A multimodal advanced approach for the stratification of carotid artery disease

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***Abstract*—The scope of this paper is to present the novel risk stratification framework for carotid artery disease which is under development in the TAXINOMISIS study. The study is implementing a multimodal strategy, integrating big data and advanced modeling approaches, in order to improve the stratification and management of patients with carotid artery disease, who are at risk for manifesting cerebrovascular events such as stroke. Advanced image processing tools for 3D reconstruction of the carotid artery bifurcation together with hybrid computational models of plaque growth, based on fluid dynamics and agent based modeling, are under development. Model predictions on plaque growth, rupture or erosion combined with big data from unique longitudinal cohorts and biobanks, including multi-omics, will be utilized as inputs to machine learning and data mining algorithms in order to develop a new risk stratification platform able to identify patients at high risk for cerebrovascular events, in a precise and personalized manner. Successful completion of the TAXINOMISIS platform will lead to advances beyond the state of the art in risk stratification of carotid artery disease and rationally reduce unnecessary operations, refine medical treatment and open new directions for therapeutic interventions, with high socioeconomic impact.**

Keywords-carotid artery disease, risk stratification tool,3D reconstruction, plaque growth, blood flow modeling

I. INTRODUCTION

According to the World Health Organization, stroke is defined as a focal, and occasionally global, loss of neurological function persisting for over 24 hours (or causing death) and is caused by vascular origin [1]. With an annual number of approximately 1.4 million cases and with 1.1 million of them resulting to death, stroke is the second most common cause of mortality in Europe. Adding to the morbidity of the condition, more than 50 percent of the surviving patients become dependent on other people for their everyday life activities, imposing a great socioeconomic burden in family members and costing healthcare systems and providers over 38 billion Euros per year [2]. In this context, carotid artery disease is considered the primary cause of ischaemic cerebrovascular events, accounting for 150,000 deaths per year from stroke, in Europe. Vascular atherosclerotic plaques in the carotid artery bifurcations lead to progressive narrowing of the vessel lumen, which may erode or rupture, causing thromboembolism and cerebral infarction, manifested as stroke [2].

Management and treatment of carotid artery disease is currently based on the percentage of stenosis, the presence of symptoms and their recency [3]. Patients with equal to, or higher than, 70% stenosis are considered at high risk of cerebrovascular events and therefore are directed towards surgery such as carotid endarterectomy or stenting. On the

other hand, patients with carotid stenosis between 50 - 70% and without any symptoms or confounding factors are subjected to optimal medication therapy [4]. However, this type of stratification has been outdated by recent advances in the field and needs to be revisited. More specifically, vulnerable plaques exhibiting a rupture-prone phenotype, have been considered the major cause of symptomatic carotid artery disease, causing transient ischaemic attack (TIA) or stroke. However, it is now apparent that an increasing proportion of acute clinical events originates from phenotypically stable plaques that lack vulnerable plaque characteristics, including lesions that do not rupture but are likely to "erode" [5]. In addition to this, it has been indicated that vulnerable plaques can lose their vulnerable characteristics, while stable plaques can become unstable with time, depending on medication therapy and lifestyle behavior, adding to the complexity of the disease [6]. Considering the new advances, the technological and molecular evolution providing big data as well as the introduction of new medication therapies, there is an unmet need for improved risk stratification strategies and guidelines able to reduce unnecessary surgical interventions. Those must ensure proper treatment of patients with lower levels of stenosis but potentially at high risk for manifesting cerebrovascular events.

TAXINOMISIS takes a bold step towards that direction, for novel disease mechanism-based stratification of carotid artery disease patients addressing the need for stratified and personalized therapeutic interventions in the current era. The study implements a multidiscipline approach based on unique longitudinal cohorts and biobanks providing clinical, imaging, histopathological and extended multi-omics datasets of plaque tissue and plasma, including deep cell profiling and pharmacogenomics, in order to unravel the pathobiology of symptomatic and asymptomatic carotid disease and identify new distinct disease phenotypes and related biomarkers. Advanced image processing tools for 3D reconstruction of the carotid artery bifurcation together with hybrid multiscale computational modeling of plaque growth, based on fluid dynamics, and agent based modeling are under development. Model predictions on plaque growth, rupture or erosion combined with big data will be utilized as inputs to machine learning and data mining algorithms in order to develop a new risk stratification software tool able to identify patients at high risk for cerebrovascular events, in a more accurate and personalized manner. The new risk stratification solution will be validated and refined during the study's lifecycle in a prospective observational clinical study, already lunched, in six clinical centers in Europe.

