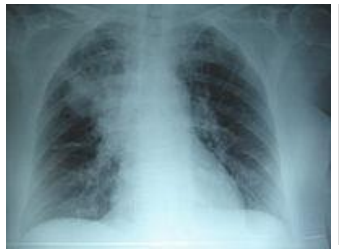
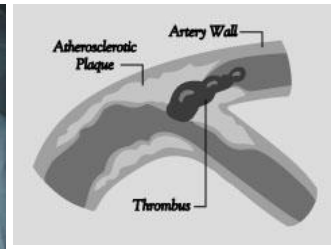
Financiado por la Unión Europea NextGenerationEU

Plan de Recuperación, Transformación y Resiliencia

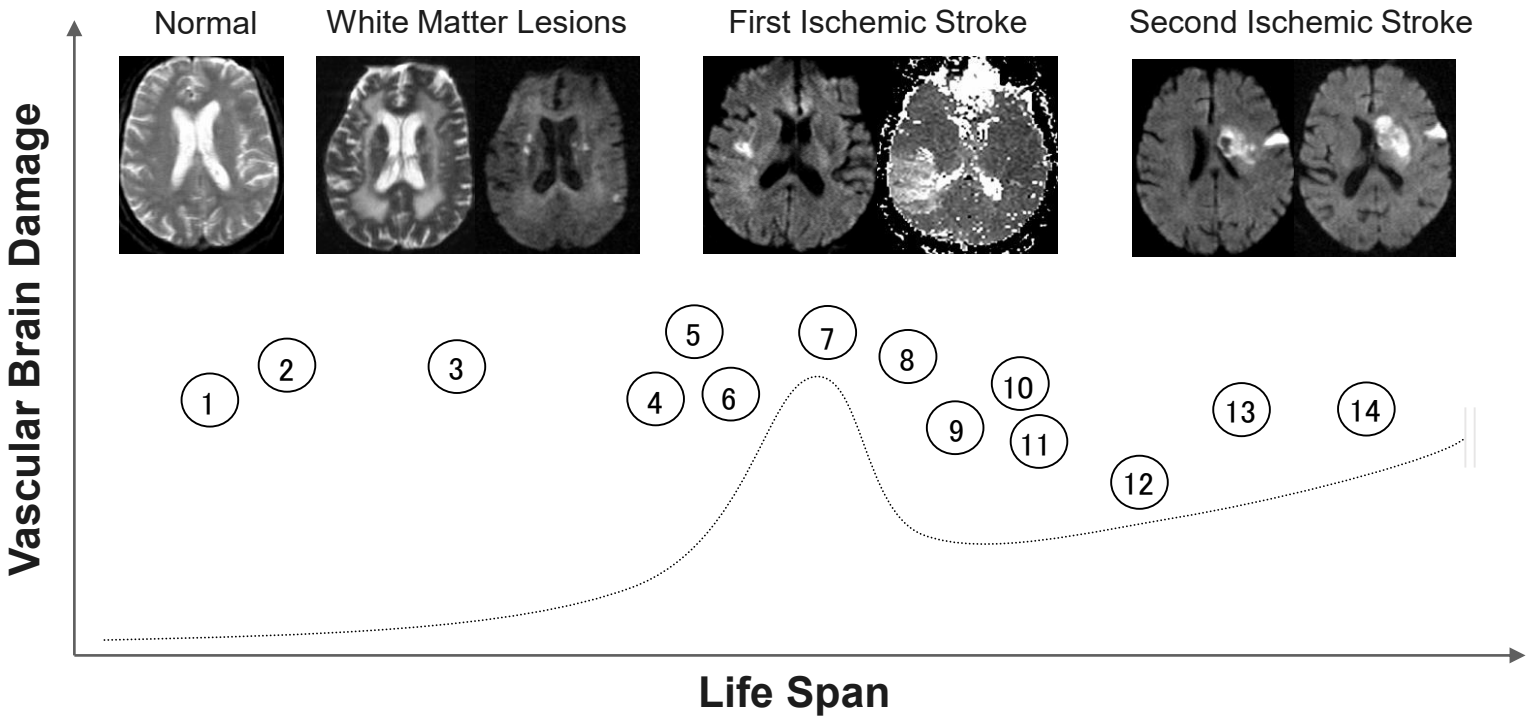
The PROMISE…

From the ambulance to the out-patients clinic, blood biomarkers based decisions will be taken soon…



Blood Biomarkers & Stroke Natural History



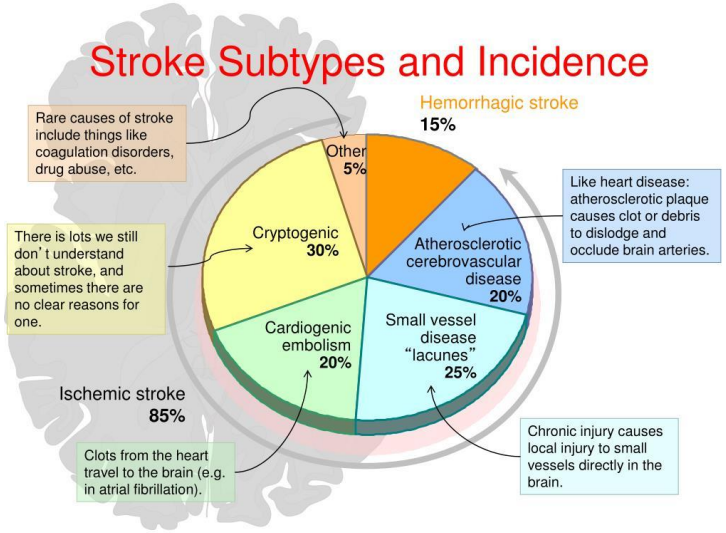
1.– Predict stroke among healthy people
2.– Predict stroke among those with vascular risk factors
3.– Identify Silent strokes
4.– Stroke vs mimics
5.– Ischemic–Hemorrhagic
6.– LVO identification
7.– Bleeding complications
8.– Futile recanalization
9.– Stroke etiology
10.– Cardiac complications
11.– Infections prediction
12.– Functional outcome & recovery
13.– Post–stroke seizures
14.– Stroke recurrence

BIOMARKERS FOR IDENTIFICATION OF STROKE AND ITS RECOVERY

- **WP1:** Biomarkers for the pre-hospital diagnosis of stroke
- **WP2:** Use of biomarkers in stroke subtypes
- **WP3:** Biomarkers for outcome (stroke complications and recovery)
- **WP4:** Biomarkers in experimental models of stroke and selected pathways

WP1: pre-hospital

WP2: stroke subtypes

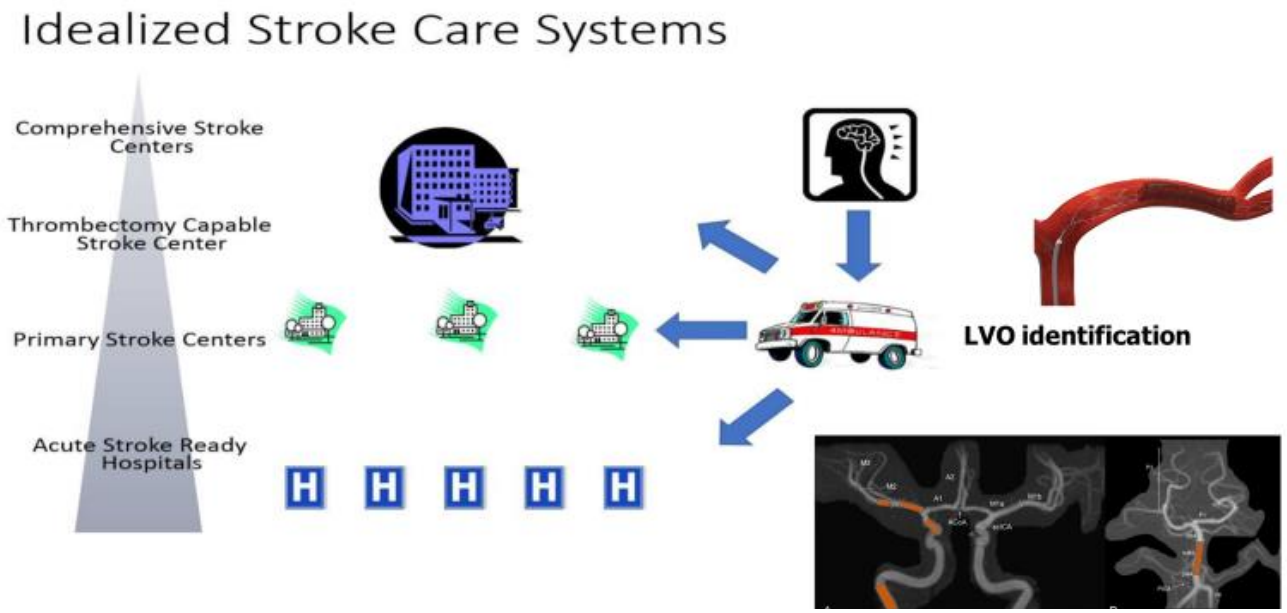


WP3: Outcome

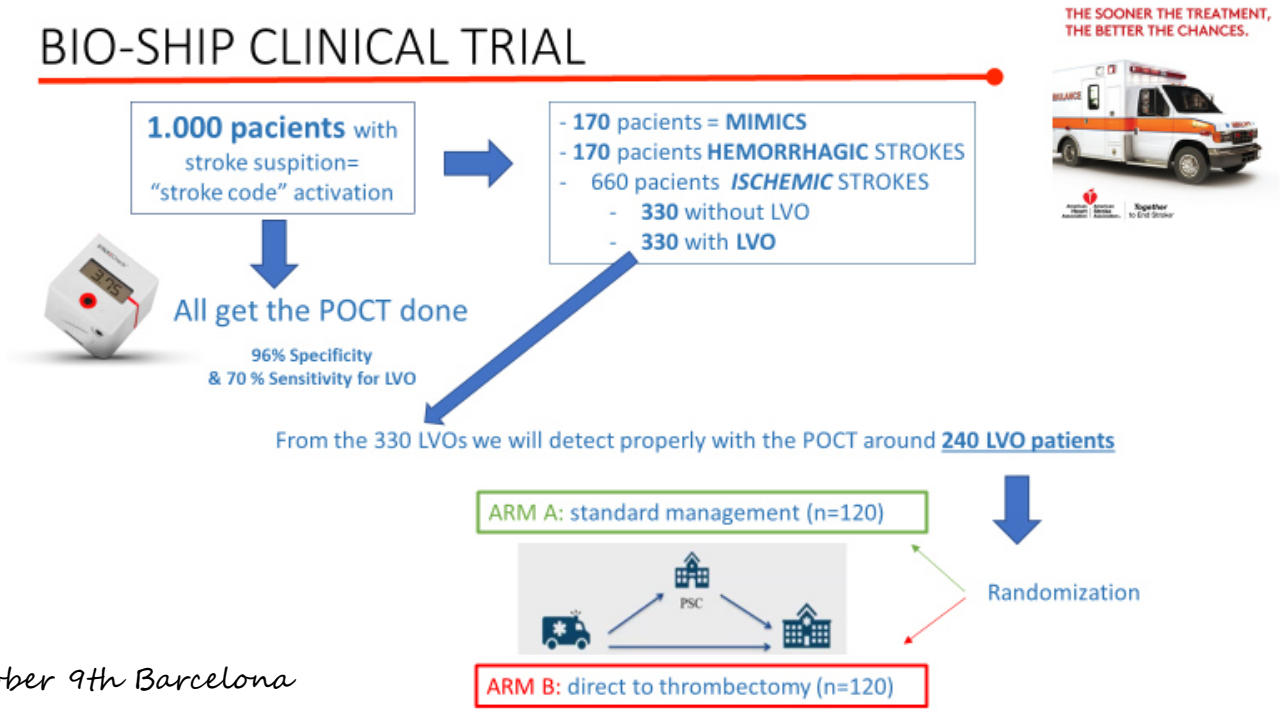
WP4: experimental

WP1.- BIOMARKERS FOR PRE-HOSPITAL DIAGNOSIS OF STROKE. As an alternative to neuroimaging, some blood-based biomarkers identified in the network have shown good predictive ability to discriminate between ischemic and hemorrhagic stroke and to identify large vessel occlusion (LVO) in the ambulances (BIO-FAST, CinicalTrials: NCT04612218). This has generated one of the largest and unique cohorts in the world in which blood samples were obtained at the ambulance that will allow discovery of new biomarkers (n=300) and brings the possibility of starting stroke therapy outside the hospital.

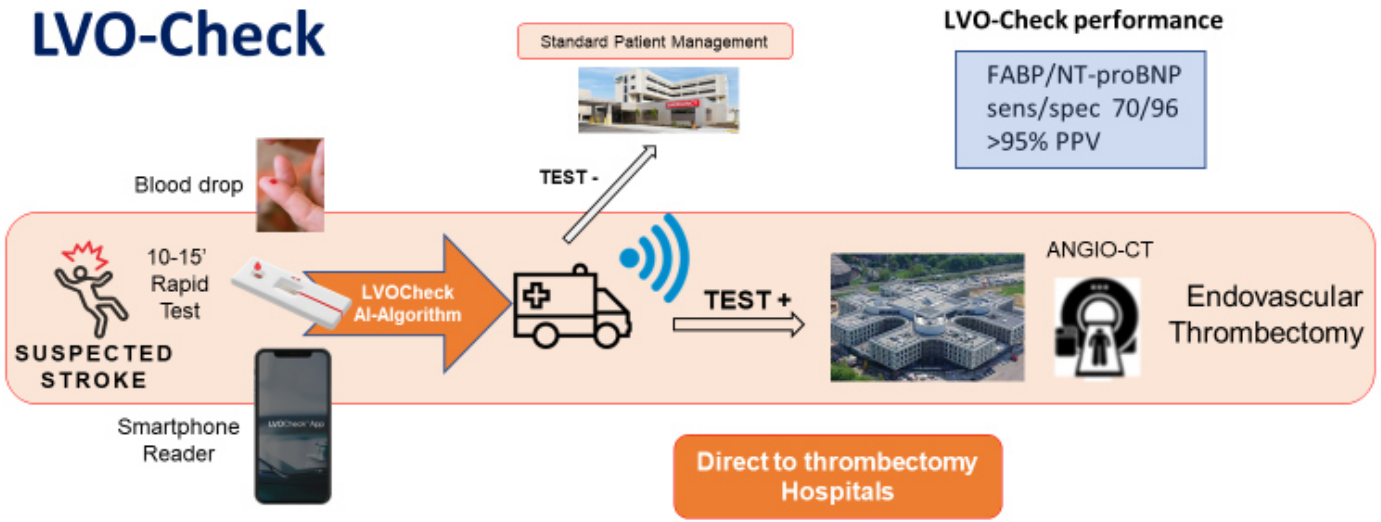
2022



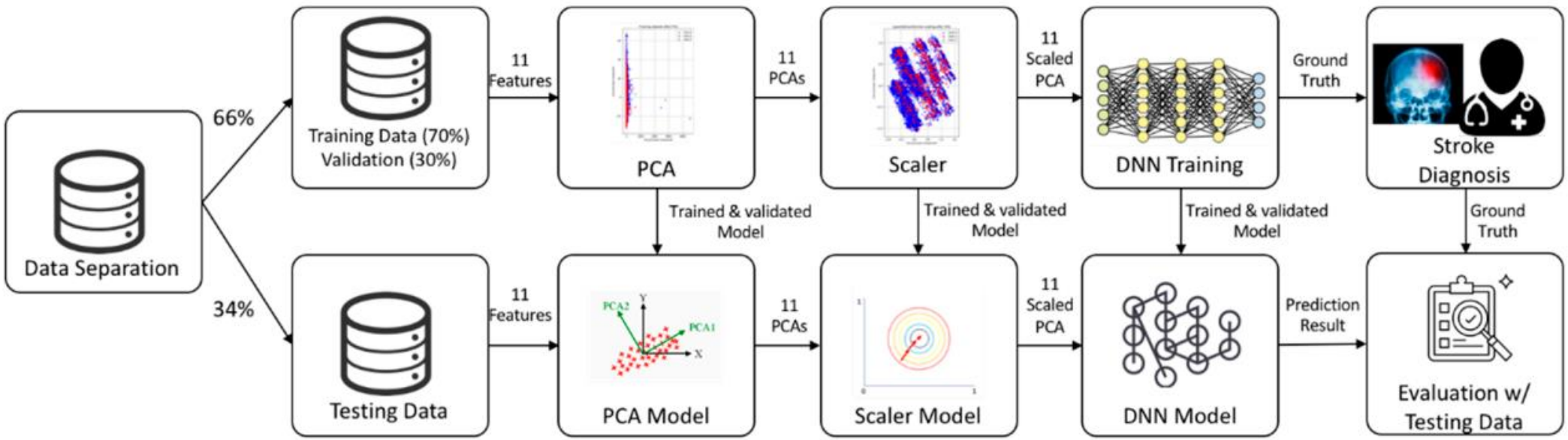
2023



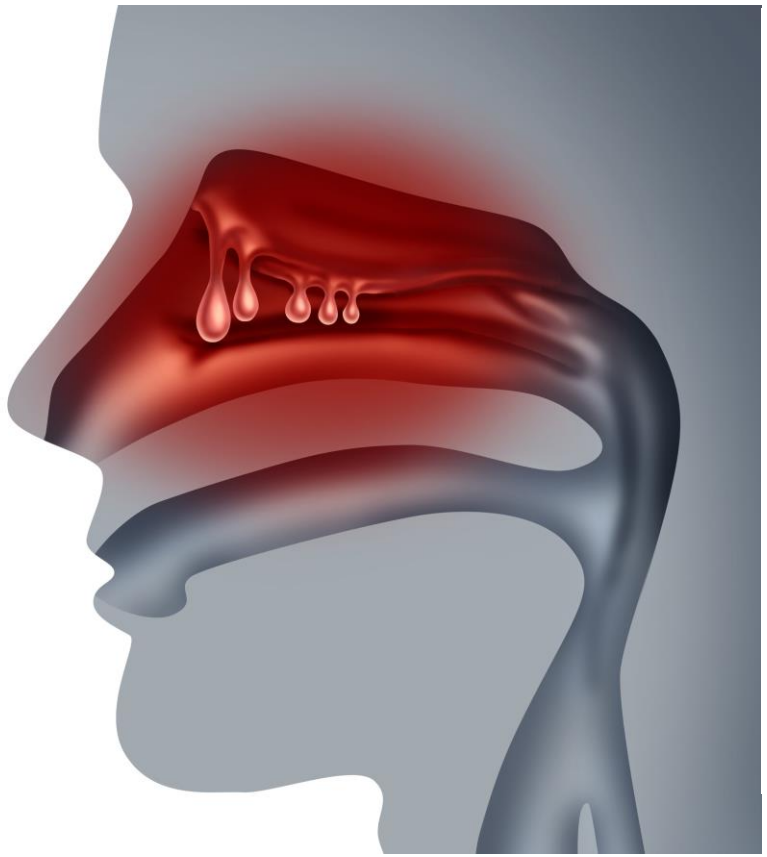
1.- Increase access to reperfusion therapies and thrombectomy centers, by detecting LVO in ambulances using blood biomarkers and clinical scales for direct transfer to the thrombectomy room. This strategy would be novel worldwide since no stroke care network is carried out such type of studies**. A multicenter study in Spain (BIOSHIP-Spain)** will be attempted in the RICORS since we already have the point-of-care technology to make these measurements. In a short time, we could carry out a study to evaluate the impact of the strategy on the prognosis of patients (our hypothesis is that this strategy will improve by 15% the percentage of patients who would achieve functional independence compared to standard managed patients).

