TAXINOMISIS

Multidisciplinary approach → stratification of patients with carotid artery disease

TAXINOMISIS plenary meeting October 08-09, 2021 (virtual)	Extension of the project due to the Covid 19 outbreak up to June 30, 2023

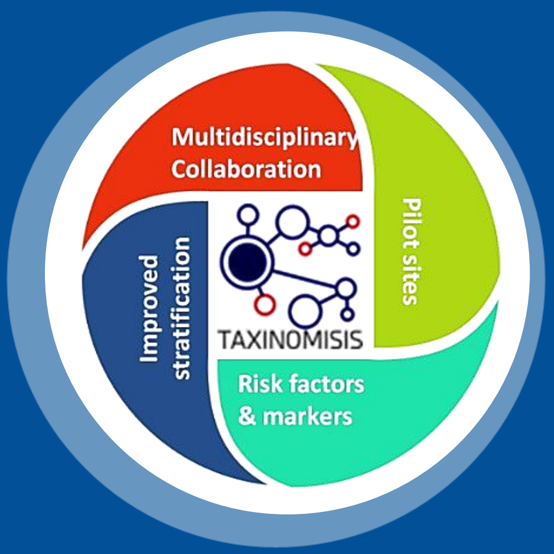
Newsletter 06 July 2021

TAXINOMISIS is a European Commission funded research project which aims to develop a new approach for the stratification of carotid artery disease patients.

TAXINOMISIS takes bold step beyond the state of the art unwinding the pathobiology underlying symptomatic plaques, discriminating distinct disease mechanism-driven states and biomarkers, and developing a multiscale risk stratification model.

TAXINOMISIS will deliver, as a main outcome, a software platform, which can perform the risk stratification.

TAXINOMISIS innovation capacity



Purpose

Provide novel disease mechanism-based stratification for carotid artery disease patients to address the need for stratified and personalised therapeutic interventions in the current era.

Objectives

→ Investigate the causal relationship of the major pathways and factors identified in symptomatic carotid artery disease

→ Study disease phenotypes and disintegrate them into endotypes according to specific pathobiological mechanisms

→ Integrate a computational model and an agent based model of plaque progression in the risk stratification tool

→ Perform a test for determining the presence of single Nucleotide Polymorphisms and predicting drug response

→ Evaluate the risk model of carotid artery disease stratification in an observational multicentre clinical study

→ Present a cost-effectiveness analysis

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 755320

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Project activities

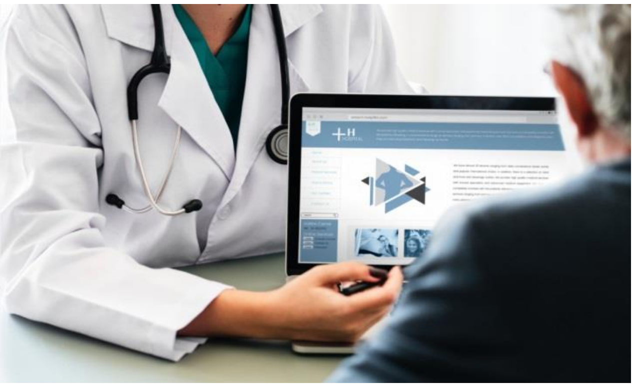
Between September 2020 and July 2021 significant project achievements have been accomplished. Specifically:

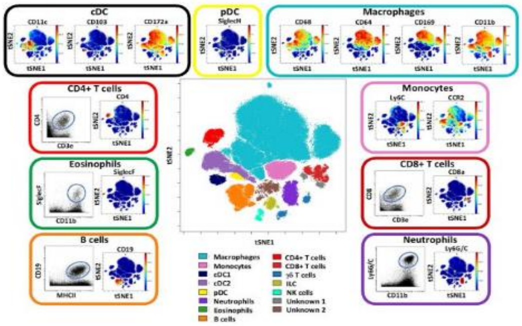
In WP1

- Bulk RNA-seq of 700 patients and plaque phenotyping. Data obtained regarding clinical presentation, risk factors and medication and other relevant patient characteristics.
- Cellular composition of fresh plaque specimens from patients undergoing CEA using CyTOF based on our panel (28 marker panel) encompassing most cell types and subtypes found in the plaque.
- Prevalence of T cells (CD4 and CD8) making up between 36 to 60% of the CD45+ population of the plaque with myeloid cells constituting the second majority with percentages ranging from 10 to 30% of all CD45+cells.
- Additional CyTOF analyses are being developed.
- Assessment of predictive ability of ceramides and phosphatidylcholines was performed, with major adverse cardiovascular events as outcome measure, showing several ceramides / phosphatidylcholines to be potential markers to identify high-risk CEA patients
- Likewise, cardiovascular disease-related proteins in plasma EV were found to associate with major adverse cardiovascular events, showing that also these proteins could therefore potentially identify high-risk patients

