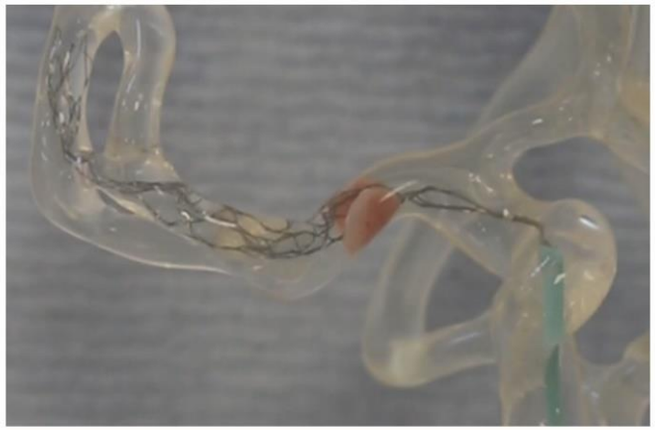
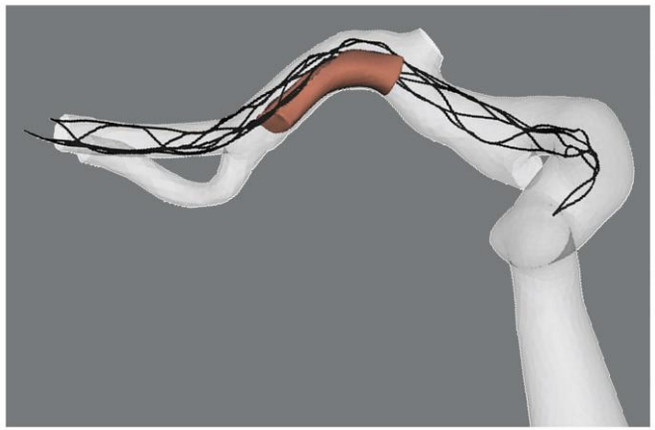
In Silico Clinical Trials for the Treatment of Acute Ischemic stroke





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Background

- Stroke is the number one cause of disability in the Western world and the 3rd most common cause of death.
- An estimated 1.3 million Europeans have a first stroke each year (on average every 25 seconds).
- This number is projected to rise to 1.5 million by 2025, largely due to the ageing population. One third of the patients with stroke will die and one third is left permanently disabled.
- 1 in 5 stroke survivors require long term institutional care.
- High societal costs: ~ €27 billion per year in Europe and another €11 billion per year for informal care provided by the patient's families.

Time is crucial in stroke.

Each hour without successful treatment, the brain loses as many neurons as it does in 3-4 years of aging. Therefore, the effectiveness of stroke treatment is strongly dependent on time to treatment.

Choice of treatment is limited:

Until recently, thrombolysis with intravenous administration of alteplase was the only available treatment. Alteplase is a recombinant tissue plasminogen activator, which helps breaking down unwanted blood clots.

Now also intra-arterial thrombectomy, a minimally invasive procedure in which the obstructing thrombus is removed, is effective in patients with intracranial large artery occlusion.

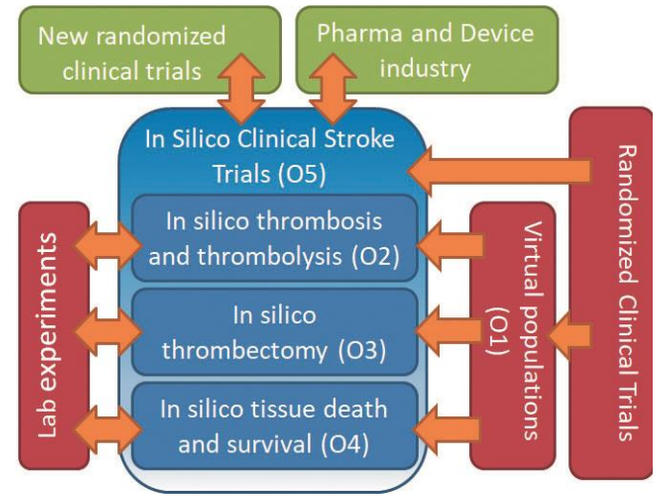
However, despite the beneficial effect of thrombectomy, almost 2 out of 3 patients with an acute ischemic stroke have an unfavourable outcome and become functionally dependent.

Further improvement of medical devices and drugs for treatment is still urgently needed.

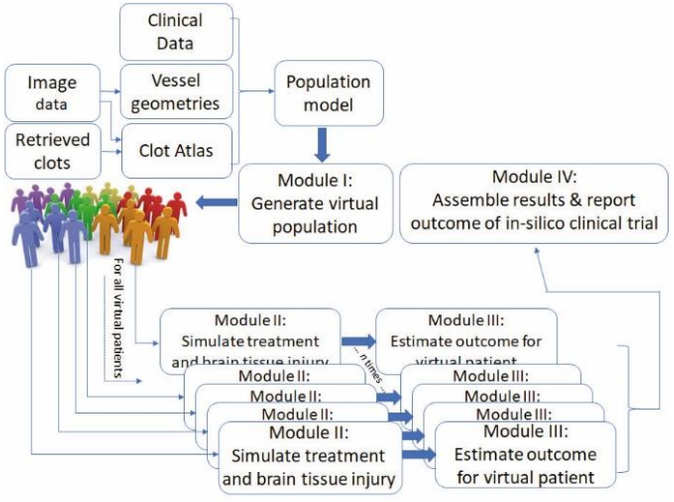
Present

INSIST objectives

- Generate virtual populations of stroke patients based on clinical, imaging, and histopathological data collected in large trials and registries (O1)
- Generate *in silico* models for the simulation of thrombosis and thrombolysis (O2), of intra-arterial thrombectomy (O3) and of microvascular perfusion and the death and healing of brain tissue (O4)
- Apply *in silico* stroke models to virtual populations of stroke patients with the goal to generate a full *in silico* stroke trial platform (O5).