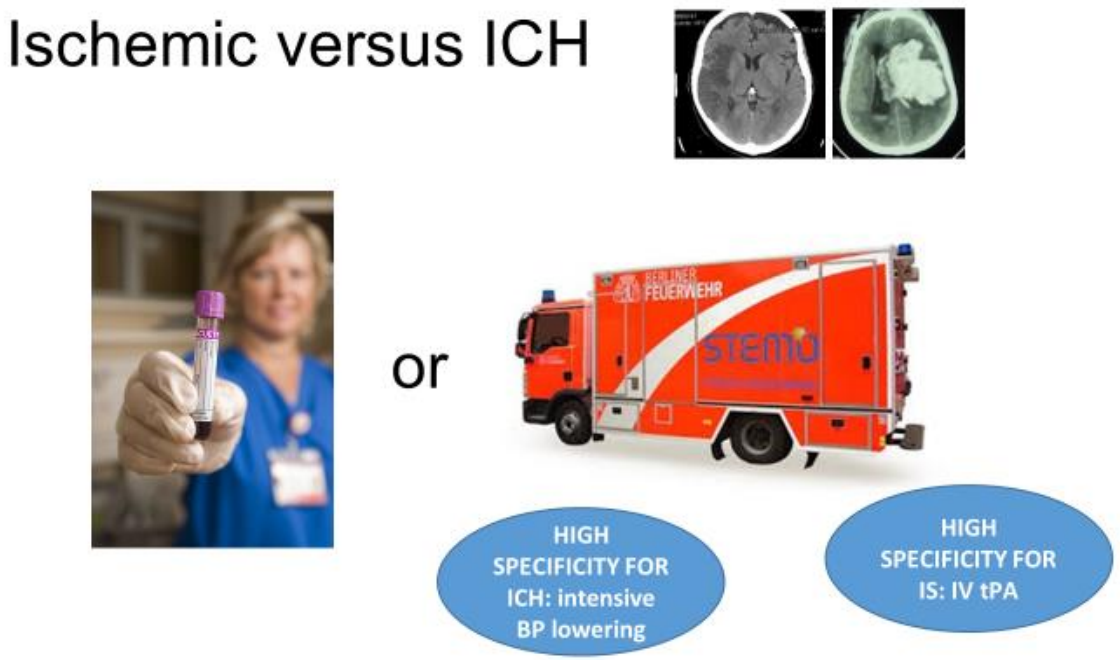


2.- Application of **machine learning techniques** on continuous hemodynamic monitoring data in patients with suspected out-of-hospital stroke and search for plasma biomarkers and clinical scale to generate predictive models of hemorrhagic vs ischemic stroke, and predictive LVO scales

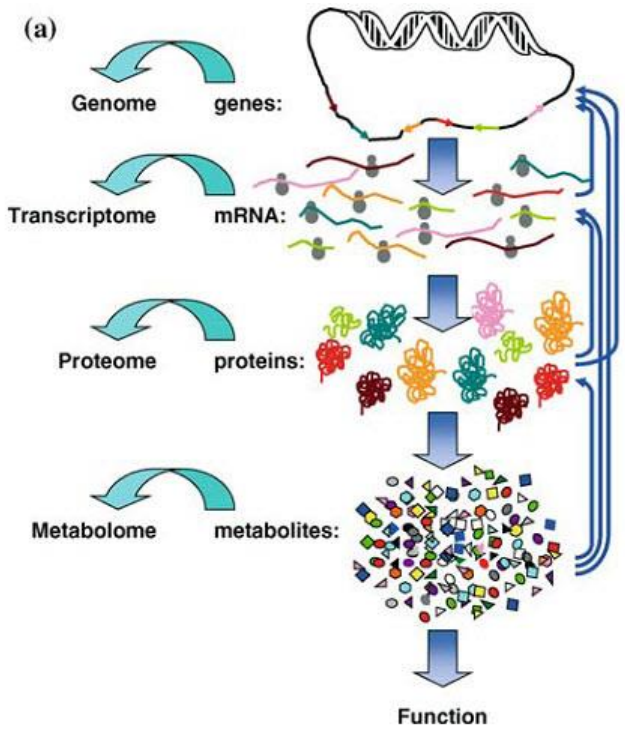


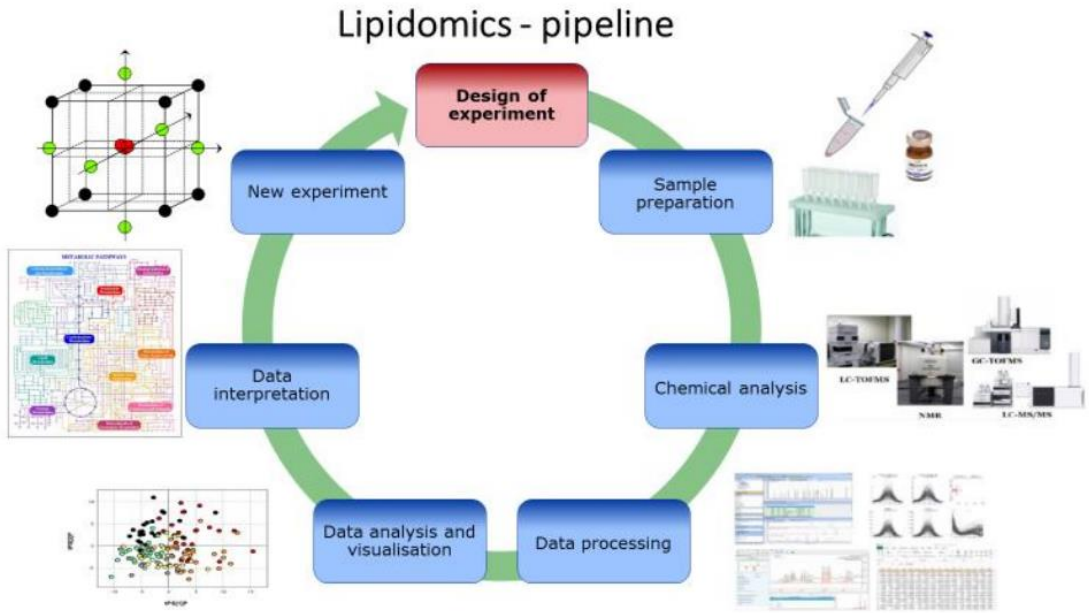
3.- Evaluation of **biomarkers through nasal exudate in stroke.** Preliminary data show metallic biomarkers (iron, copper, zinc, cadmium) in nasal exudate that allowed the differentiation between ischemic and hemorrhagic stroke (García-Cabo et al., Cerebrovasc Dis. 2020). This innovative strategy will be expanded by the network.





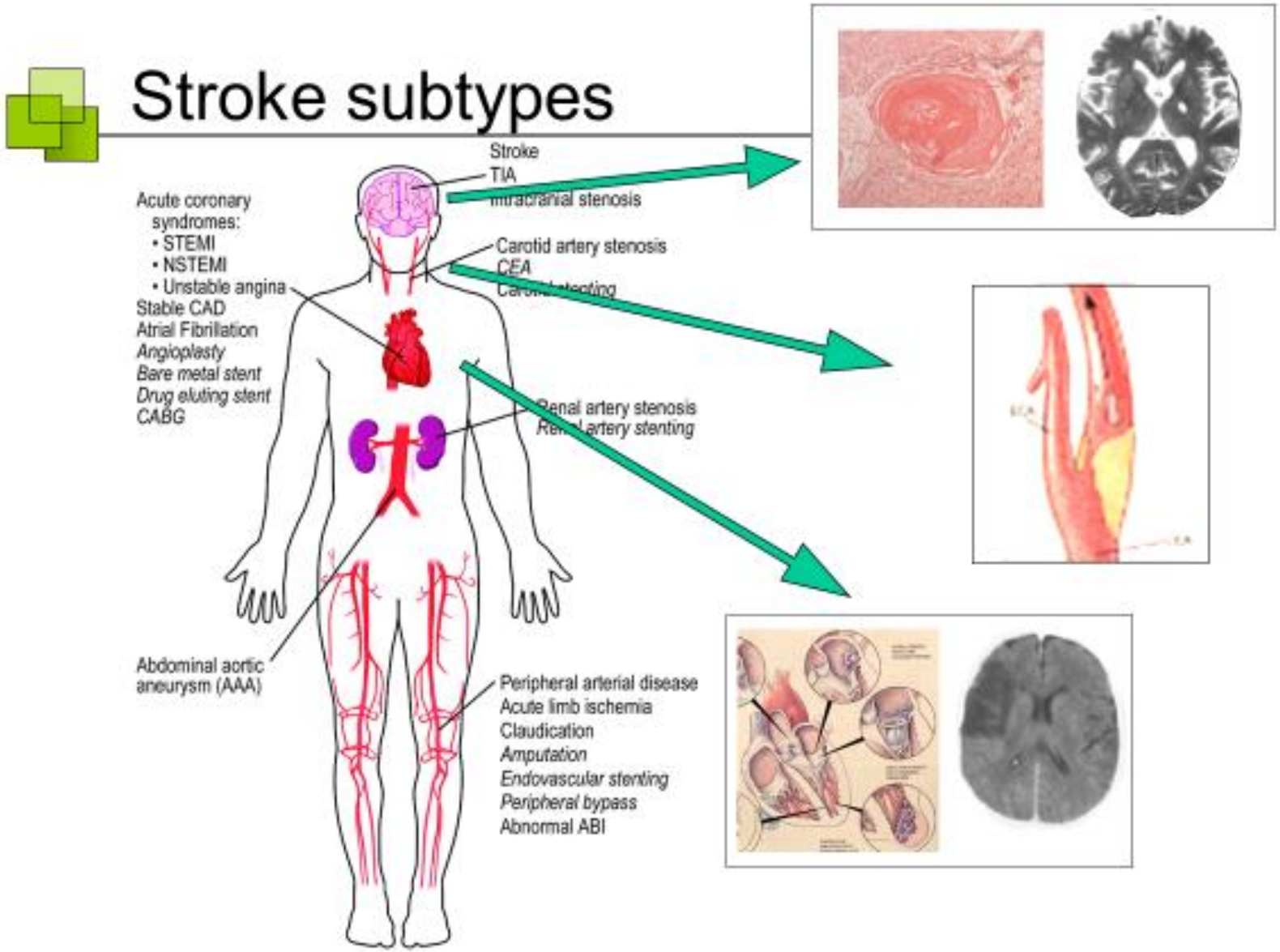
4.- Study of the **metabolomic and lipidomic profile of subjects** with suspected stroke and identification of an omics profile related to a) the certainty of the diagnosis of ischemic stroke, hemorrhagic stroke and mimic b) the presence of intracranial occlusion c) time of evolution of symptoms and the presence of penumbra at risk tissue.



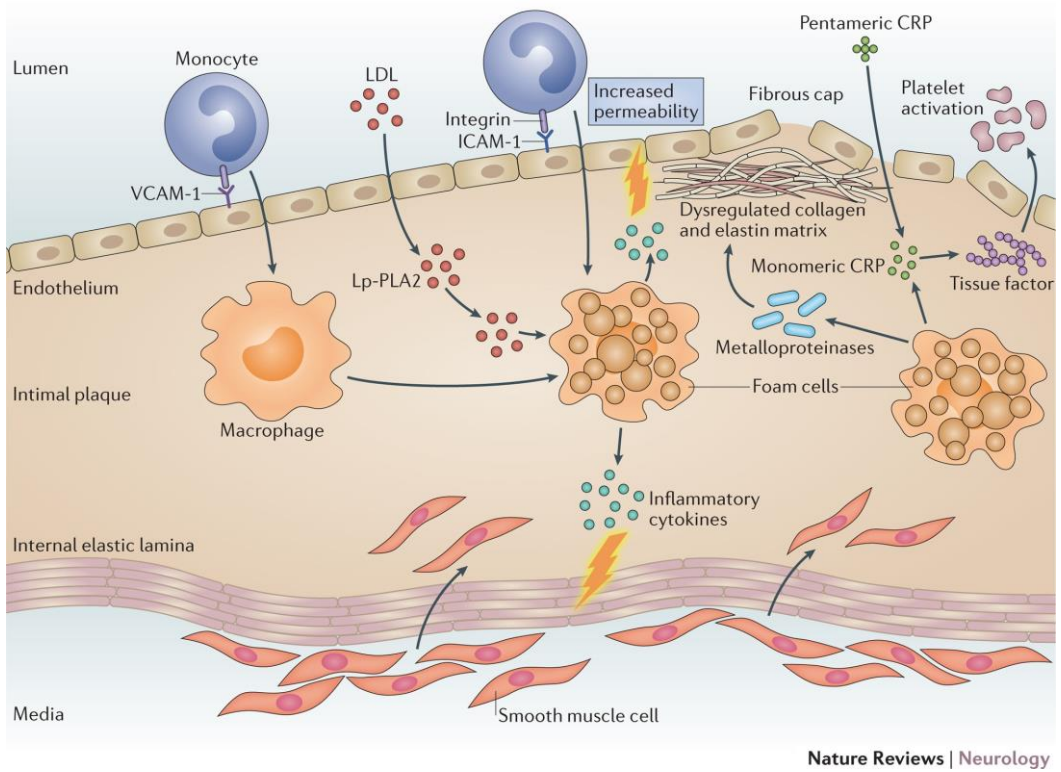


The steps involved in a lipidomic workflow. Adapted from the Swedish Metabolomics Centre (SMC).

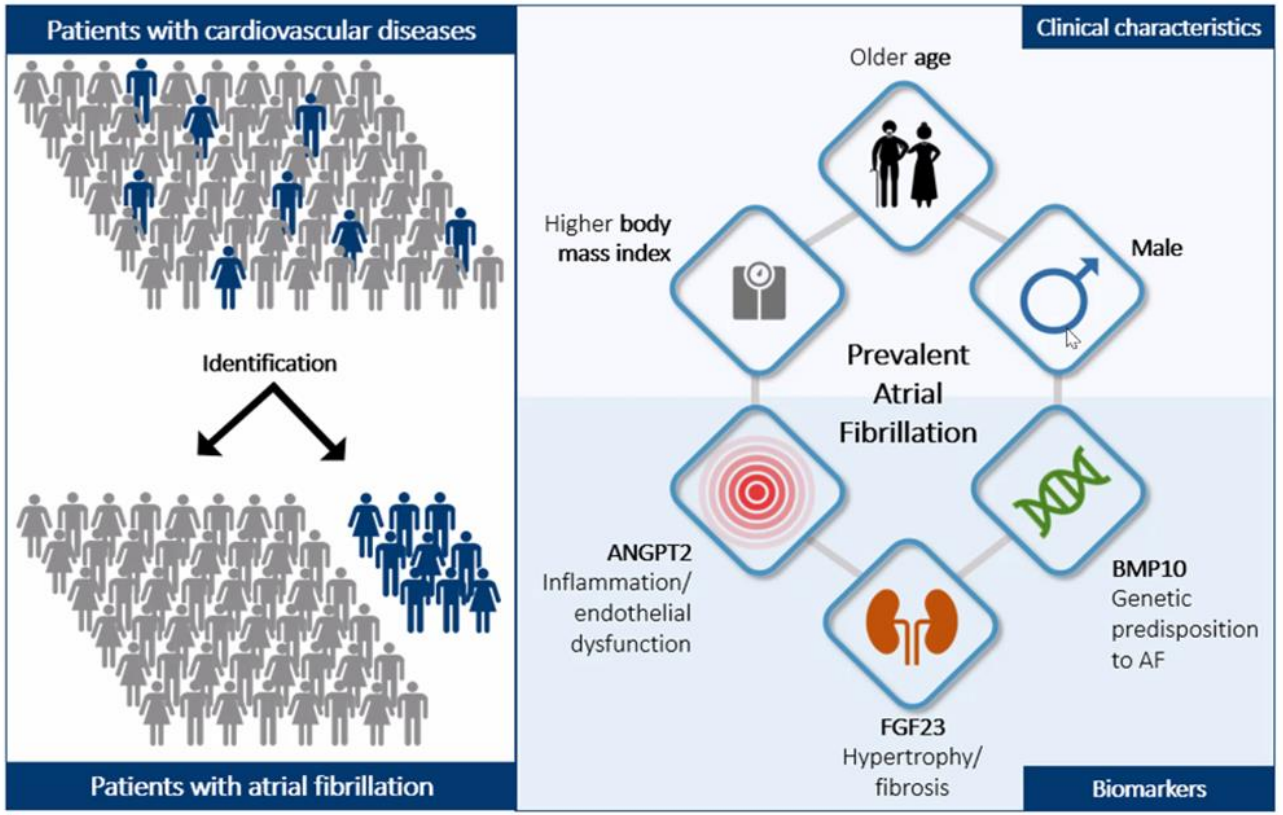
WP2.- USE OF BIOMARKERS IN STROKE SUBTYPES. We will identify new stroke markers to accelerate its diagnosis and therefore improve the treatment and prognosis of patients. Systemic biomarkers of active intracranial atherosclerosis plaque, predictive markers of vulnerable plaque and carotid angioplasty complications. Biomarkers of cardioembolic stroke to develop a predictive model for the presence of atrial fibrillation. Metabolomic, lipidomic, genetic and epigenetic markers of hemorrhagic stroke (ICH and SAH).



1.- To identify systemic biomarkers of **active intracranial atherosclerosis plaque** is an unmet need that will be addressed by the network, as well as predictive biomarkers (proteins and miRNAs) of vulnerable plaque in patients with carotid stenosis through analysis of atheroma plaques and blood (miRNAs) samples from patients with different diagnosis. Among those receiving carotid revascularization, identification of predictors of carotid angioplasty complications with the idea of improving the prognosis of patients who receive angioplasty/carotid stenting using predictive biomarkers of hyper-perfusion syndrome and restenosis, the two most feared complications among those patients, will be also attempted.



2.- Biomarkers of **cardioembolic stroke**. To develop a predictive model for the presence of atrial fibrillation in patients with recent ischemic stroke, based on clinical, biochemical, echocardiographic and neuroimaging markers, by means of a retrospective cohort study for the development and internal validation of a predictive model for the diagnosis of de novo atrial fibrillation in patients hospitalized for ischemic stroke, as well as the implementation of a screening for atrial fibrillation in patients with stroke of undetermined etiology.