In WP2

- Five new Endotypes of carotid artery disease were defined by clustering atherosclerotic plaque and plasma patient samples into biologically and clinically relevant disease subtypes: Fibrous (Endotype 1), Inflammatory (Endotype 2), Lipo-necrotic (Endotype 3), Fibro-inflammatory (Endotype 4), and Fibro-productive (Endotype 5).
- Endotypes 3 and 4 are associated with higher risk states, Endotype 2 with intermediate risk states and Endotypes 5 and 1 with lower risk states.
- The five new Endotypes were clustered based on unsupervised gene expression analysis, pathway analysis and histological characterization and were further associated with the presence of symptoms, plaque instability, circulating biomarkers and clinical characteristics.





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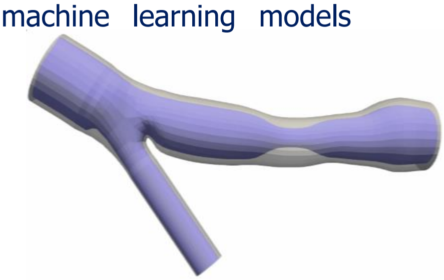
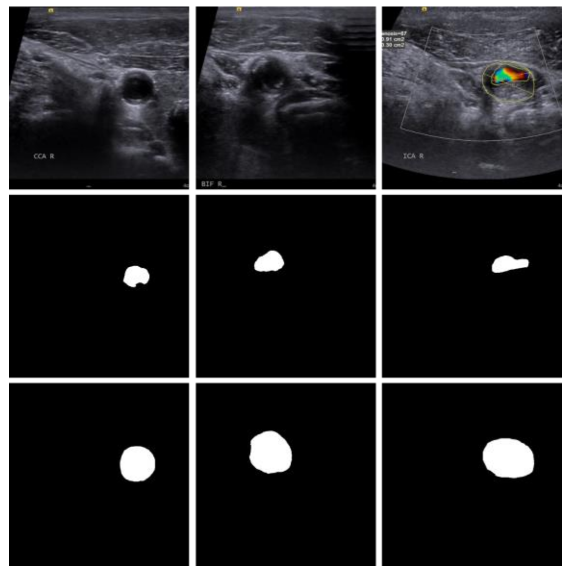
Project activities

In WP3

- The conceptual framework of the TAXINOMISIS Risk Stratification Tool has been defined.
- 3D carotid artery reconstruction and plaque characterization methodologies based on carotid MRI, CT and US imaging have been developed and implemented in patients of the TAXINOMISIS prospective clinical study.
- Non-imaging based machine learning models have been developed.