Herein, we present the conceptual architecture framework of the TAXINOMISIS project, depicted in Fig.1, together with a brief description of the different types of medical data and the components of the new risk stratification tool. Finally, we provide some preliminary results of the fluid dynamics modeling of wall shear stresses (WSS) applying on the 3D-reconstructed carotid artery bifurcations from patients enrolled in the prospective clinical study.

II. MATERIALS AND METHODS

Clinical Data Management Infrastructure

TAXINOMISIS includes an observational prospective clinical study derived by six European clinical centers located in Serbia, the Netherlands, Germany, Greece, Italy and Spain. The clinical protocol has been defined providing the inclusion and exclusion criteria, the primary and secondary endpoints and the methodologies of patient examination and follow-ups. Ethical approval has been obtained in each clinical site and the study has been registered at ClinicalTrials.gov, under the reference number NCT03495830.

For the purposes of the project, an electronic Case Report Form (eCRF) has been developed as a web-based platform for data curation and management using the infrastructure services (IaaS) of a third-party cloud provider. Data Protection by design is implemented in all data processing stages ensuring compliance with the new EU's General Data Protection Regulation (GDPR).

The eCRF platform has been developed using "OpenClinica", an open-source software for clinical research (www.openclinica.com). OpenClinica has a modular design with separate modules for study setup, data submission, data monitoring and data extraction. Data can be submitted to the eCRF by manual entry or by uploading, either via the user interface or via the OpenClinica web services.

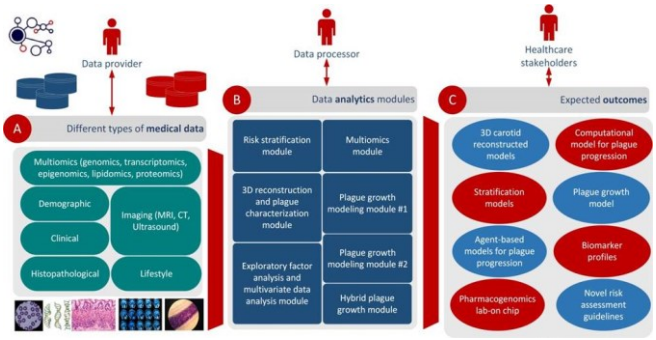

Fig. 1: The initial TAXINOMISIS project architecture.

The main features of the TAXINOMISIS eCRF include: a) management of diverse clinical sites through a unified interface, b) clinical data entry and validation, c) data extraction, and d) study oversight, auditing, and reporting. The platform works with controlled access through user accounts and authorizations while encryption is supported by password storage encryption and SSL Host Authentication. Indicative snapshots of the eCRF developed for the purposes of the prospective clinical study are illustrated in Fig. 2, showing the subject matrix and the informed consent tabs of the platform as defined by the medical doctors.

Risk Stratification Tool

TAXINOMISIS project main outcome will be the delivery of a new risk stratification platform in the form of a software tool. The main components of the platform under development are: a) a computational multiscale model of plaque progression based on fluid dynamics and finite element analysis of 3D-reconstructed carotid artery bifurcations based on different imaging modalities, b) a plaque growth agent based model, c) a hybrid model based on the integration of the two models, and d) big data analytics implementation, including machine learning and data mining approaches for the integration of model outcomes with available big data in order to stratify patients according to the risk of manifesting cerebrovascular events. The performance of the new risk stratification platform will

be validated during the lifecycle of the prospective clinical study, in three follow-ups within a period of 36 months. The risk stratification tool will be trained and validated for the prediction of plaque evolution as well as the plaque's thromboembolytic potential