Our planned *in silico* clinical trials for acute ischemic stroke will thus consist of four main software Modules: one module containing the population model to generate virtual populations of stroke patients, one to simulate treatment and brain tissue injury, a third where the outcome for each individual



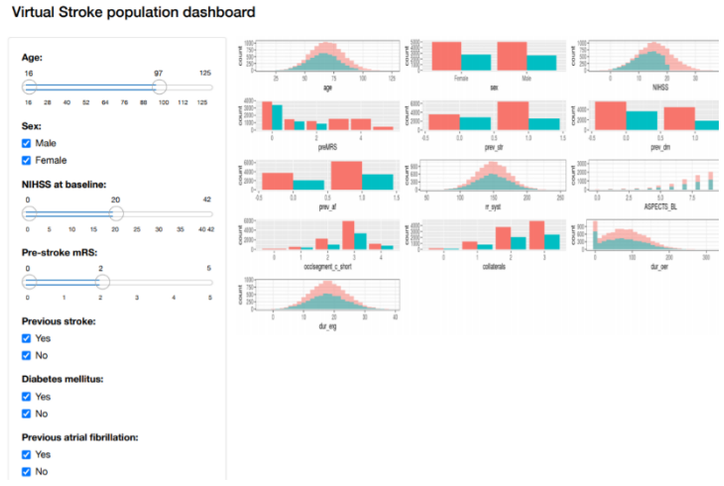
virtual stroke patient is estimated, and the final module where all results will be assembled and the outcome reported.

INSIST first results

Objective 1: virtual populations

Here we develop and validate a virtual population model from which virtual stroke patients can be sampled and selected to undergo virtual stroke treatments followed by outcome assessment. These patients represent real stroke patients incorporating important prognostic clinical and imaging characteristics such as age, sex, cardiovascular comorbidities, collateral status and location of the occlusion. We now include distributions and covariations of 15 prognostic clinical and imaging characteristics.

We also provide an online tool for sampling of virtual stroke patients, based on in-and exclusion criteria of interest. This tool will be integrated within the *in silico* stroke trial platform.

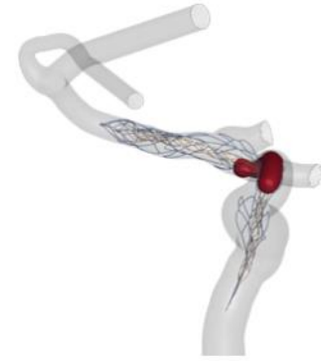


Additionally, we are developing statistical models to estimate clinical outcome for cohorts of virtual stroke patients after virtual stroke treatment.

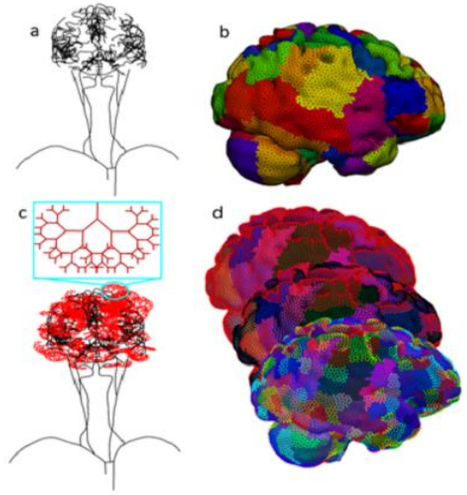
Objective 2-4*: in silico* models

Our thrombus, thrombolysis and thrombectomy models are based on patient-specific details of thrombus characteristics and intra-arterial thrombectomy procedures. Geometry of the stent-retriever models faithfully replicates the actual devices. This provides realistic simulations, rather than animations, of thrombus lysis and thrombus extraction.

This workflow can be used to predict intervention outcomes and will allow optimizing the procedures itself or the stent-retriever design, with further possibilities for supporting thrombolysis strategy.



Our new models of blood flow and oxygen transport cover the full range of inflow vessels, from the main arteries supplying the brain to the capillaries. This allows modelling of local blood flow and oxygen delivery in unprecedented detail. These models are used for simulating the effect of thrombus formation and thrombectomy on the fate of brain tissue. We include the release and downstream lodging of micro-thrombi in our models, using parameter estimations that are based on experimental data generated within our consortium.



Future

Computer modelling plays an increasingly important role in research and development of new treatments. *In silico* models hold the promise that, in combination with patient models that accurately represent important patient characteristics, they can be used to set up *in silico* clinical trials in which "virtual" patients are treated with "virtual" treatments.

***In silico* clinical trials** can potentially reduce, refine, and partially replace human clinical trials. Because *in silico* modelling allows early and fast hypothesis testing and supports trial design, the next generation clinical stroke trials can greatly benefit from *in silico* clinical stroke trials. This holds the promise that *in silico* models enable enhanced efficacy, cost reduction, and speed up the introduction of new therapies, devices, and medication for acute ischemic stroke.

The public-private INSIST collaboration started in 2017. While our goals are ambitious, the work so far has demonstrated feasibility, providing the promise of a major contribution of in silico methods as part of future clinical studies.

More information:

INSIST; www.insist-h2020.eu

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