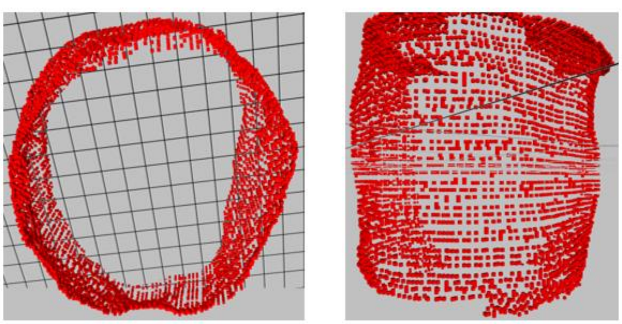


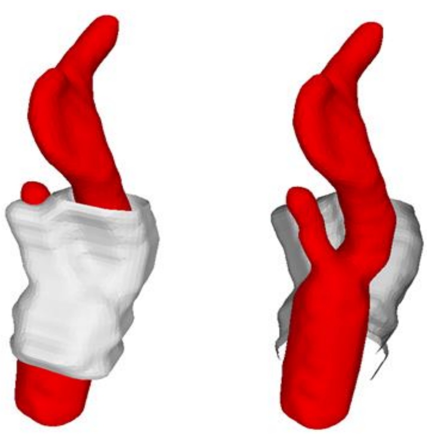
3D models based on US

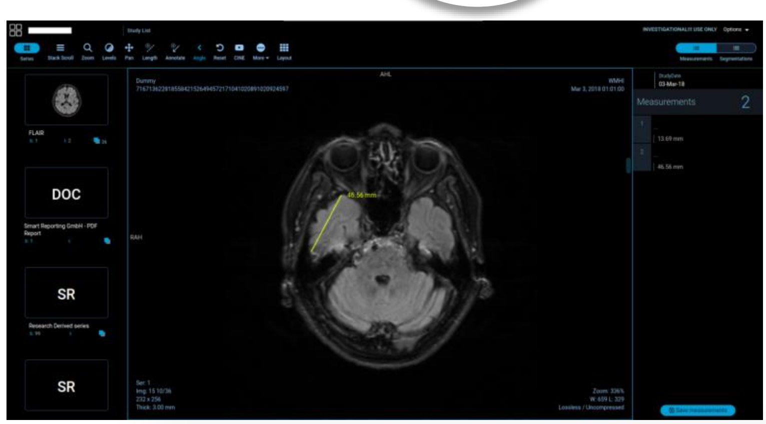


Carotid US images for one patient. The first row represents the original images, the second and the third rows show the predicted lumen and wall regions, respectively.

3D models based on MRI







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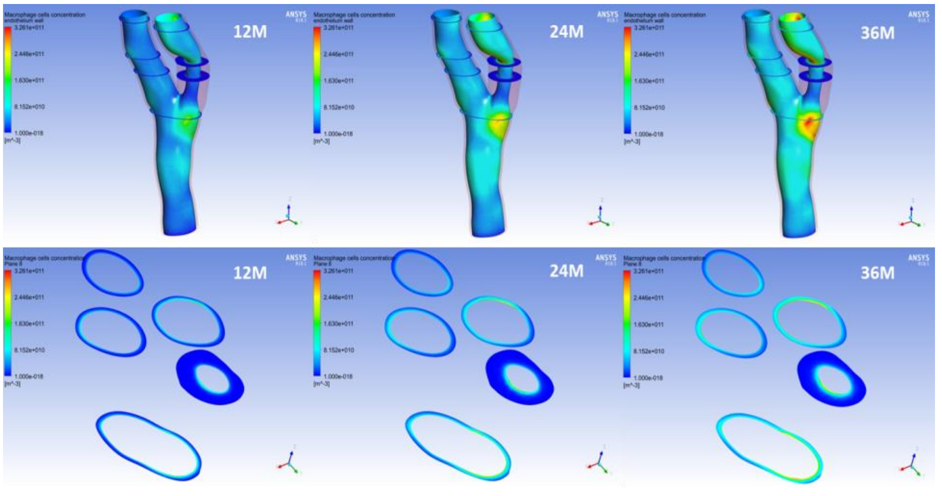
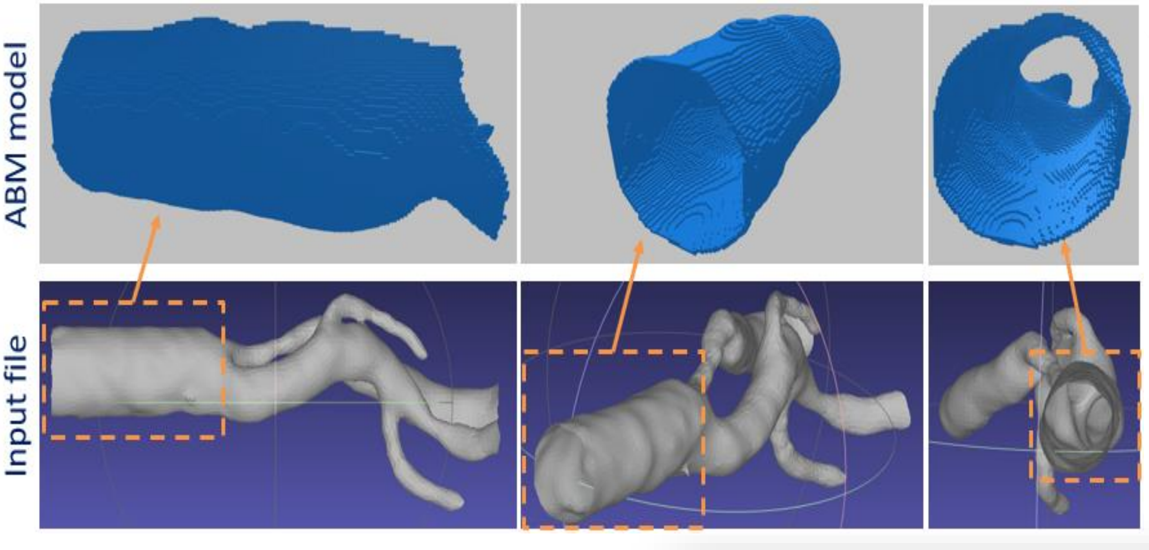
Project activities