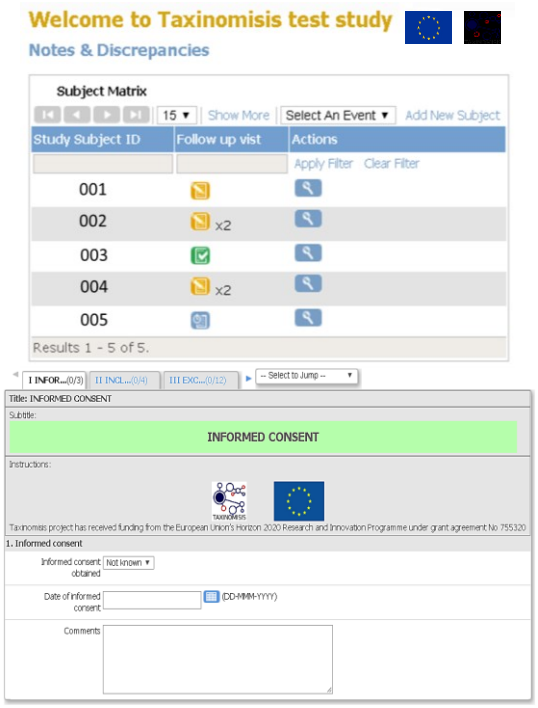

Fig. 2. TAXINOMISIS electronic case report form snapshots

B1. Computational Multiscale Model of Plaque Progression

The computational multiscale model includes three levels. The first level comprises advanced 3D-reconstruction of the carotid artery bifurcation together with plaque type identification and characterization. In this level, the imaging data from the patients are used for the reconstruction of the carotid arteries, as well as the plaque identification and characterization. MRI imaging is used to accurate identify the lumen and outer vessel wall borders and the active contours theory will be implemented for image segmentation and reconstruction of the carotid arteries. In addition to this, Computed Tomography Angiography (CTA) imaging modality is utilized to provide detailed 3D models of carotid arteries and their atherosclerotic plaques, based on a 3D level set segmentation approach. In the second level a blood flow modeling approach is implemented, together with the transport of lipoproteins into the arterial wall, based on finite element analysis. The Navier Stokes equations are solved to estimate blood velocity, pressure and wall shear stress (WSS), whereas convection-diffusion equations are used for modeling the accumulation of lipoproteins into the arterial wall. This second level aims to identify the regions of low WSS and high LDL accumulation, since these regions are highly correlated with sites of atherosclerotic plaque progression [7, 8]. The third level models the major mechanisms of atherosclerotic plaque growth including mechanisms of monocyte infiltration and differentiation into macrophages, oxidation of LDL, foam cell formation and smooth muscle cell proliferation.

Blood flow modeling involves the calculation of WSS values and the detection of areas of low WSS (0-2 Pa). In order to achieve that, blood flow simulations are carried out, initially assuming that the arterial wall is rigid. In order to model blood flow, we used the Navier-Stokes and the continuity equations:

$$-\mu\nabla^2 u + \rho(u\cdot\nabla)u + \nabla p = 0,$$

$$\nabla u = 0,$$

where u is the blood viscosity, p is the pressure, ρ is the blood viscosity and μ is the blood viscosity. Appropriate boundary conditions are applied to perform the necessary blood flow simulations. At the inlet, a patient-specific velocity deriving from the respective ultrasound test is applied as a boundary condition, whereas, for the two outlets, zero pressure is applied as a boundary condition. Regarding the arterial wall, a no-slip and no-penetration boundary condition is applied for the WSS calculation. The properties of a Newtonian fluid were applied regarding blood, with density 1050 kg/m3 and dynamic viscosity 0.0035 Pa·s. The blood flow was considered laminar and incompressible. Following the initial blood flow simulation, a LDL transport model is applied [8]. A solute flux from the lumen to the arterial wall is prescribed and the following Kedem-Kattchalsky equations are used to describe the boundary conditions that are applied at the wall and the luminal side of the endothelium, respectively:

$$J_v = L_p(\Delta p - \sigma_d \Delta\pi)$$

$$J_s = P\Delta c + (1-\sigma_f)J_u\bar{c}$$

where J_v is the transmural velocity, J_s is the solute flux through the endothelium, L_p is the hydraulic conductivity, Δp and $\Delta\pi$ are the pressure difference and the oncotic pressure diference across the endothelial membranes, c is the solute concentration and σ_d and σ_f are the reflection coefficients. The LDL results are presented unitless because they have been normalized to the blood LDL concentration (i.e. the patient-specific LDL concentration value) that is used in the respective boundary condition.