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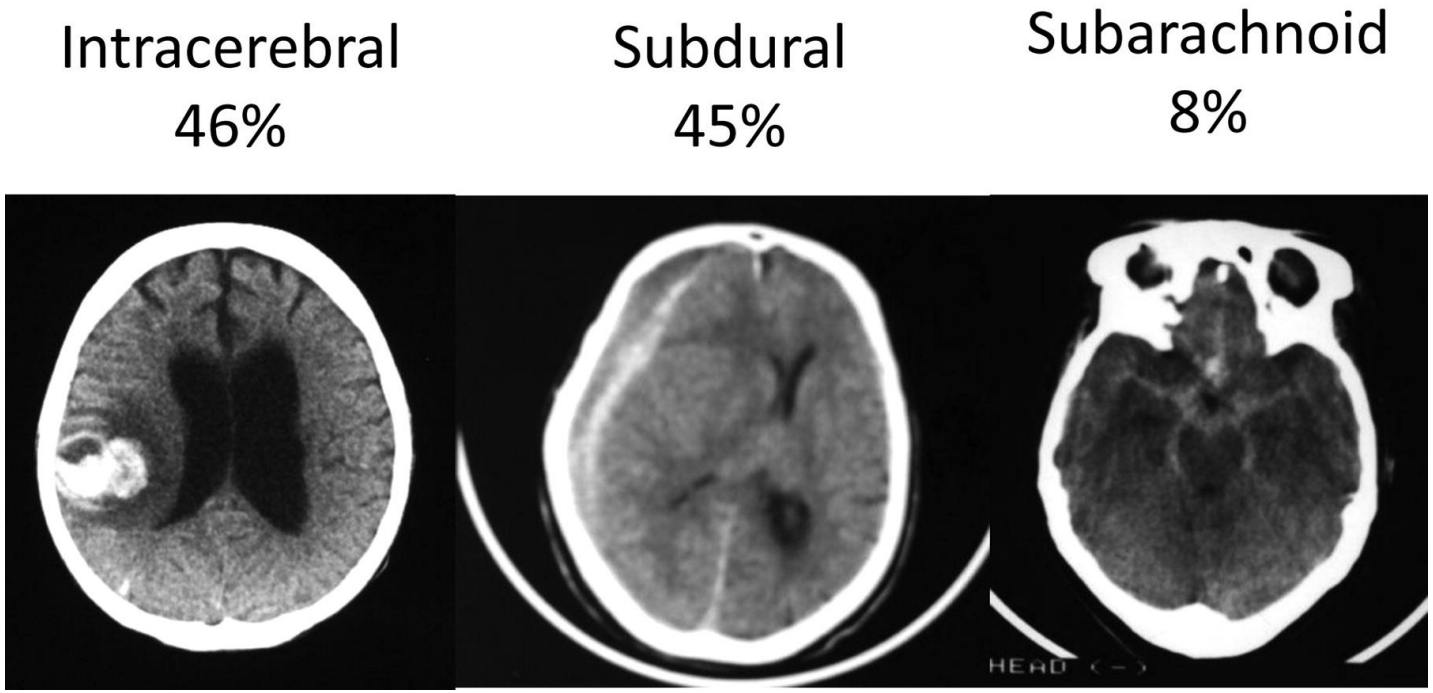
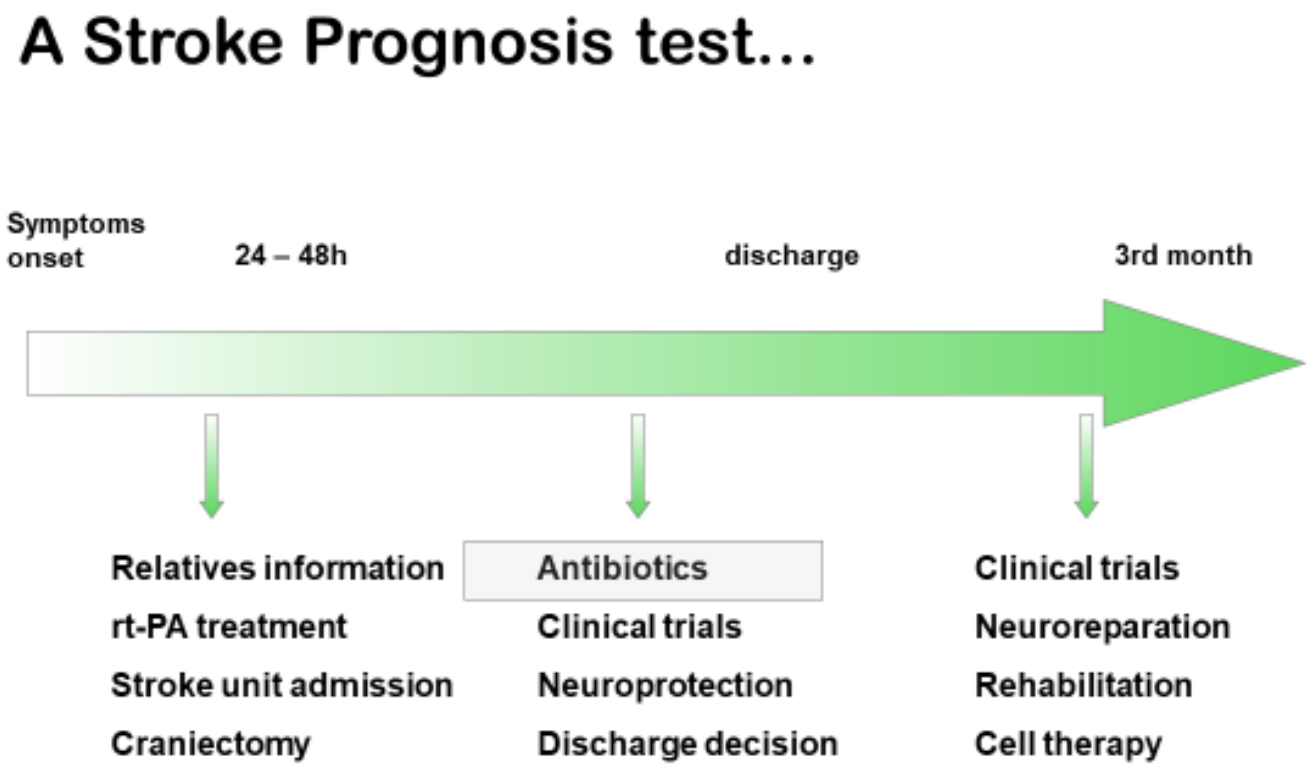
3.- **Biomarkers of hemorrhagic stroke.** Study of the metabolomic and lipidomic profile related to the etiology and prognosis of patients with intracranial hemorrhage (ICH). Identification of genetic and epigenetic variants associated with ICH and its functional prognosis (GWAS). Characterization of a CSF biomarker profile in patients with amyloid angiopathy and its validation. We will also address the study of biomarkers in subarachnoidal hemorrhage (SAH), through the study of neuroimaging, blood and CSF biomarkers of early and delayed ischemic damage and functional recovery in spontaneous SAH. That will be complemented by exploring genetic and epigenetic variants associated with SAH and its functional prognosis. (GWAS, EWAS) and analyzing the complications of SAH: by means of a multi-omic analysis.

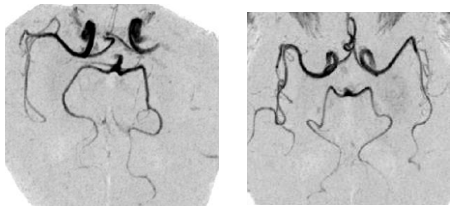


WP3.- BIOMARKERS FOR OUTCOME (STROKE COMPLICATIONS AND RECOVERY). We will study predictive biomarkers of complications associated with reperfusion therapies (HT, futile recanalization) to improve reperfusion rates and benefits/risk balance. We will also study predictive biomarkers of growth of ischemic and hemorrhagic (ICH and SAH) brain injury. The composition of the extracted thrombus and the implication on stroke outcome will be also explored to improve the diagnosis, treatment, and prognosis of those patients. Finally, we will determine different biomarkers related to functional recovery and post-stroke cognitive impairment.

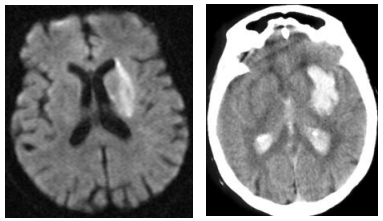


1.- **Lesion growth and tissue viability biomarkers**. Application of machine-learning techniques on continuous hemodynamic monitoring data to generate predictive models of death, re-bleeding and hemorrhagic transformation. Those will be combined with predictive blood biomarkers of complications associated with reperfusion therapies in patients with acute ischemic stroke (AIS). In fact, a great importance will be given to biomarkers of **FUTILE RECANALIZATION**, that importantly limits response to endovascular treatment in AIS (NORDICTUS network). We will try also to identify predictive biomarkers of growth of ischemic and hemorrhagic brain injury. Specifically, analyzing non-coding RNAs and cell-free DNA (cf-DNA) to identify circulating non-coding RNAs (miRNAs, lncRNAs and circRNAs) that predict hematoma growth in patients with ICH. Complementary neuroimaging markers will be also used to analyze whether the brain CT-perfusion (TCP) study increases the sensitivity in the detection of Spot-Sign (SS) and to investigate whether perihematoma hypoperfusion is associated with hematoma growth and its impact on the prognosis of patients (Deep Learning). Some specific pathways (dimetilarginines and other peri-hematoma damage biomarkers) will be explored.

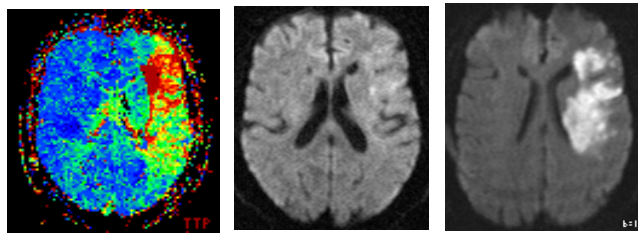
Vessel recanalization



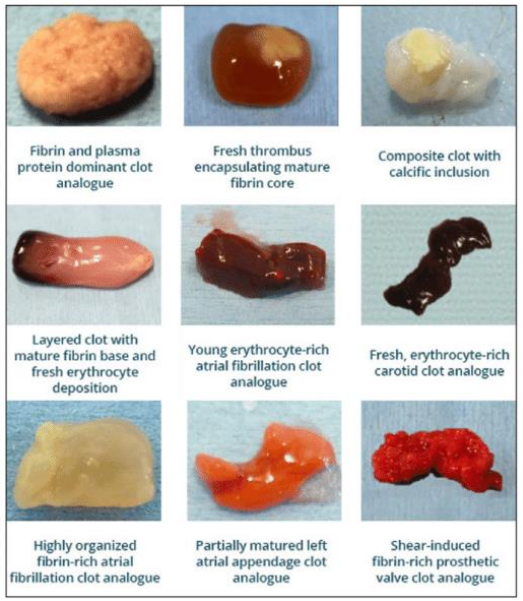
Bleeding Complications

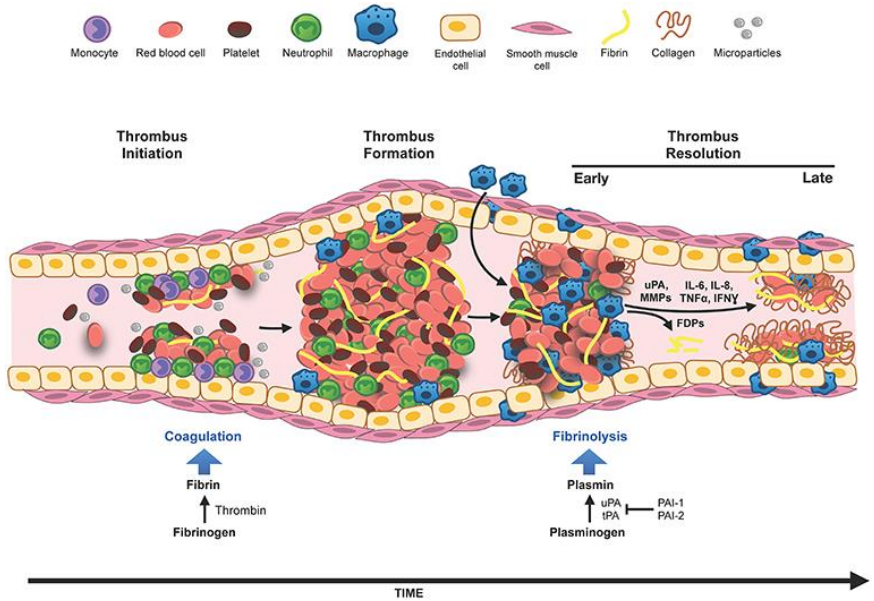


Tissue Viability, biological clock



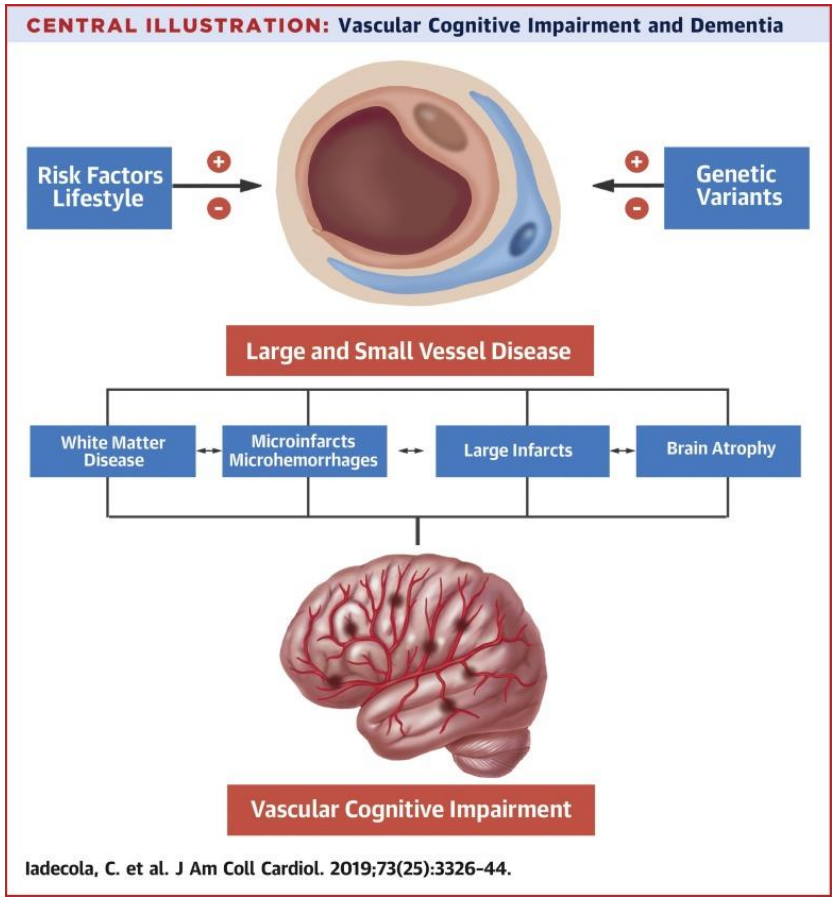
2.- Biomarkers **of the extracted thrombus**. The network will explore associations between macroscopic and radiological images, thrombus composition, blood biomarkers and angiographic/neurofunctional result; attempting the identification of a molecular/cellular signature with diagnostic/prognostic potential. Association of adherence and composition of the Mediterranean diet with the composition of thrombi in patients with AIS treated by mechanical thrombectomy will be explored. Thrombus molecular and cellular level to establish biomarkers of etiology and resistance to recanalization that allow improving their diagnosis, treatment and prognosis of patients will be explored through the study the transcriptome of extracellular vesicles (EVs) from thrombi and plasma samples. Also, redox proteomics applied to the diagnosis of ischemic stroke biomarkers to identify protein biomarkers by proteomic analysis, in thrombi obtained from thrombectomies and peripheral blood.





3.- **Global FUNCTIONAL OUTCOME biomarkers**. In this objective, we intend to identify new predictive biomarkers of brain damage and biomarkers of post-rehabilitation functional recovery, using different lab techniques. This will involve the identification and monitoring of both brain and peripheral markers. Baseline imaging markers predictors of recovery after stroke will be implemented in forecasting algorithms based on AI. Specifically, we intend to identify genetic and epigenetic variants associated with stroke and its functional prognosis. To analyze temporal variation in DNA methylation after a stroke, and its association with its severity and clinical evolution.

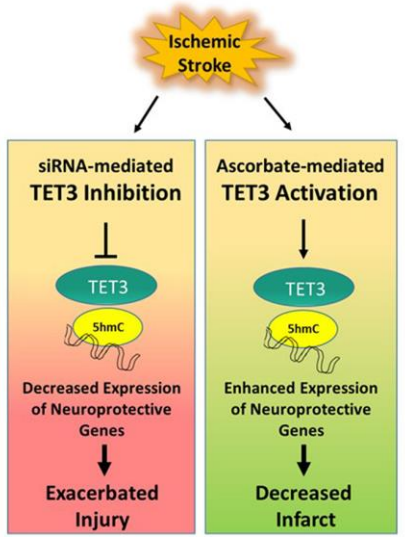
4.- **Biomarkers of cognition decline following stroke**. Study of post-stroke cognitive deficit markers by a metabolomic study and neuroimaging in animal models and in patients. Those will be complemented by the study on the value of functional near infrared spectroscopy (fNIRS) as a prognostic biomarker in patients with cerebral infarction and executive dysfunction.



WP 4.- BIOMARKERS IN EXPERIMENTAL MODELS OF STROKE AND SELECTED PATHWAYS FOR DIAGNOSIS AND THERAPY.

The main goal of this WP is to use experimental models to identify new outcome biomarkers and confirm the ones identified in previous WP. Identification of new predictive biomarkers of brain damage and worsening in murine models of cerebral ischemia by comparing those who die/survive at different timepoints after MCAO will bring new candidate biomarkers to the stroke field. We use a dynamic study of cerebral infarction and reperfusion in a humanized model of stroke in pigs through endovascular access, using imaging markers.

Those biomarkers identified in a cohort of stroke patients, corresponding to **functional polymorphisms of genes**, identified as key in experimental studies evaluating the balance between brain damage and repair in murine models of ischemia and hemorrhage will be further explored in vitro and in vivo. Functional studies will be performed in an in vitro model of atherosclerosis to elucidate its role in the progression and instability of atherosclerosis. Functional studies will also be carried out in an in vitro model of ICH to provide information on the role of the identified non-coding RNAs in controlling the expression of their targets and in cell viability and permeability. Proteomic studies to identify biomarkers involved in brain damage and recovery after ischemic stroke, focused on biological sub-compartments, addressing studies limited to known targets and of potential interest. Finally, evaluation of neuroinflammation **biomarkers in preclinical ischemic stroke** will be carried out. Study of brain and peripheral receptors as potential experimental therapeutic targets will be addressed and evaluation of neuroimaging biomarkers for PET/MRI imaging in preclinical ischemic stroke conducted together with the study of brain receptors and lipidomics.