In WP3

- Results from in-depth phenotypic analysis of carotid plaques performed during WP1 and WP2 provided important information for cell populations and biological processes involved in plaque progression which was incorporated in a new version of the computational plaque growth model.
- A first version of the agent based model of plaque progression has been developed. The cellular and molecular mechanisms adopted into the first version of the agent based model are the mass transport of LDL and leukocyte transendothelial migration, cytokine and LDL spatial diffusion and leukocyte chemotaxis, mechanisms that lead to accumulation of inflammatory cells, plaque growth and Glagov remodeling of the arterial wall.





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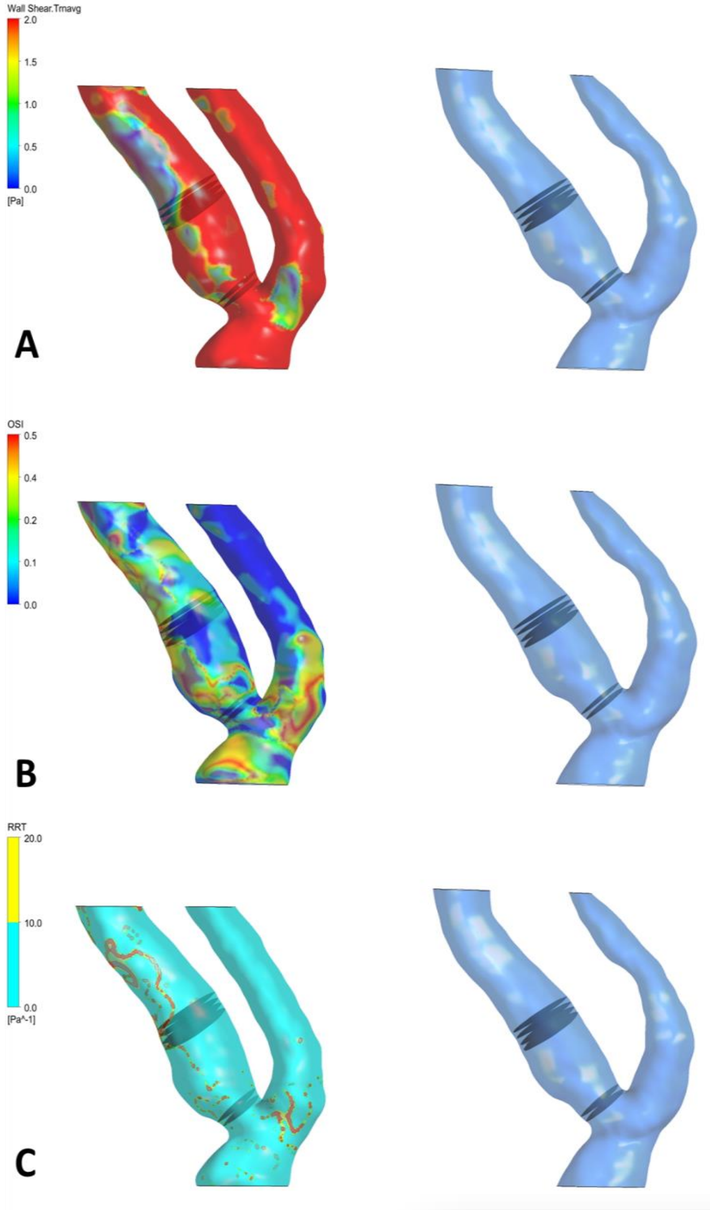
Project activities

In WP3

▪Blood flow and rupture models have been established.

▪Clinical and technical partners have worked together and four unresolved areas in the current standard of care have been selected in which TAXINOMISIS can contribute to improve risk stratification and management of carotid artery disease patients.