III. Results

In Fig. 3, WSS distribution is depicted in the examined case of a patient enrolled to the prospective clinical study. In Fig.4, the normalized LDL concentration is presented.

IV. Discussion

This paper presented the conceptual framework of the TAXINOMISIS project. The data management infrastructure established for the needs of the observational clinical study was described, together with the components of the new risk stratification tool. Finally, preliminary results were provided concerning the fluid dynamics modeling of WSS applying on the 3D-reconstructed carotid artery bifurcations from two patients enrolled to the prospective clinical study.

From our preliminary results, it can be observed that the inner bifurcation area presents higher WSS values, whereas at the outer areas of the two side branches, lower values of WSS are identified, constituting them prone to develop atherosclerosis. This is in agreement with the current literature proposing that increased atherosclerosis is prone on developing at the outer side of the bifurcation site [9, 10].

Although several efforts have been undertaken to improve risk stratification of symptomatic and asymptomatic carotid artery disease, most researchers have followed single discipline approaches, focused mainly on imaging

modalities such as ultrasound, MRI and CTA [11-13]. However, in the field of big data, multidisciplinary strategies exploiting the wealth of information produced from different sources might offer new valuable information and insights for better stratifying carotid artery disease, providing increased statistical and clinical significance, but also requiring advanced analytical approaches.

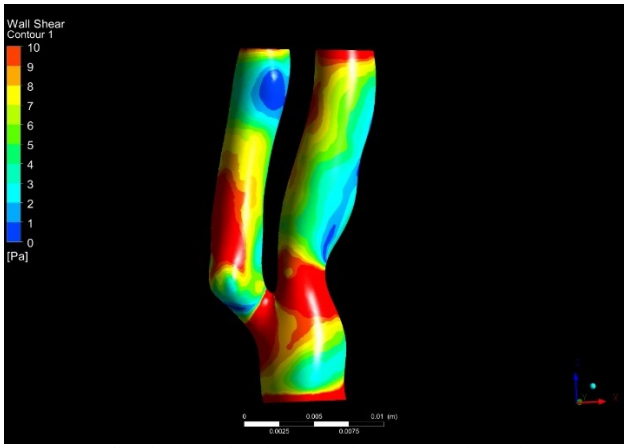

Fig.3. WSS distribution. The blue areas depict areas of very low WSS (0-0.5 Pa). The orange circles indicate the areas of low WSS.

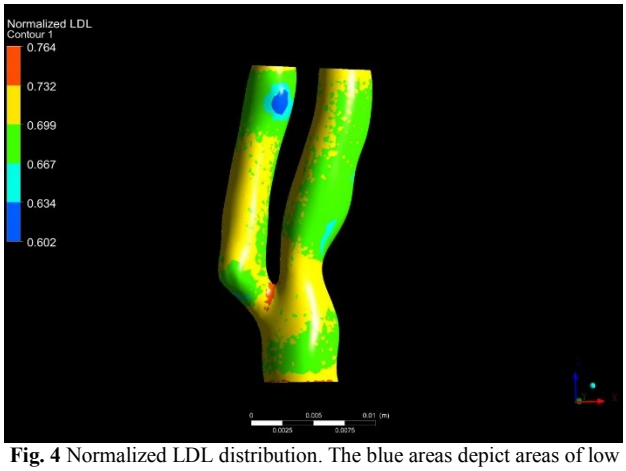

Fig. 4 Normalized LDL distribution. The blue areas depict areas of low LDL concentration.

TAXINOMISIS takes advantage of the technological and molecular evolution in the current era and exploits the power of big data, aiming to provide a novel mechanism-based stratification of carotid artery disease and identify high risk patients targeted to endarterectomy or stenting, and potentially low risk patients, targeted to optimal medication therapy and monitoring.

V. CONCLUSIONS

TAXINOMISIS has been successfully launched as a first of its kind international collaboration implementing a multidisciplinary approach for the stratification of carotid artery disease. Based on a highly multidisciplinary group of researchers, the access to big data and the advanced modeling and analytical tools under development, the study has strong foundations and the potential to change the state-of-the-art in carotid artery disease improving medical treatment and opening new avenues for therapeutic interventions, with great socioeconomic impact.

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