• **WP1:** Biomarkers for the pre-hospital diagnosis of stroke

1. BIOSHIP
IBIS-Sevilla
VHIR-Barcelona
HUCA- Asturias
HCU Valladolid
Germans Trias-Badalona
IRB-Lleida
GCA-Aragón Associated clinical Group (Dr. Javier Marta)

2. Machine Learning
IBIS-sevilla
HCU Valladolid
IIS IP-UCM (HU Princesa, Madrid): data integration and machine learning techniques for the joint analysis of pre-hospital biomarkers
Patricia Calleja. Hospital Universitario Doce de Octubre. (Proyecto La Princesa Vivancos)
IDIPAZ-Madrid: escala Madrid-Direct y estudio promovido por el hospital de la Princesa para la identificación de otros biomarcadores prehospitalarios.
Germans Trias-Badalona
IRB-Lleida
GCA-Aragón Associated clinical Group (Dr. Javier Marta)
IIS IP-UCM: data modeling techniques (HU Princesa, Madrid)

3. Nasal Biomarkers
HUCA- Asturias
Alberto Alcázar. Grupo Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Hospital Ramón y Cajal, Madrid. (CSF biomarker profile)

4. Metabolomic/lipidomic
HUCA- Asturias
Patricia Calleja. Hospital Universitario Doce de Octubre
IRB-Lleida
GCA-Aragón Associated clinical Group (Dr. Javier Marta)

• **WP2:** Use of biomarkers in stroke subtypes

1. Intracranial atherosclerosis
HUCA- Asturias
HCU Valladolid
HOSPITAL UNIVERSITARIO PUERTA DE HIERRO. DR J CARNEADO RUIZ.
Germans Trias-Badalona
IRB-Lleida
GCA Málaga – Carlos de la Cruz Cosme
GCA-Aragón Associated clinical Group (Dr. Javier Marta)
IDIBGI-Serena
IS La Fe Valencia RD21/0006/0014
IBIS-sevilla (SHP)

2. Cardioembolic
IBIS-Sevilla
VHIR-Barcelona
HUCA- Asturias
TORRECÁRDENAS - Almería
HCU Valladolid
HOSPITAL UNIVERSITARIO PUERTA DE HIERRO. DR J CARNEADO RUIZ.
IdiPAZ-Madrid
Germans Trias-Badalona
IRB-Lleida
Patricia Calleja. Centro de Ictus. Hospital Doce de octubre.
GCA Málaga – Carlos de la Cruz Cosme.
GCA-Aragón Associated clinical Group (Dr. Javier Marta)

3. ICH
HUCA- Asturias
HCRB-IDIBAPS - Barcelona (SAH studies: neuroimaging, blood and CSF biomarkers and genetic studies)
IdiPAZ-Madrid. papel de los exosomas como biomarcador en HC, con estudios de proteómica de su contenido.
GCA Málaga – Carlos de la Cruz Cosme
GCA-Aragón Associated clinical Group (Dr. Javier Marta)
IIS La Fe Valencia RD21/0006/0014: biomarkers in subarachnoidal hemorrhage (SAH)
IRB-Lleida

• **WP3:** Biomarkers for outcome (stroke complications and recovery)

1. Growth/FUTILE…
IBIS-sevilla
HUCA- Asturias
i+12 Madrid
IDIS - Santiago
Futile recanalization: HCU Valladolid (NORDICTUS)
HOSPITAL UNIVERSITARIO PUERTA DE HIERRO. DR J CARNEADO RUIZ.
IdiPAZ-Madrid: Estamos desarrollando el estudio GLIAS-TM (financiación ISCIII AES 2021) para el estudio de microRNA/glicemia en el daño por isquemia-reperfusión
Germans Trias-Badalona
GCA Málaga – Carlos de la Cruz Cosme
GCA-Aragón Associated clinical Group (Dr. Javier Marta)
IIS IP-UCM: data modeling techniques (HU Princesa, Madrid)
IDIBGI-Serena
IRB-Lleida

2. Thrombus
IBIS-Sevilla (trombo/plasma correlación biomarkers)
HUCA- Asturias
i+12 Madrid
HCU Valladolid (thrombectomy bank)
HOSPITAL UNIVERSITARIO PUERTA DE HIERRO. DR J CARNEADO RUIZ.
IdIPAZ-Madrid: Tenemos una colección de trombos con los que podríamos colaborar.
Alberto Alcázar. Grupo Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Hospital Ramón y Cajal, Madrid
Patricia Calleja. Hospital Universitario Doce de Octubre.
GCA Málaga – Carlos de la Cruz Cosme
GCA-Aragón Associated clinical Group (Dr. Javier Marta)
IIS Princesa-Santa Cristina (Martínez Ruiz & Marina) - Redox proteomics (HU Princesa, Madrid)
IDIBGI-Serena
IIS La Fe Valencia RD21/0006/0014: Association of adherence and composition of the Mediterranean diet with the composition of thrombi
IRB-LLeida

• **WP3:** Biomarkers for outcome (stroke complications and recovery)

3. Global Outcome
IBIS-Sevilla
VHIR-Barcelona
HUCA- Asturias
i+12 Madrid
HOSPITAL UNIVERSITARIO PUERTA DE HIERRO. DR J CARNEADO RUIZ.
HCRB-IDIBAPS - Barcelona (in collaboration with Sant Pau): Study of the influence of intestinal microbiota on the evolution of ischemic stroke. Measurable criteria: functional prognosis at 3 months.
Alberto Alcázar. Grupo Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Hospital Ramón y Cajal, Madrid
GCA Málaga – Carlos de la Cruz Cosme
IRB-Lleida

4. Cognition
HUCA- Asturias (pacientes)
i+12 Madrid
TORRECÁRDENAS - Almería
GCA Málaga – Carlos de la Cruz Cosme
GCA-Aragón Associated clinical Group (Dr. Javier Marta)
IRB-Lleida

- **WP4:** Biomarkers in experimental models of stroke and selected pathways

1. Experimental & targets
IBIS-sevilla
i+12 Madrid
TORRECÁRDENAS - Almería
IDIS - Santiago
HCRB-IDIBAPS - Barcelona: Blood biomarkers of severity (including infection and inflammation) and time course evolution according to the progression of damage and recovery. We are interested in collaborative studies of proteomics and lipidomics.
IdiPAZ-Barcelona: estamos trabajando con modelos animales de hemorragia cerebral para identificación de biomarcadores.
Germans Trias-Badalona
Alberto Alcázar. Grupo Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Hospital Ramón y Cajal, Madrid
IIS-IP-Santa Cristina Javier Egea & Antonio Martínez: **(HU Princesa, Madrid)**
IDIBGI-Serena
IIS La Fe Valencia RD21/0006/0014: Identification of new predictive biomarkers of brain damage and worsening in murine models of cerebral ischemia
IRB-Lleida

1. BIOMARKERS FOR IDENTIFICATION OF STROKE AND ITS RECOVERY (interim scientific production)

Diagnosis and prognosis in stroke patients is challenging due to the limited accuracy of current models. Biomarkers could enhance diagnostic and prognostic capabilities by providing additional information. The goal is to identify new biomarkers that allow rapid diagnosis and prognosis, improving therapy and patient outcomes.

PREVIOUS RESULTS. The research groups participating in this line have made significant progress with relevant publications in the 4 WPs we explored.

WP1. Biomarkers for the pre-hospital diagnosis**:** for reperfusion therapies (7).

WP2. Use of biomarkers in stroke subtypes: linked to atrial fibrillation, cerebral amyloid angiopathy, intracerebral hemorrhage and transient ischemic attack (8-12).

WP3. Biomarkers for outcome (stroke complications and recovery): Focuses on biomarkers for thrombectomy, futile reperfusion, recurrence prevention and post-stroke epilepsy (13-16).

WP4: Biomarkers in experimental models: such as extracellular vesicles and markers of hemorrhagic transformation (17,18).

Finally, **3 collaborative projects** open to network members are: a) **BIOSHIP** (led by IBIS-Sevilla) was launched with the involvement of several groups within the network and is expected to be completed in the coming years. This study aims to validate the potential use of a rapid Point-of-Care device for the pre-hospital diagnosis of ischemic stroke due to large vessel occlusion, enabling direct transport from the ambulance to thrombectomy centers. It is anticipated that this approach will increase by 15% the percentage of patients who achieve functional independence compared to those managed through standard care; b) MACHINE-Learning: (led by La Princesa-Madrid), focuses on developing predictive models for outcomes like mortality and hemorrhagic transformation; and c) **RACE-PLUS**, (German Trias i Pujol), works on validating the RACE-PLUS algorithm using machine learning to differentiate ischemic stroke subtypes in out-of-hospital patients.

Publications

WP1: Marcadores para el tratamiento trombolítico prehospitalario (Parody-Rua et al., Eur J Health Econ. 2023)

WP2: Biomarcadores para diagnóstico y pronóstico del ictus usando espectrometría de masas o biomarcadores (Cortés et al., Analyst.. 2023; Avila-Gómez et al., J Clin Med. 2022; Marta-Enguita et al., Neurologia (Engl Ed). 2022) Biomarcadores para el diagnóstico del ictus del despertar (Hervella et al., BMC Neurol 2022) Biomarcadores plasmáticos y radiológicos para el diagnóstico de fibrilación auricular en pacientes asintomáticos y con/sin demencia (Pala et al., Front Cardiovasc Med 2022. J Stroke Cerebrovasc Dis 2022; Plos One 2022; Schweizer et al., J Am Coll Cardiol. 2022) Marcadores de diagnóstico de angiopatía neurovascular y leucoaraiosis (da Silva Candal et al., Ann Clin Transl Neurol. 2022)

WP3: Biomarcadores de vulnerabilidad de placa en pacientes con estenosis carotidea (Carballo-Perich et al., Int J Mol Sci. 2022). Marcadores de predicción de transformación hemorrágica en pacientes (Krishnamoorthy et al., Cerebrovasc Dis. 2022; Honegger et al., Eur Stroke J. 2023) y a nivel experimental (Gubern-Mérida et al., Mol Neurobiol. 2022) Pronóstico del tratamiento con trombectomía (López et al., Cerebrovasc Dis Extra. 2022; Millan et al., Stroke 2022) o marcadores de imagen para selección de pacientes para trombectomía (Aguirre et al., Neuroradiol J. 2023) Prevención de recurrencias (Gil-Nuñez et al., Neurologia (Engl Ed). 2022; McCabe et al., Stroke 2023) Inestabilidad neurológica (Iglesias-Rey et al., Transl Stroke Res. 2022) Variabilidad glucémica en la predicción pronóstica de los pacientes con infarto cerebral agudo. (Gu errez-Zúñiga et al. Neurología 2023)

WP4: Marcadores de transformación hemorrágica en estudios experimentales (Gubern-Mérida et al., Mol Neurobiol. 2022) Marcadores de imagen para selección de pacientes para trombectomía (Aguirre et al., Neuroradiol J. 2023) Vesículas extracelulares circulantes como biomarcador de patogenia en modelo preclínico de hemorragia intracerebral (Laso-García et al., Front Cell Neurosci 2023).

BIOMARCADORES PARA LA IDENTIFICACIÓN DEL ICTUS Y SU RECUPERACIÓN

Nuestro objetivo es identificar nuevos biomarcadores diagnósticos y de pronóstico en el ictus. Los biomarcadores incluirán biomarcadores sanguíneos (genéticos, proteínas, exosomas, miRNAs, etc.) y biomarcadores de imagen. Esta línea de investigación es también una línea transversal a las otras 4 líneas, ya que uno de los objetivos principales es realizar un diagnóstico y pronóstico rápido que tendrá efectos directos en el proceso terapéutico y en la evolución de los pacientes. Esta será una línea de investigación con presencia de todos los grupos de la RICORS. Cuatro paquetes de trabajo:

- WP1: Biomarcadores para el diagnóstico prehospitalario del ictus;
- WP2: Uso de biomarcadores en subtipos de ictus;
- WP3: Biomarcadores para el resultado (complicaciones del ictus y recuperación);
- WP4: Biomarcadores en modelos experimentales de ictus y vías seleccionadas para el diagnóstico y la terapia.

Presentación de la línea.

Propuesta de Colaboración – BIOSHIP-training

Propuesta de Colaboración – MachineLearning

Propuesta de Colaboración – Estudio de nuevos biomarcadores en una cohorte de pacientes de vasculitis cerebral primaria

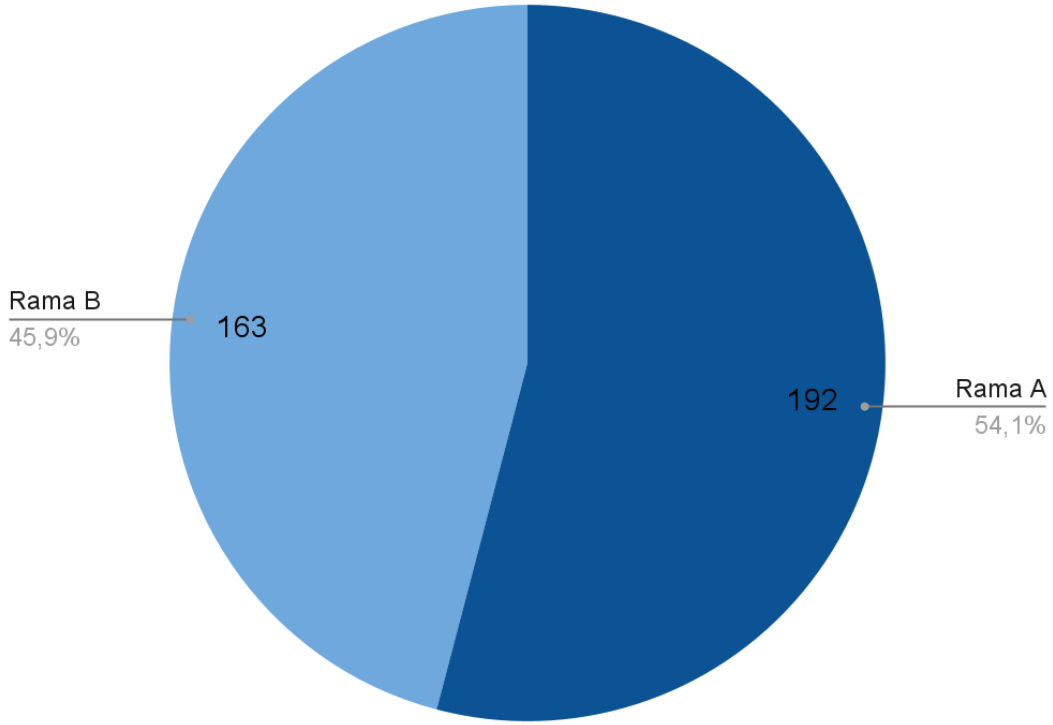
PUBLICACIONES

septiembre 2024 (1)
agosto 2024 (5)
julio 2024 (1)
junio 2024 (1)
mayo 2024 (2)
abril 2024 (5)
marzo 2024 (11)
febrero 2024 (19)
enero 2024 (14)
diciembre 2023 (17)
noviembre 2023 (20)
octubre 2023 (9)
septiembre 2023 (14)
agosto 2023 (11)
julio 2023 (17)

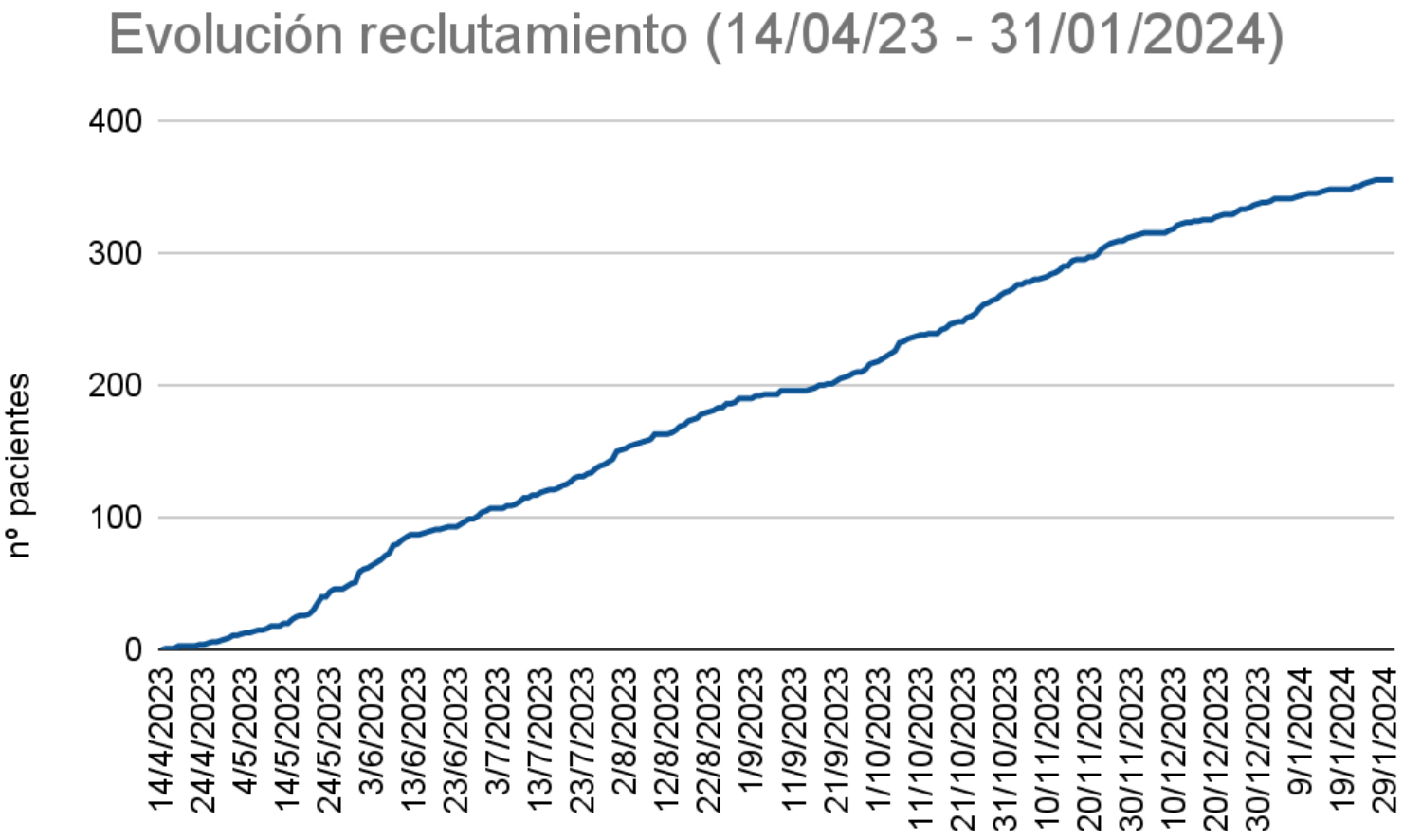
BIOSHIP-training se **cierra con 355 pacientes incluidos** (2 de ellos se excluyen del análisis por diagnóstico dudoso tras revisión por el equipo).