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Project activities

In WP4

- Informative pharmacogenetic markers for patient stratification and personalized (precision) treatment
- Single cavity pipet PCR devices and thermal controller enabling the different temperature steps (PCR cycling)
- Fluidic testing of multiple cavity lab-on-a-chip
- Optimization of the individual PCR reactions on lab-on-a-chip and work for the demonstration of the multiplex PCR using a single lab-on-a-chip

In WP5

- Clinical trial protocol.
- Protocol submission in www.clinicaltrials.gov (study ID: NCT03495830).
- Ethical Approval obtained.
- More than 300 patients recruited.
- First follow up visit performed in 80% of the patients.
- Electronic Case Report Form developed.
- The concept of the Risk stratification tool has been accepted among the clinical partners. Four unresolved areas in the current standard of care have been selected.

In WP6

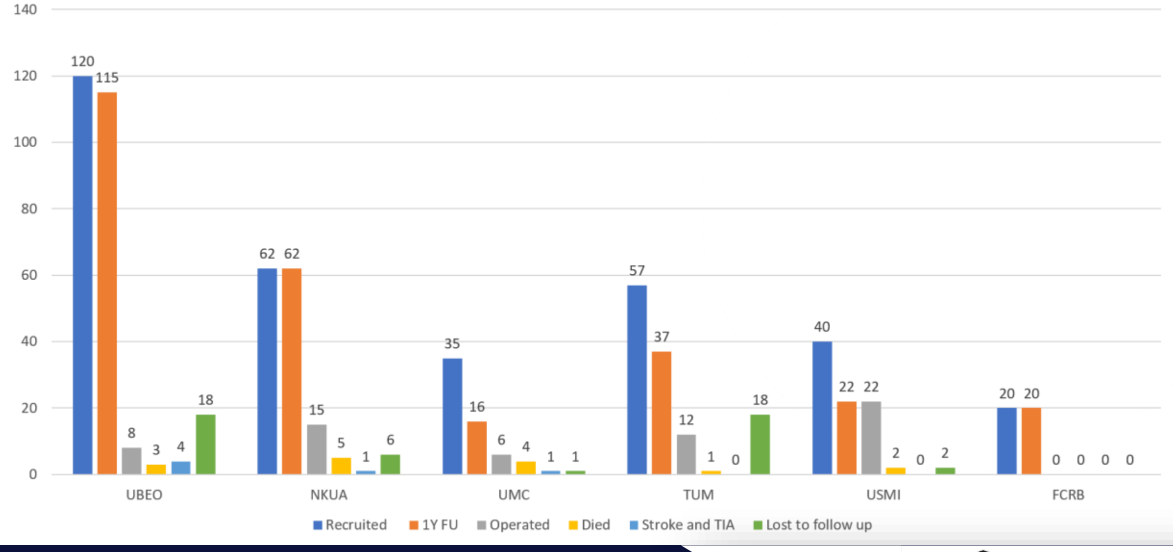
- Clinical centers monitored by ESCVS.
- Ethical and Legal issues addressed by the clinical study protocol.

In WP7

- Communication and dissemination activities (v2)
- Exploitation and innovation plan (v1)

Prospective observational clinical study in WP5

Recruitment, follow up (1Y, 2Y and lost), operated, died, stroke



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Consortium

TAXINOMISIS encompasses a highly multidisciplinary group of researchers with remarkable track record and complementarity from 12 world-leading institutions of clinical and research excellence and 3 pioneering SMEs including:

- Medical experts
- Vascular surgeons
- Cardiologists
- Neurologists
- Biologists
- Software engineers
- Biomedical engineers
- Lab-on-a-chip experts
- Health research experts

TAXINOMISIS researchers are international leaders in their respective fields and have contributed to our current understanding of:

- the **clinical medicine surrounding carotid artery disease** (UMC, TUM, UBEO, USMI, FCRB, NKUA),
- **the molecular mechanisms** driving atherosclerosis in carotid and coronary arteries (UMC, TAUH, BRFAA, ZORA, USMI, UOXF),
- the **immuno-inflammatory processes involved** (UMC, BRFAA, USMI, UOXF, UBEO),
- the identification of **diagnostic markers and treatments** for cardiovascular disorders (TAUH, ZORA, IMEC, UMC, TUM, USMI, FCRB),
- **the development of new algorithms and simulation tools for atherosclerotic plaques and CVDs** (UOI, BIOIRC, END),
- **the development of risk prediction models** (UOI, BIOIRC),
- the design and production of **lab-on-a-chip devices** based on nanoelectronics (IMEC) and
- the provision of **retrospective data and cohorts** (NIVEL, TAUH, UMC)

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