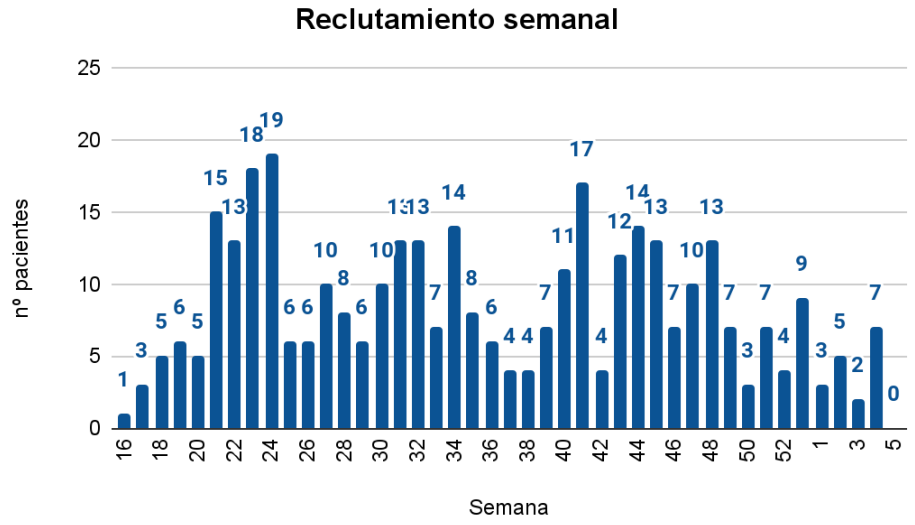
Rama A (pre-hospitalaria) = 54% (192 sujetos)
Rama B (hospitalaria) = 46% (163 sujetos)

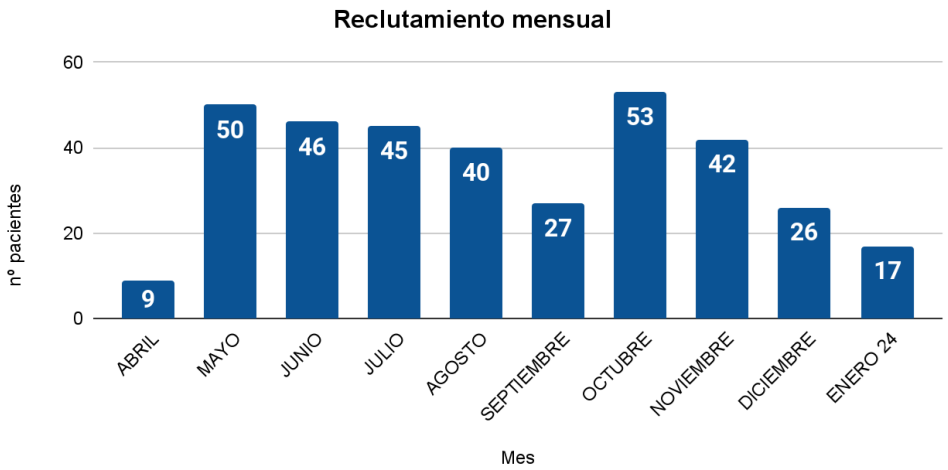
**NOTA: se buscaba un 60% rama A y 40% rama B, pero se ha encontrado mayor dificultad para obtener CI firmado en rama A dando lugar a más SF.*



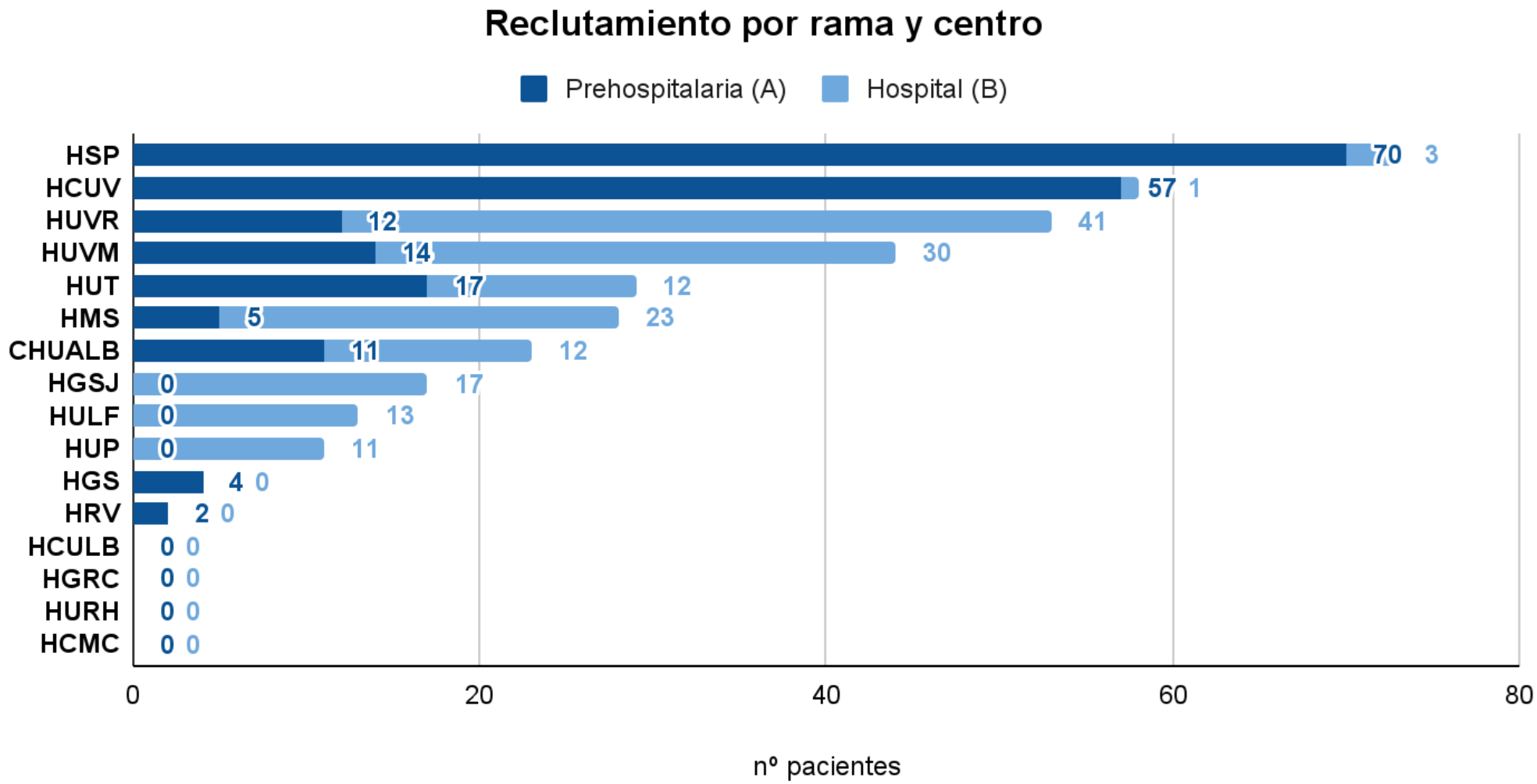
Evolución reclutamiento



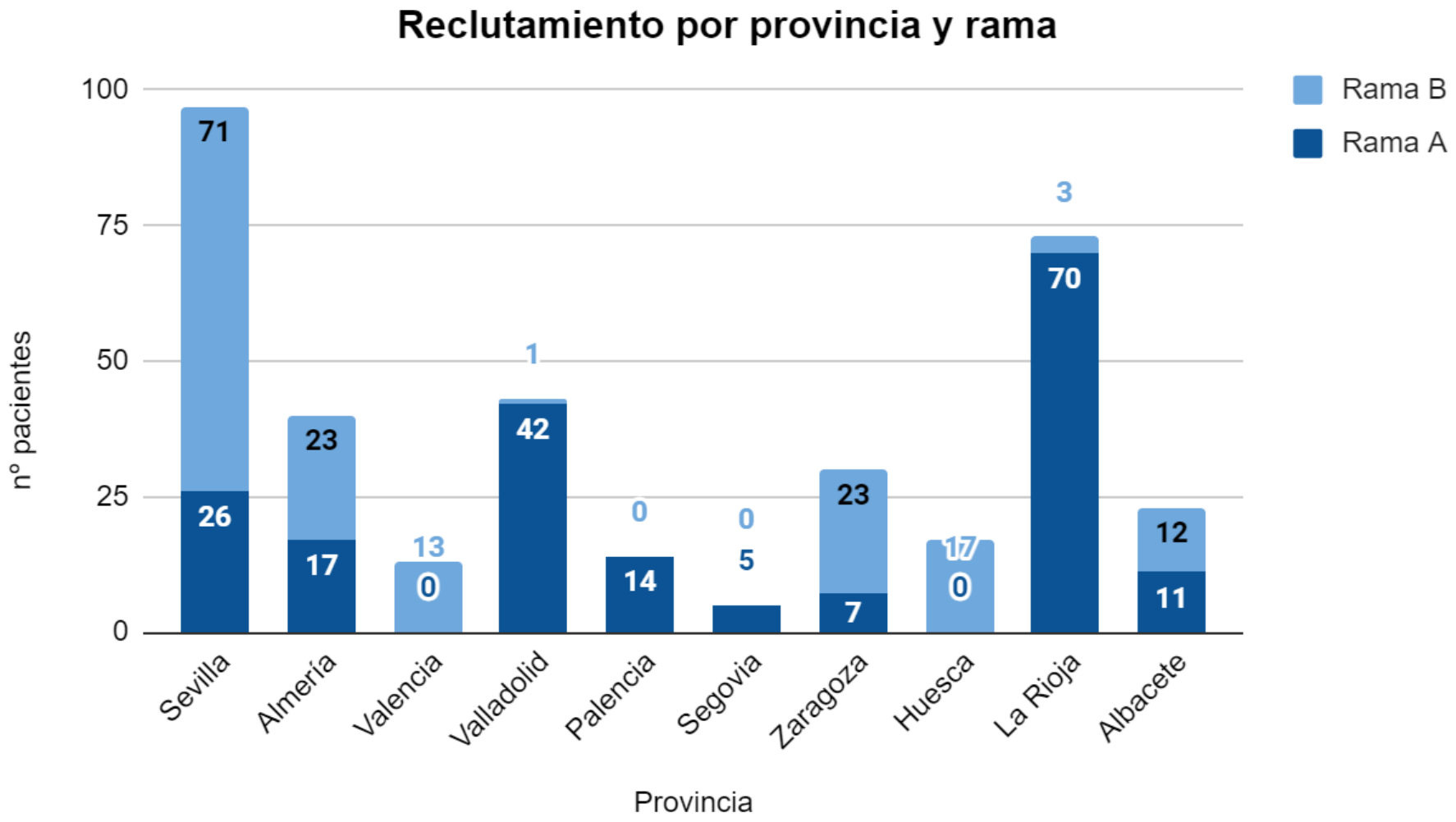




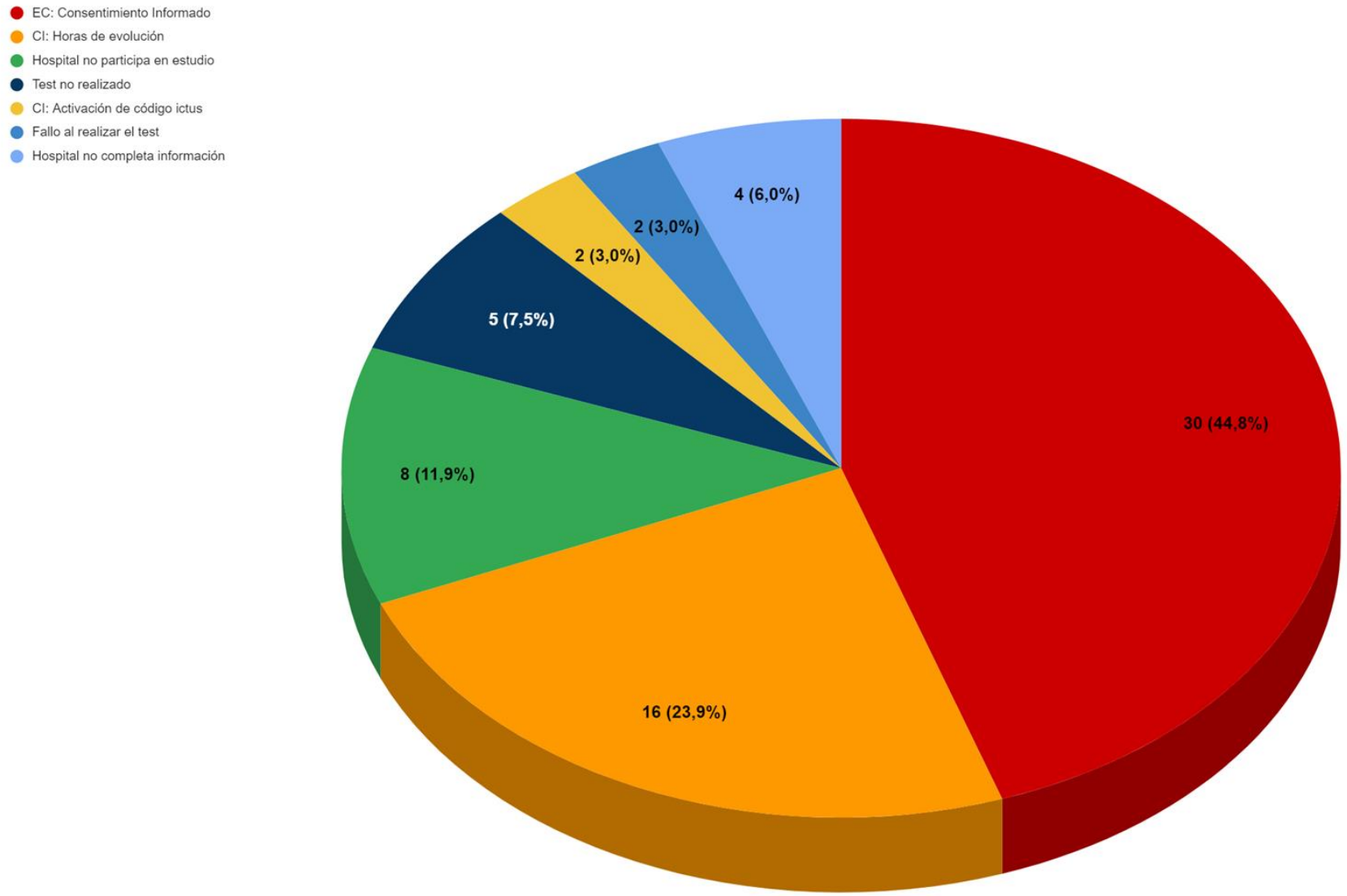
Reclutamiento por centros y ramas

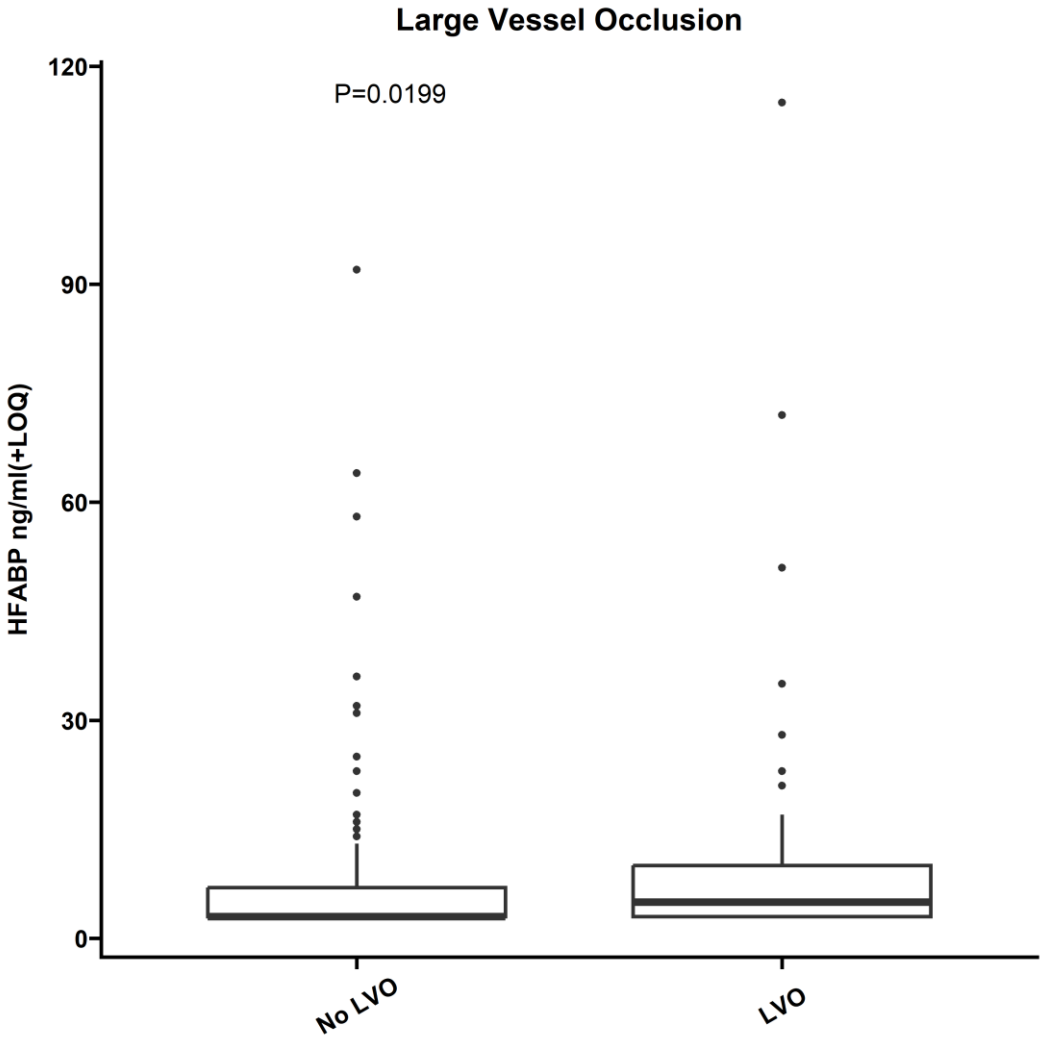


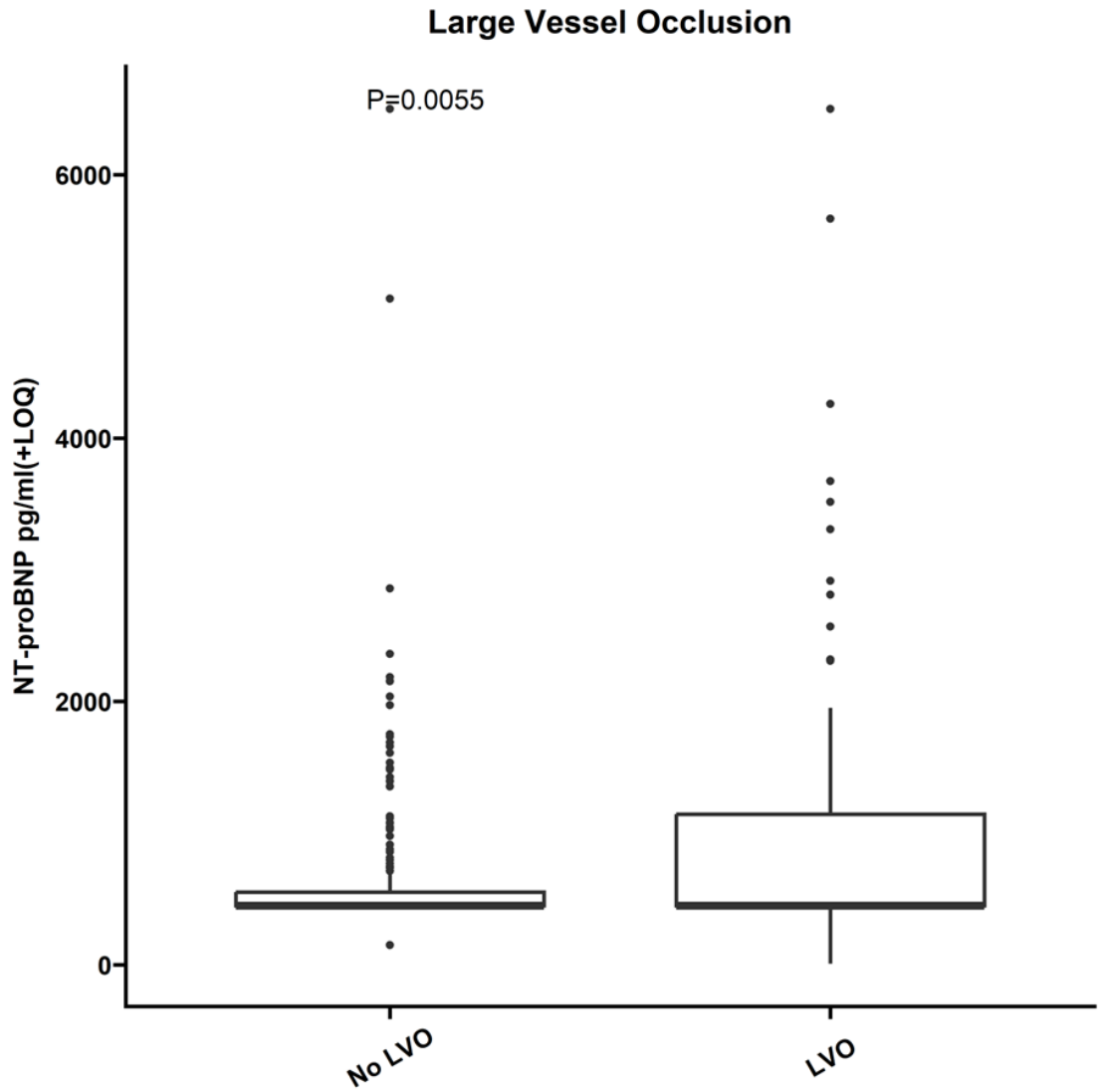
Reclutamiento por provincias y ramas



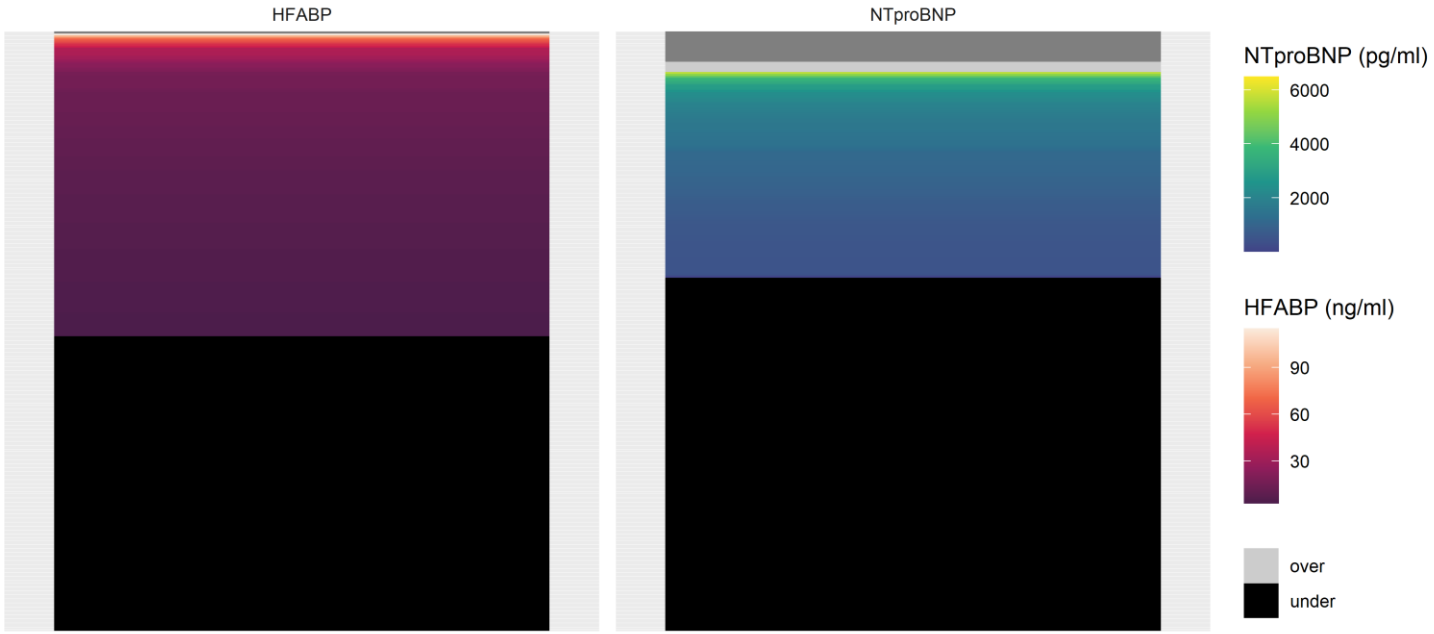
Motivos de fallos de screening




Large Vessel Occlusion
P=0.0199
HFABP ng/ml(+LOQ)
120
90
60
30
0
No LVO
LVO

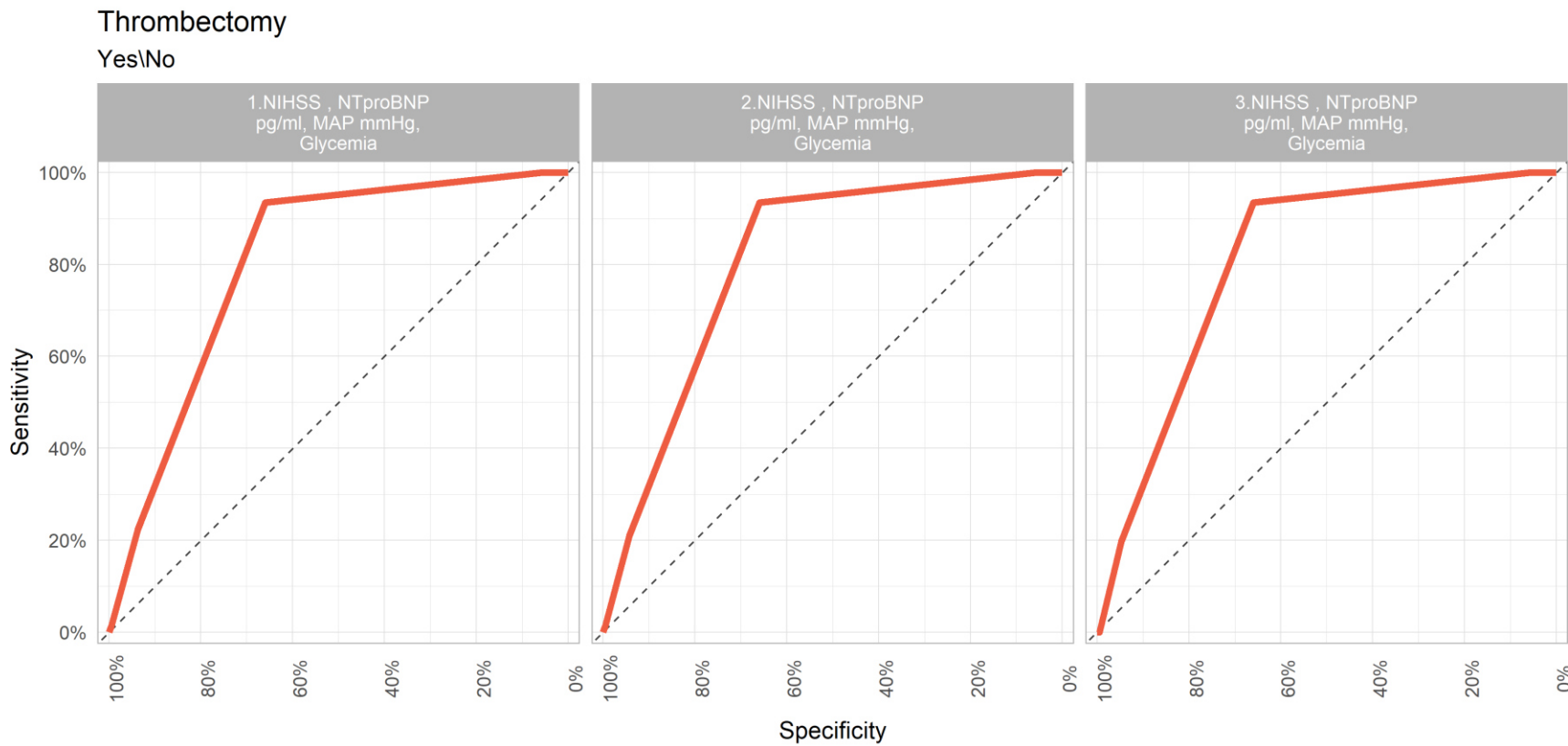

Large Vessel Occlusion
P=0.0055
NT-proBNP pg/ml(+LOQ)
6000
4000
2000
0
No LVO
LVO

DUOCHECK Values
BIOSHIP

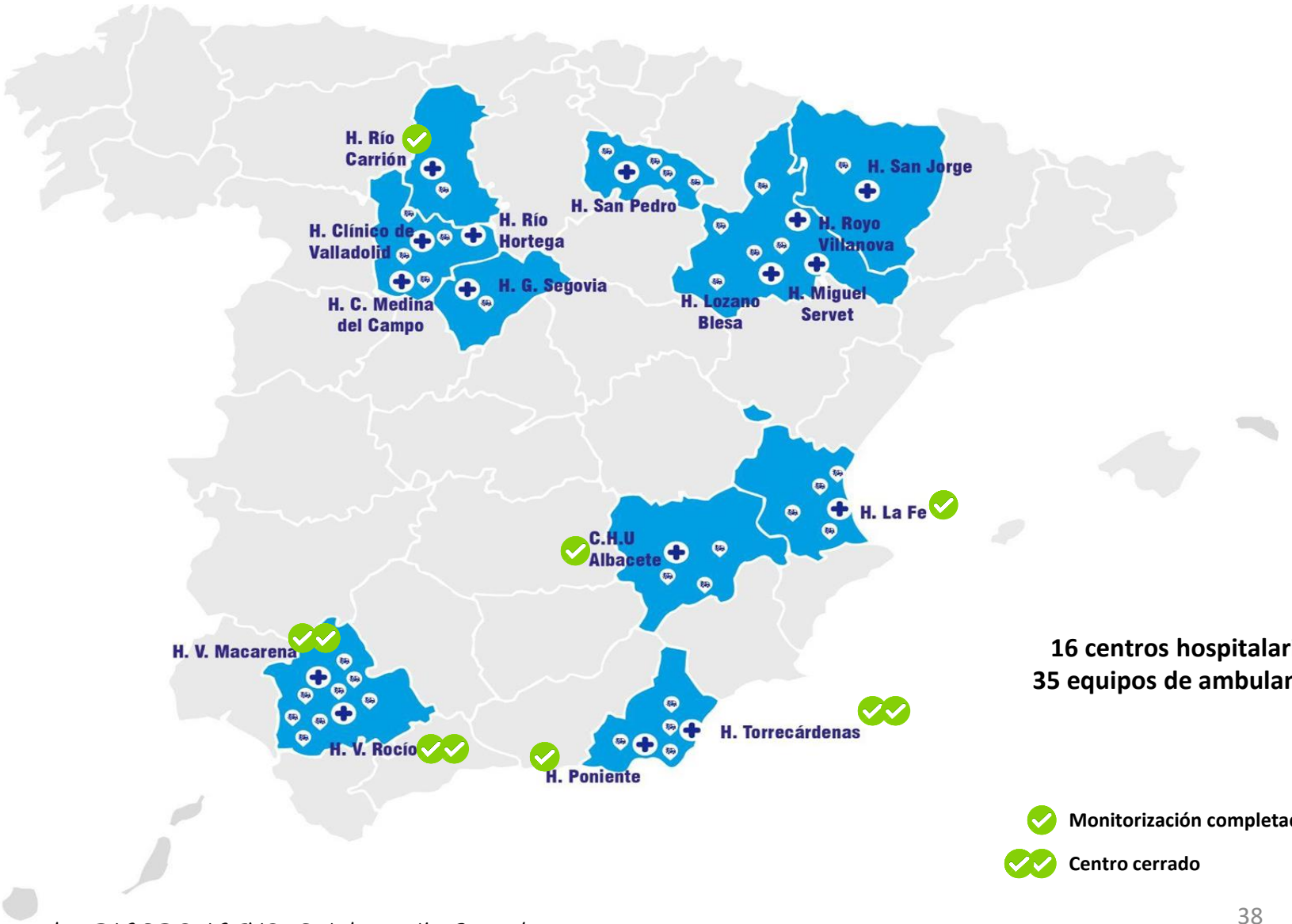


	Marker		Total
	HFABP	NTproBNP	
Measure			
over	0 (0%)	5 (1.7%)	5 (0.8%)
under	146 (49%)	175 (59%)	321 (54%)
value	150 (51%)	102 (34%)	252 (42%)
Unknown	1 (0.3%)	15 (5.1%)	16 (2.7%)

```
Training parameters:
                    min.constr =  ()
                    predictors =
                    response = thrombect
                    levels = No Yes
Executed in 10.85 secs (ended on 2024-05-24 11:38 GMT)
                    iterations =
Performance on training set ( patients:  No,  Yes):
                    sensitivity = 0.950
                    specificity = 0.674
[[1]]
Thresholds:
                    nihss0 > 8.5
                    ntbnp_lod > 1399
                    map < 133.167
                    gluc > 206
                    positive when >= 2.
[[2]]
Thresholds:
                    nihss0 > 8.5
                    ntbnp_lod > 1434.5
                    map < 133.167
                    gluc > 206
                    positive when >= 2.
[[3]]
Thresholds:
                    nihss0 > 8.5
                    ntbnp_lod > 1526.5
                    map < 133.167
                    gluc > 206
                    positive when >= 2.
```



Los protagonistas del estudio BIOSHIP-training



16 centros hospitalarios
35 equipos de ambulancias

Monitorización completada

Centro cerrado

EQUIPO COORDINADOR

Grupo de Investigación Neurovascular:

Ana Barragán Prieto
IP Coordinadora
abarraganprieto@gmail.com

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Rosa M. Delgado Sánchez, PhD
Project Manager
rosadelgado.neuro@gmail.com

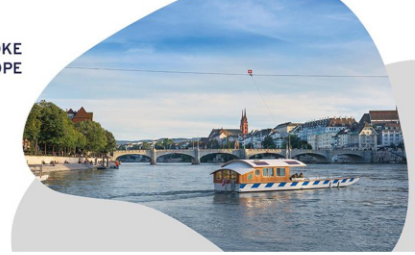
Hospital Universitario Virgen Macarena (HUVM)

Instituto de Biomedicina de Sevilla (IBiS)

ESOC 2024 — 10TH ANNIVERSARY — THE VOICE OF STROKE IN EUROPE

10th European Stroke Organisation Conference

15–17 May 2024, Basel, Switzerland



A FAST AND SIMPLE BLOOD TEST USING A SMARTPHONE READER PREDICTS OUTCOME AMONG THROMBECTOMY TREATED STROKE PATIENTS

Joan Montaner[1,3], Ana Barragán Prieto[1], Ana Asensio[1], Marcel Lamana Vallverdu[2], Rosa M Delgado[1], Carmen De Jesús-Gil[1], Aynara Zamora[3], Diego Villagrán Sancho[4], Antonio Cristobal Luque Ambrosiani[4], Alejandro González García[4].

1. Hospital Universitario Virgen Macarena, Sevilla, Spain; 2. Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain; 3. Instituto de Biomedicina de Sevilla (IBiS), Sevilla, Spain; 4. Hospital Universitario Virgen del Rocío, Sevilla, Spain;

INTRODUCTION

- Fatty Acid Binding Protein (FABP) and NT-proBNP are brain damage blood biomarkers with prognostic value among stroke patients.
- Almost half of thrombectomy patients suffer futile recanalization but we have NO effective tool or device to forecast those with bad outcome is spite of effective recanalization of the occluded brain vessel.

AIM

- A smartphone APP reading a rapid blood test measuring those biomarkers has been developed to be used at the angio-suite to predict outcome among large vessel occlusion (LVO) patients that receive thrombectomy.

METHOD

- Consecutive patients (n=308) with confirmed LVO and receiving thrombectomy included in the ARTISTA prospective registry were recruited. Blood samples were obtained at thrombectomy, samples were centrifuged, and plasma was biobanked. A rapid POC test measuring both markers at the same time and scanned with a smartphone APP that offered quantitative values of each biomarker was performed. Functional outcome at 3 months was the main endpoint.

DUOCheck test — Reading APP

SCAN the QR code to learn how to perform the test:

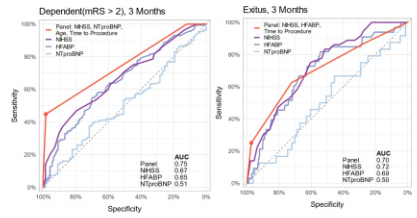
RESULTS

- Following thrombectomy 143 patients (46.4%) remained independent (mRS 0-2) and 37 died (12.1%) at 90 days. Clinical factors significantly associated with poor outcome in multivariate models were age, baseline NIHSS, previous mRS, diabetes and time from symptoms onset to blood sampling. FABP was highly elevated among dependent and deceased patients (p<0.001). Using Panelomix software we identified optimal cutoffs in two panels of biomarkers+clinical parameters to predict outcome with excellent specificity.

Characteristic	mRS=<2, N = 143[1]	mRS>2, N = 165[1]	p-value[2]
Sex (Female)	60 (42%)	83 (50%)	0.14
Age	68 (57, 76)	75 (68, 82)	<0.001
NIHSS Admission	12 (7, 19)	19 (12, 23)	<0.001
Previous mRS			<0.001
0	116 (81%)	88 (54%)	
1	21 (15%)	30 (18%)	
2	6 (4.2%)	23 (14%)	
3	0 (0%)	19 (12%)	
4	0 (0%)	3 (1.8%)	
Wake-Up Stroke	58 (41%)	69 (42%)	0.8
Diabetes Mellitus	43 (30%)	59 (36%)	0.3
Procedure SBP	150 (137, 168)	150 (139, 170)	0.8
Symptoms to Blood Collection Min.	277 (167, 579)	365 (220, 565)	0.10

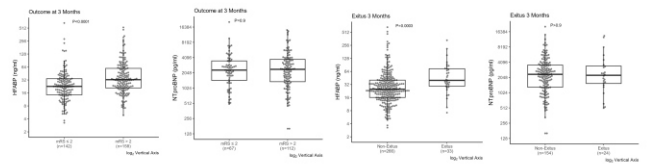
[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test



3 months mRS>2 prediction: *specificity= 98.3% and sensitivity= 44.8% (panel= NIHSS/FABP/NT-proBNP/age/previous mRS/sampling time)*

3 months mortality prediction: *specificity = 97.3% and sensitivity = 25% (panel= NIHSS/FABP/NT-proBNP/sampling time)*



CONCLUSIONS

- A friendly smartphone device might predict outcome among those patients that get endovascular therapies.
- This might aid in future decisions about limiting endovascular therapies efforts or adding neuroprotectants in those with predicted poor outcome despite successful reperfusion.
- A prospective study using whole blood at the angio-suite is running to confirm these findings.

ACKNOWLEDGEMENT

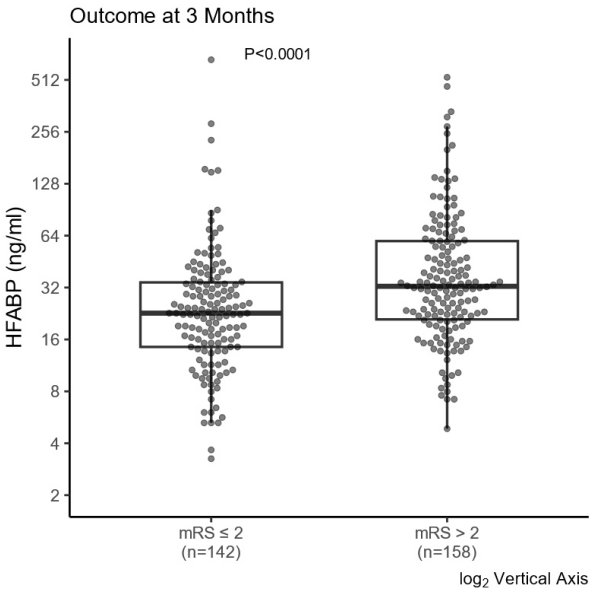
PIN-0139-2020 (BIOSHIP) — TED2021-131742B-I00 (LVOCHECK-TOOL) — DTS19/00135 (BIOFAST) — DTS22/00078 (LVOCHECK-SPAIN) — PIF-0009-2021 (LVOCHECK) — PI21/01158 (ETNAS)

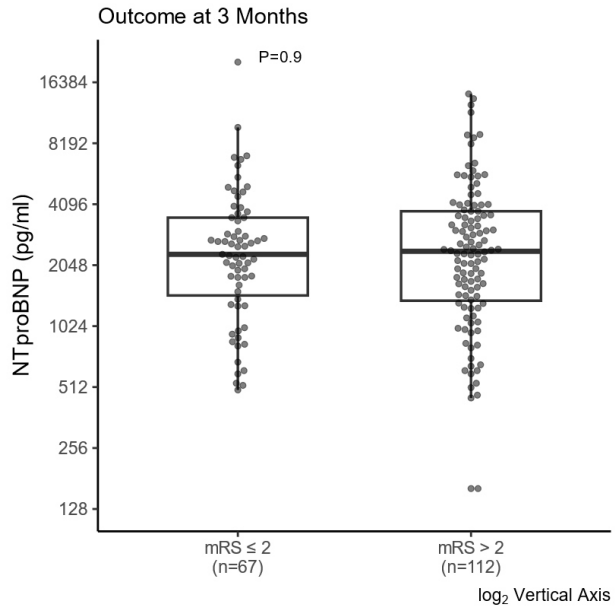
CONTACT INFORMATION

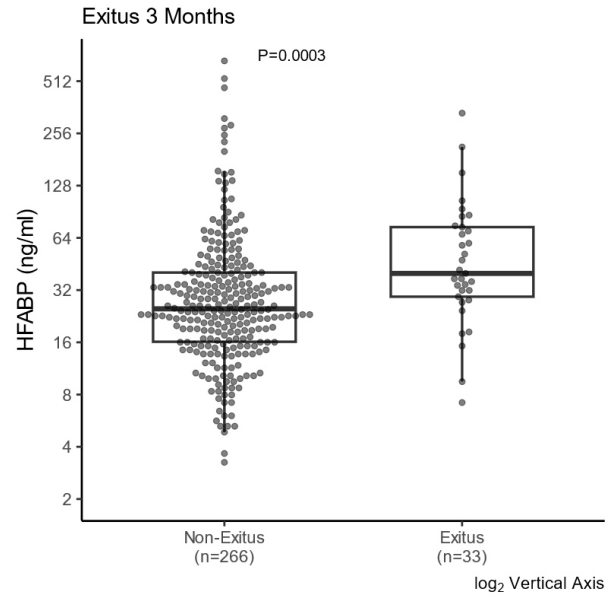
jmontaner-ibis@us.es

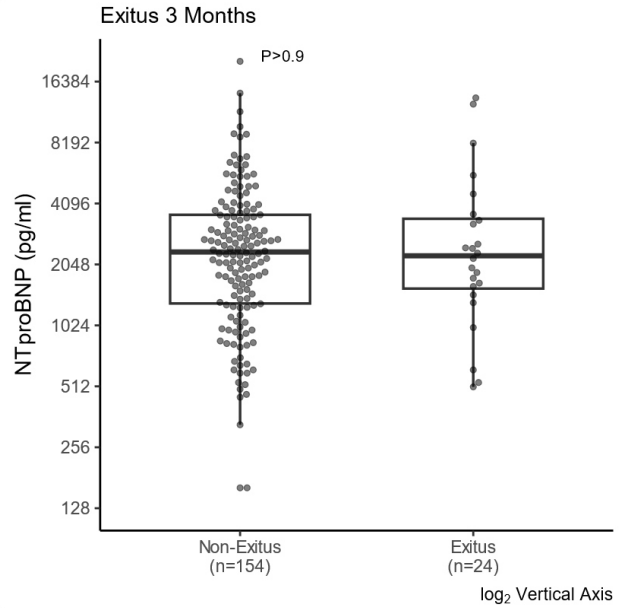
https://www.ibis-sevilla.es/es/investigacion/neurociencias/neurovascular/

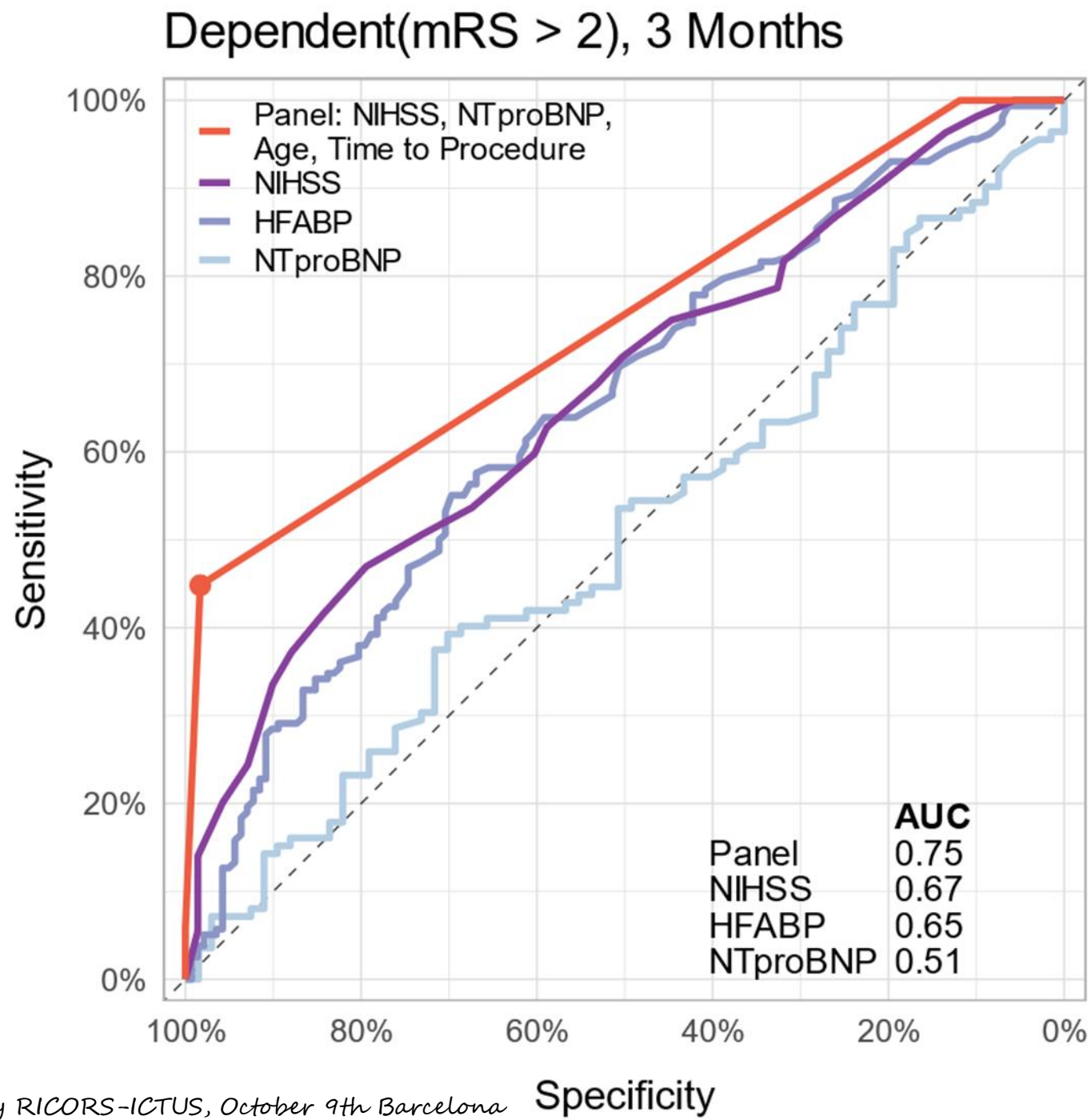
III Stroke Congress by RICORS-ICTUS, October 9th Barcelona


Outcome at 3 Months
P<0.0001
HFABP (ng/ml)
512
256
128
64
32
16
8
4
2
mRS ≤ 2
(n=142)
mRS > 2
(n=158)
log2 Vertical Axis


Outcome at 3 Months
P=0.9
NTproBNP (pg/ml)
16384
8192
4096
2048
1024
512
256
128
mRS ≤ 2
(n=67)
mRS > 2
(n=112)
log2 Vertical Axis


Exitus 3 Months
P=0.0003
HFABP (ng/ml)
512
256
128
64
32
16
8
4
2
Non-Exitus
(n=266)
Exitus
(n=33)
log2 Vertical Axis


Exitus 3 Months
P>0.9
NTproBNP (pg/ml)
16384
8192
4096
2048
1024
512
256
128
Non-Exitus
(n=154)
Exitus
(n=24)
log2 Vertical Axis


Dependent(mRS > 2), 3 Months
Panel: NIHSS, NTproBNP, Age, Time to Procedure
NIHSS
HFABP
NTproBNP
Sensitivity
100%
80%
60%
40%
20%
0%
100%
80%
60%
40%
20%
0%
Specificity
AUC
Panel 0.75
NIHSS 0.67
HFABP 0.65
NTproBNP 0.51

TROMBOPOCT: Estado actual (n=250)

TROMBOPOCT

Inicio de reclutamiento: 8 de ABRIL de 2024

Número de pacientes reclutados: 169

Hospital Universitario Virgen Rocío (HUVR)

Dr. Alejandro González García
IP Coordinador del estudio e IP del centro

HOSPITAL UNIVERSITARIO Virgen del Rocío

Número de pacientes reclutados: 81

Hospital Universitario Reina Sofía (HURS)

Dr. Fernando Delgado
IP del centro

HURS

Co-funded by the European Union

RICORS - ICTUS

Colaboración IntraRed

Visibilidad en la página web RICORS (INDICAR Si/No): Sí

Marcar una de las dos opciones:
☐ Solicitud de colaboración
X Propuesta de colaboración

Marcar una de las dos opciones:
X Ficha de proyecto
☐ Fichas de plataforma técnica

Características (rellenar con la mayor brevedad posible):

1. Nombre del grupo: **NEUROLOGÍA IIS PRINCESA**
2. Título del proyecto: **Aplicación de técnicas de machine learning sobre datos de monitorización continua hemodinámica en pacientes diagnosticados ingresados (a1) o con sospecha de ictus extrahospitalarios y búsqueda de biomarcadores plasmáticos y de escala clínica (a2).**
3. Persona y email contacto: **gemmareig@hotmail.com, Jose.L.Ayala@gmail.com, jvivancos@neurogps.com.es**

4. Línea de investigación:
   A. **Biomarcadores**
   B. Tratamiento fase aguda
   C. Cerebroprotección
   D. Reparación cerebral y Recuperación Funcional
   E. Prevención Secundaria

Objetivo principal/Breve descripción: **Generar modelos predictivos de: a1) exitus, resangrado y transformación hemorrágica en pacientes diagnosticados; a2) ictus hemorrágico vs isquémico, y escala predictiva de gran vaso en pacientes con sospecha de ictus en medio extrahospitalario.**

5. Tipo de colaboración: *estudio multicéntrico con datos clínicos y/o muestras, ofrecimiento de técnica o plataforma,...***estudio multicéntrico con datos clínicos**
6. Criterios de inclusión (si es un estudio con pacientes): **pacientes atendidos como código ictus extrahospitalario por servicio de emergencias extrahospitalario y/o pacientes ingresados en la unidad de ictus.**
7. Si se requieren muestras: breve descripción del tipo de muestra y procesamiento de la misma. **N/A (inicialmente, se podría ampliar en un futuro)**
8. Proyecto financiado con presupuesto para los centros colaboradores: **No (pendiente de resolución Proyectos de I+D+I en Salud 2022)**

Co-funded by the European Union

RICORS - ICTUS

Colaboración IntraRed

Visibilidad en la página web RICORS (INDICAR Si/No): SI

Marcar una de las dos opciones:
☐ Solicitud de colaboración
■ Propuesta de colaboración

Marcar una de las dos opciones:
■ Ficha de proyecto
☐ Fichas de plataforma técnica

Características (rellenar con la mayor brevedad posible):

1. Nombre del grupo: **IMAS12. Instituto de Investigación Biomédica Hospital Doce de Octubre.**
2. Título del proyecto: **Estudio de nuevos biomarcadores en una cohorte de pacientes de vasculitis cerebral primaria.**
3. Persona y email contacto:
   Manuel Navarro (manuna02@ucm.es)
   Ignacio Lizasoain (ignacio.lizasoain@med.ucm.es)
4. Línea de investigación:
   A. Biomarcadores
   B. Tratamiento fase aguda
   C. Cerebroprotección
   D. Reparación cerebral y Recuperación Funcional
   E. Prevención Secundaria
5. Objetivo principal/Breve descripción:
   Estudiar posibles nuevos biomarcadores en muestras obtenidas de pacientes diagnosticados con vasculitis cerebral primaria y analizar los niveles de NOD-1 y de otros marcadores inflamatorios.
6. Tipo de colaboración: ***estudio multicéntrico con datos clínicos y muestras de sangre.***
7. Criterios de inclusión (si es un estudio con pacientes): **pacientes diagnosticados con vasculitis cerebral primaria**
8. Si se requieren muestras: breve descripción del tipo de muestra y procesamiento de la misma.
   Obtener una muestra de sangre (1 tubo de suero y 1 tubo de plasma) de pacientes diagnosticados con vasculitis cerebral.
9. Proyecto financiado con presupuesto para los centros colaboradores: **No**

Modelos de predicción de ictus con técnicas de aprendizaje automático

ESTUDIO INTRAHOSPITALARIO Y PREHOSPITALARIO

Hospital Universitario de La Princesa

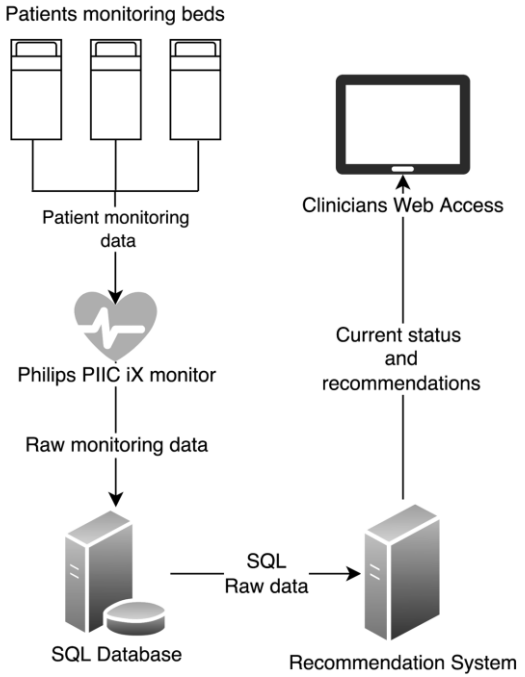
UNIVERSIDAD COMPLUTENSE MADRID

JL Ayala
N Riera
G Reig
M Ríos
L García-Terriza
J Vivancos

III Stroke Congress by RICORS-ICTUS, October 9th Barcelona

Estudio intrahospitalario: Sistema predictor y recomendador

RECOMENDADOR EN FUNCIONAMIENTO EN LA UNIDAD DE ICTUS. VALORANDO PERFIL DE SATISFACCIÓN y UTILIDAD



Exitus probability

#	NHC	Exitus probability (%)	Mean Accumulated exitus probability (%)
1	[redacted] Edit	Wait a few more seconds for results	N/A
2	[redacted] Edit	0.00%	0.00%
3	[redacted] Edit	Insert patient information (1)	N/A
4	[redacted] Edit	0.05%	0.04%
5 (4)	[redacted] Edit	99.49% (2)	86.84% (3)

#	EV	FR	FC	SPO2	Rhythm Estimation	ST-II	Perfusion	Feedback
Last observation (5)	0	23	66	92	Ritmo SV	0.2	1.8	
Recommendation #1 - (keep for 2.5 mins) (6)	0	17	67	96	Ritmo sinusal	-0.57	4.34	(8)
Recommendation #2 - (keep for 2.5 mins)	0	17	61	96	Ritmo sinusal	-0.57	4.31	(7)
Recommendation #3 - (keep for 2.5 mins)	0	17	67	96	Ritmo sinusal	-0.57	4.31	

IMPLEMENTACIÓN EN TIEMPO REAL . TABLETS/ ESTACIÓN DE TRABAJO CONTROL ENFERMERÍA

SISTEMA PREDICTOR:

Modelo diagnóstico subtipo ictus
RF: F1Score 99% en 5min 100% en 25 min

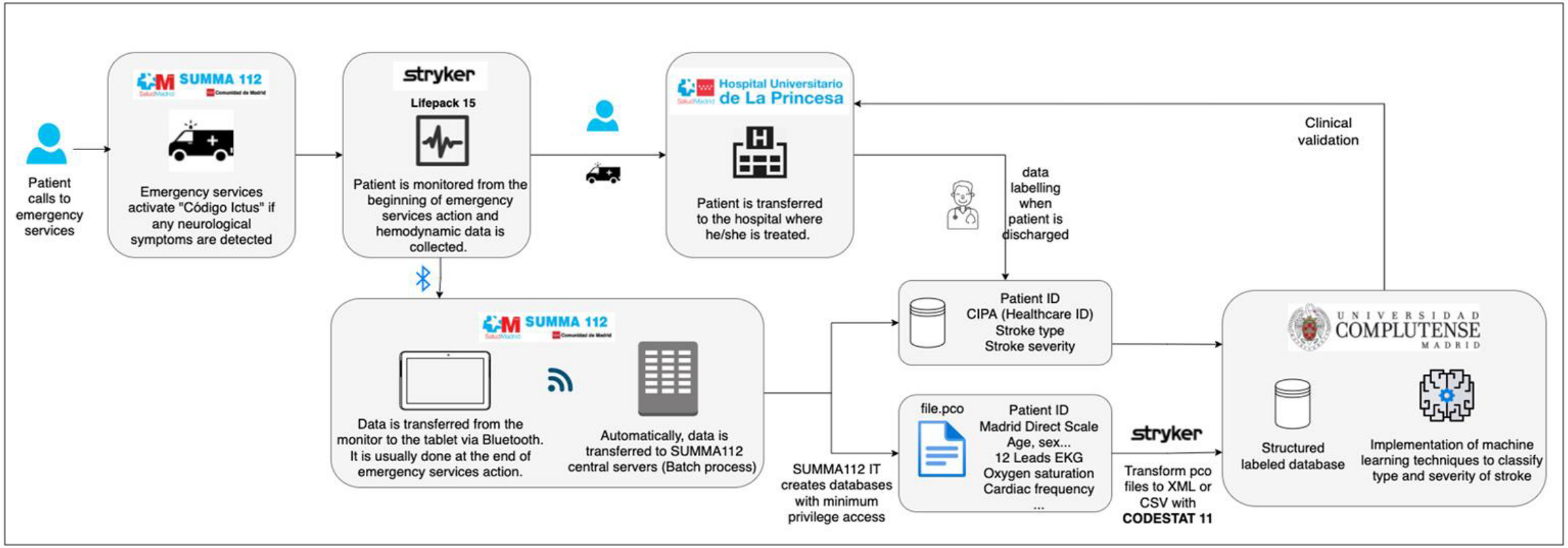
Modelo predicción EXITUS
GBT: F1Score 99% 1 horas 100% 2h

Modelo resangrado
GBT: F1Score 99% en 1 horas 100% en 48h
RF: F1Score 100% en 2h

Study design – Prehospital

Patient and data protocol

PENDIENTE DE ANALIZAR 2023



RESULTADOS 2022 pendiente de publicación

Modelo de predicción oclusión de gran vaso: F1 score 81% sensibilidad 93% especificidad 65% (KNN)

La información hemodinámica mejora el modelo

- En la fase intrahospitalaria hemos conseguido mejorar y confirmar los modelos de predicción, que están pendientes de presentar en una tesis y de publicar.
- La fase del sistema recomendador está en funcionamiento, en fase de análisis de utilidad y satisfacción mediante una encuesta al personal de la unidad de ictus, para poder hacer mejoras y una posterior implementación a tiempo real en la estación de trabajo de la misma unidad y en dispositivos portátiles.
- De la parte prehospitalaria tenemos ya resultados del 2022 (pendientes de publicar - artículo em fase de redacción). Y vamos a analizar el 2023 (ya etiquetado), pero hay que analizar datos hemodinámicos para confirmar y mejorar modelos de predicción.

Utility of Pro-Adrenomedullin determination in stroke code: The PRESTO Study

IP: José Vivancos. Centro promotor H.U. La Princesa
Responsables: Santiago Trillo y Cristina Sanabria

ABSTRACT:

Introduction:
Proadrenomedullin (Pro-ADM) is a precursor of adrenomedullin, a peptide similar to procalcitonin. Adrenomedullin functions as a vasodilator, with additional effects on immune modulation and metabolism. The utility of pro-adrenomedullin as a biomarker in cerebrovascular diseases is unknown. The objective of PRESTO study (ProadRenomedullin valuE STroke cOde) was to analyze its potential diagnostic and prognostic utility in patients attended as stroke code (SC).

Methods:
A prospective, observational, single-center study was conducted on patients evaluated as SC (May 2023 - April 2024). Serum levels of pro-ADM were analyzed from emergency extractions prior to neuroimaging. Differences in plasma levels between patients with large vessel occlusion (LVO) defined by T-carotid, M1, M2, or basilar artery, and their association with prognosis were evaluated.

Results:
A total of 130 patients were included. The final diagnosis was ischemic stroke (70.7%), intracerebral haemorrhage (13.1%), and stroke mimic (16.2%). Mean pro-ADM levels were 0.7 pmol/L (SD: 0.29). These levels were significantly higher in older patients ($p<0.001$), those with a history of atrial fibrillation ($p=0.006$), those diagnosed with ischemic stroke due to LVO ($p=0.04$), and those with cardioembolic etiology ($p=0.007$). As a prognostic predictor, pro-ADM correlated with NIHSS at discharge ($p<0.001$), mRS at discharge ($p=0.03$), and at 3 months ($p=0.001$). Pro-ADM levels >1.2 were associated with higher rates of LVO ($p=0.048$) and intra-hospital mortality ($p=0.02$).

Conclusions:
PRESTO study suggests that pro-ADM could be an important biomarker in cerebrovascular diseases.
Pro-ADM levels were associated with LVO diagnosis and cardioembolic etiology, potentially being higher in ischemic compared to hemorrhagic stroke. It also showed prognostic potential.

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UTILIDAD DE LA DETERMINACIÓN DE PRO-ADRENOMEDULINA EN EL CÓDIGO ICTUS: ESTUDIO PRESTO (ProadRenomedulina valuE STroke cOde).

C. Sanabria Gago(1), R. Berbegal Serralta(1), J. Alonso Maroto(1), V. Escribano Hernández(2), B. Colino Galian(2), E. Salgado Barbado(2), M. Sobrado Sanz(3), C. Ramos Marín(1), Á. Ximénez- Carrillo(1), E. De La Fuente(1), A. Gonzalez-Martinez(1), C. Sánchez-Rodríguez(1), A. Somovilla(1), J.A. Vivancos Mora(1) y S. Trillo Senín(1)
(1)Neurología, (2)Análisis Clínicos, (3)Fundación de Investigación Biomédica. Hospital Universitario de la Princesa. Madrid (Madrid).

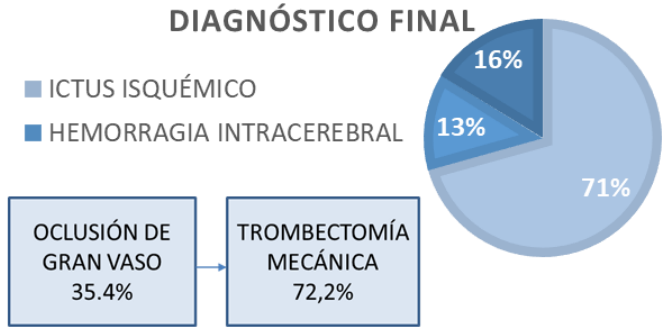
OBJETIVO: analizar su potencial utilidad diagnóstica y pronóstica en pacientes atendidos como código ictus (CI).

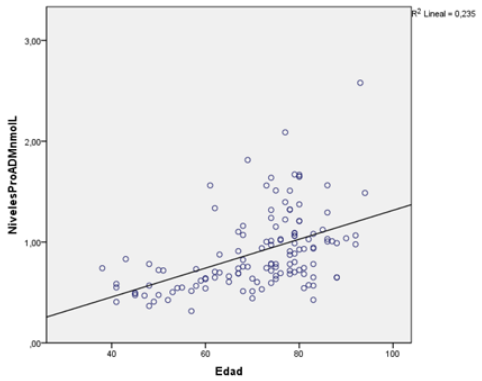
MATERIAL Y MÉTODOS

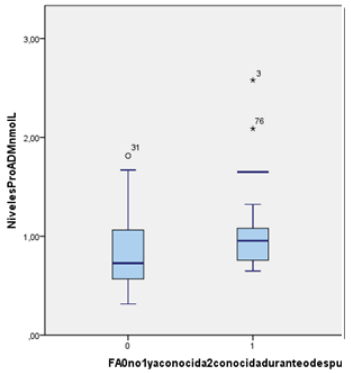
- Estudio observacional prospectivo unicéntrico de pacientes valorados como CI (mayo/23-abril/24).
- Se analizaron los niveles séricos de pro-ADM extraídos de emergencia, previo a la neuroimagen.
- Se evaluaron diferencias en los niveles plasmáticos entre pacientes con oclusión arterial de gran vaso (OGV) definida por T-carotídea, M1, M2, o arteria basilar, y su asociación con el pronóstico.

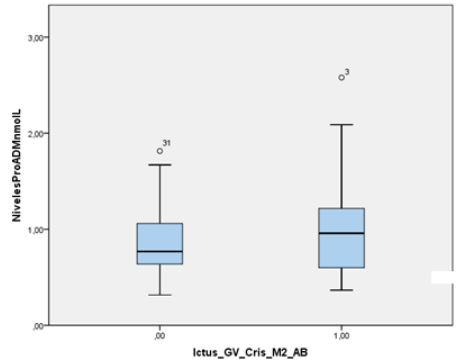
RESULTS

CARACTERÍSTICA	VALOR
Nº de pacientes	130
Sexo (%)	Hombres 60%/Mujeres 40%
Edad media (años)	72 (DE: 13)
NIHSS basal (mediana)	10 (RIC: 4-18)









Niveles de pro-adm significativamente mayores en pacientes con ictus isquemico de etiología cardioembólica: P = 0.007

PRO-ADM y NIHSS ALTA	COEFICIENTE DE CORRELACIÓN (rho): 0,3	P<0,001
PRO-ADM y mrs AL ALTA	COEFICIENTE DE CORRELACIÓN (rho): 0,7	P = 0.003
PRO-ADM y mrs A LOS 3 MESES	COEFICIENTE DE CORRELACIÓN (rho): 0.4	P < 0.001

Pro-adm > 1.2 y OGV	Chi-cuadrado de pearson: 0+04	P = 0.05
Pro-adm >1.2 y muerte intrahositalaria	Chi-cuadrado de pearson 0.01	P = 0,02

Estudio de nuevos biomarcadores en una cohorte de pacientes de vasculitis cerebral primaria:

Nos hemos reunido con 8 grupos de distintos hospitales de la red:
- Hospital de Cruces, Bilbao
- Hospital Virgen de la Arrixaca, Murcia
- Hospital de Donostia, San Sebastián
- Hospital del Mar, Barcelona
- Hospital de Navarra, Pamplona
- Hospital Virgen de la Victoria, Málaga
- Hospital Puerta de HIerro, Madrid
- Hospital Sant Pau, Barcelona

Todos los grupos han mostrado interés en recoger muestras de pacientes con vasculitis cerebral primaria.
El siguiente paso será establecer una serie de criterios de inclusión que deben de cumplir estos pacientes y determinar cuando y qué tipo de muestras se recogerán.
Una vez hayamos puesto en común todos estos criterios, se lo haremos llegar al resto de miembros de la red por si surge algún otro grupo interesado.

Determination of ischemic stroke onset and salvageable tissue by omics signature: OMIC IS BRAIN

Francisco Purroy H.U. Arnau de Vilanova-IRBLleida

Project status: Recruitment finished, omic analysis ongoing

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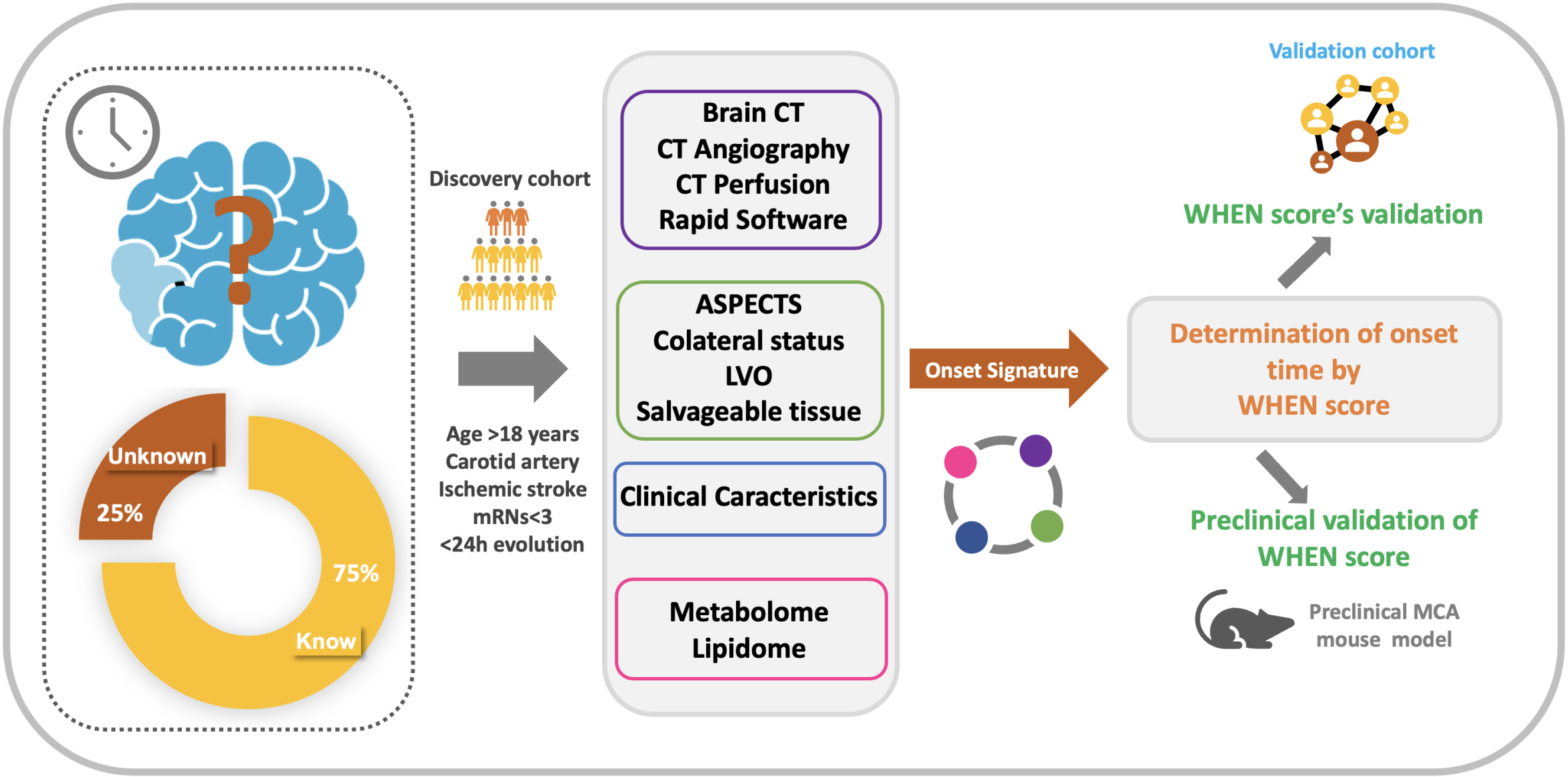
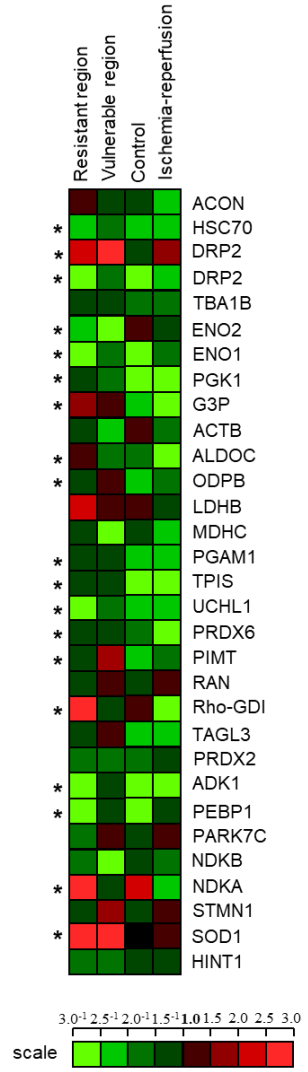
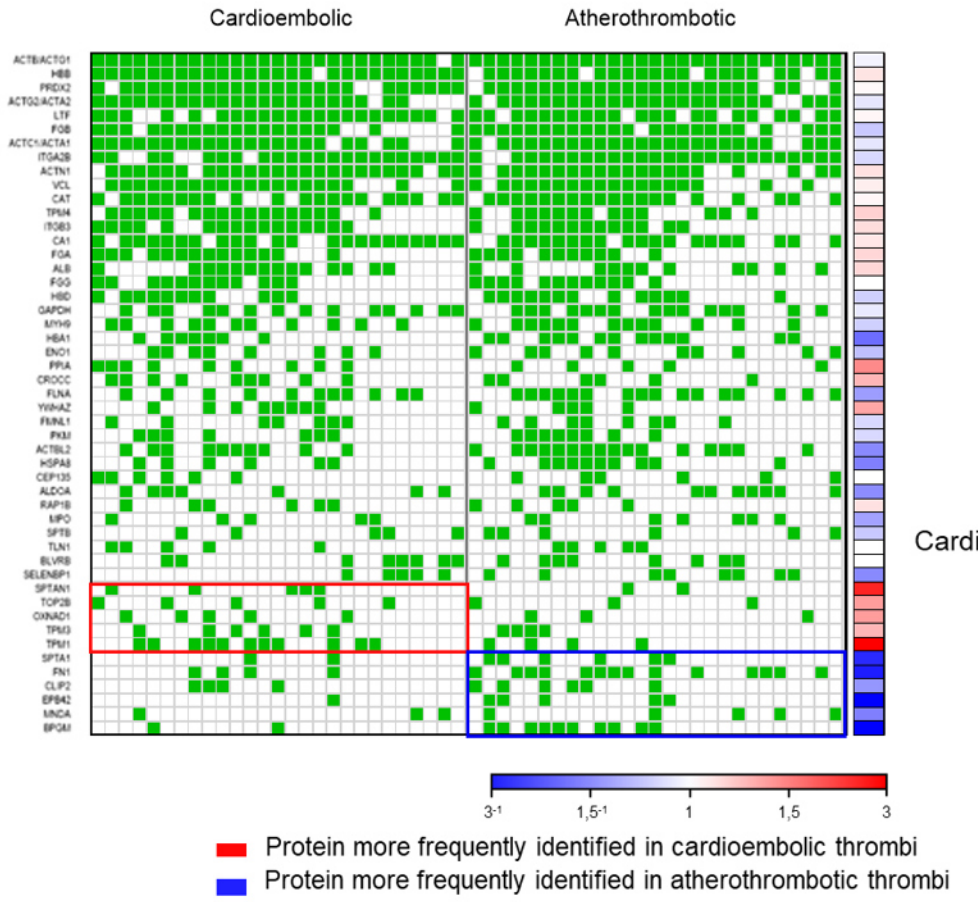
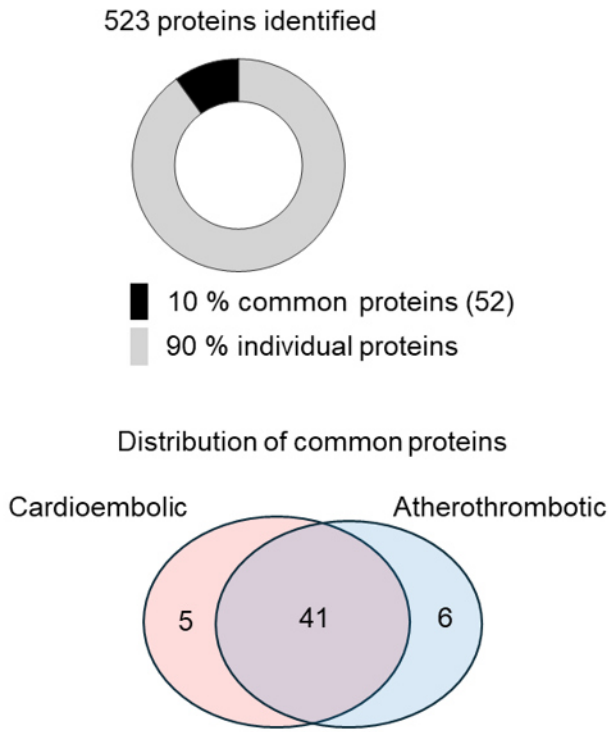

Unknown
25%
75%
Know
Discovery cohort
Age >18 years
Carotid artery
Ischemic stroke
mRNs<3
<24h evolution
Brain CT
CT Angiography
CT Perfusion
Rapid Software
ASPECTS
Colateral status
LVO
Salvageable tissue
Clinical Caracteristics
Metabolome
Lipidome
Onset Signature
Validation cohort
WHEN score's validation
Determination of onset time by WHEN score
Preclinical validation of WHEN score
Preclinical MCA mouse model







Heat map showing the levels of differentially identified proteins in resistant (cortex) and vulnerable (hippocampal CA1) regions, and in control and ischemic samples, in experimental transient global cerebral ischemia. Proteins with asterisk had significant differences compared to their respective control, and may be biomarkers of protection or vulnerability in transient cerebral ischemia.

Identification of proteins in thrombi of cardioembolic and atherothrombotic origin. Color map of the common proteins identified in thrombus samples. Color scale (red/blue) represents their frequency of appearance between cardioembolic and atherothrombotic thrombi. Five and six proteins were found with differences in appearance between both types of thrombi.