

## Global Spotlights

# REACT initiative: early cure of atherosclerosis through precision prevention

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Globally, almost one-third of all deaths are caused by cardiovascular diseases (CVD), mainly related to atherosclerosis.<sup>1</sup> At present, atherosclerotic CVD (ASCVD) is by far first treated once symptoms arise (infarction, stroke, etc.) or when the risk factors reach dangerously high levels. However, this late-stage treatment is unsustainable. Novel preventive approaches against ASCVD are urgently needed.

Atherosclerosis often develops from early in life and progresses silently for decades before manifesting clinically.<sup>2</sup> This silent phase represents a grossly underused window of opportunity. Cumulative lifetime exposure to even moderate or 'high-normal' levels of risk factors like LDL-C or blood pressure significantly increases ASCVD risk.<sup>3,4</sup> Thus, early control of LDL-C has a greater impact on reducing future ASCVD events compared to interventions initiated later in life.<sup>5</sup> This urges a redefinition of 'normal' risk factor levels in primary prevention,<sup>6</sup> particularly for young people.

Silent atherosclerosis burden (detected by imaging) has been shown to be independently associated with ischaemic events<sup>7</sup> and with all-cause mortality.<sup>8</sup> In the early stages, the progression of atherosclerosis can be halted or even regress or disappear if risk factors are controlled.<sup>4</sup> This forms the basis for the concept of early detection—visualization—of atherosclerosis allowing early interventions as a novel means to reduce ASCVD.

At present, primary prevention of ASCVD is based on the calculation of the mid-term (10 years) risk of suffering a major CVD event. However, risk scores, e.g. SCORE-2,<sup>9</sup> do not consider individuals below 40 years of age, and below the age of 50 years, almost only smoking men reach the recommended threshold for interventions,<sup>9</sup> leaving the young population unprotected. This is relevant since young individuals are more vulnerable to risk factors in terms of silent atherosclerosis progression.<sup>4</sup>

The broad individual variability in the susceptibility to risk factors explains that risk calculators, such as SCORE-2, work better at the population than at individual level. Overall, there seems to be a strong rationale for directing

ASCVD prophylactics against identified—visualized—atherosclerosis rather than against a sum of risk factors with variable impact between individuals for developing atherosclerosis.

Coronary calcium scoring is a well-validated surrogate of future CVD events, but calcification occurs in mid- or late stages of atherosclerosis making it less ideal for early detection. Vascular ultrasound (VUS) of peripheral arteries accurately detects early stages (i.e. small plaques) of atherosclerosis.<sup>10</sup> Detection and quantification of atherosclerotic plaques, and not intima-media thickness (IMT) determination, in carotid and femoral arteries, is a very good surrogate marker for global plaque burden.<sup>10</sup>

### Background summary for the REACT initiative

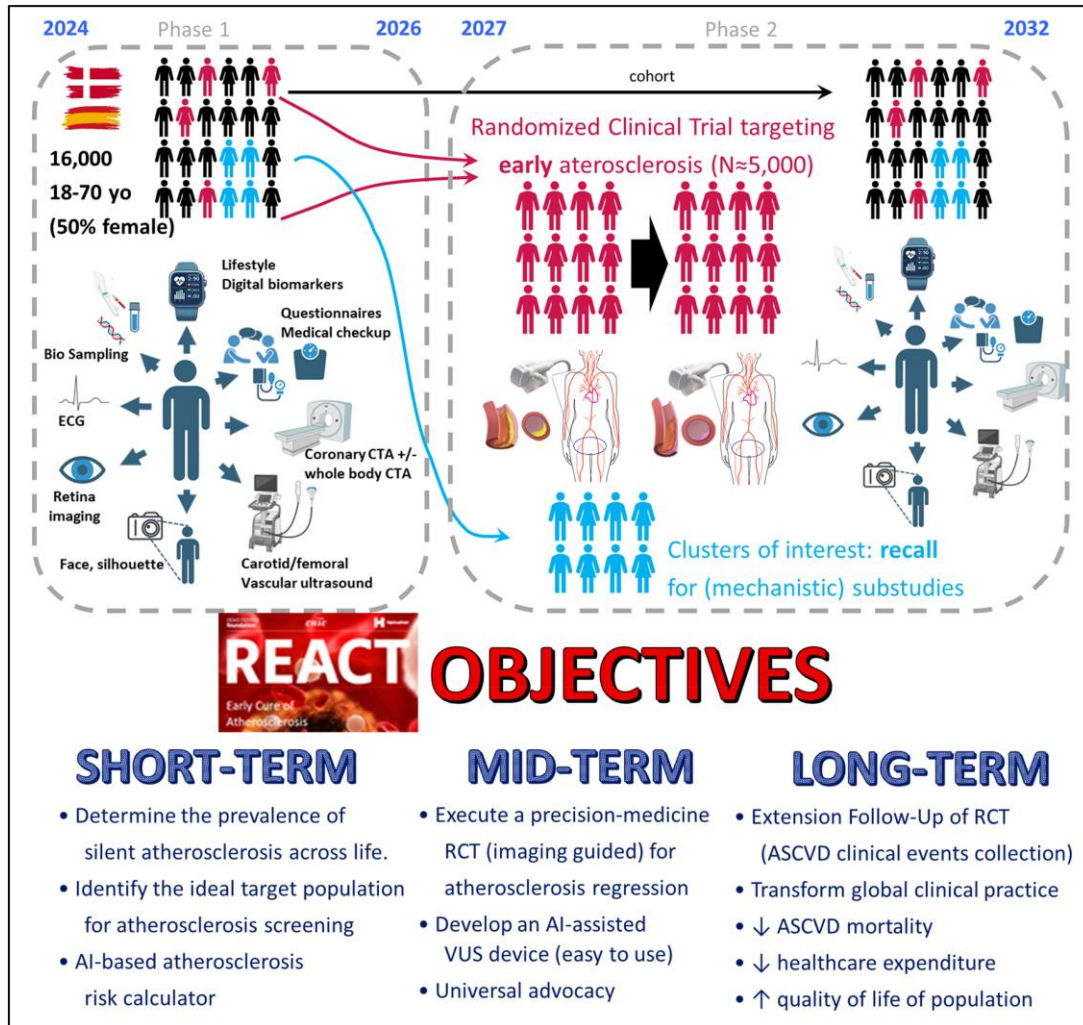
- *Window of opportunity:* Atherosclerosis, which underpins most CVD presentations, progresses silently in most arterial beds over decades.
- *Anticipation:* Exposure to risk factors at an early age is associated with future ASCVD events; however, current guidelines pay little attention to individuals under 50 years of age.
- *Tool for Precision:* The burden of silent atherosclerosis, as detected by noninvasive imaging of peripheral arteries, and its progression, is independently associated with long-term mortality.

## REACT initiative

REACT (early cure of atherosclerosis) is an international initiative executed through a collaboration between Rigshospitalet in Copenhagen, Denmark and Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Madrid, Spain. REACT has been designed to investigate a ground-breaking precision medicine approach to prevent ASCVD. The summary of objectives, timeline, and test performed is presented in [Figure 1](#).

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**Figure 1** Scheme of REACT project activities and objectives. Screening for the presence of silent atherosclerosis will be performed at the beginning and end of the project by means of carotid and femoral vascular ultrasound, coronary calcification determination, coronary computed tomography angiography (CCTA), and whole-body CTA in a subpopulation. Simultaneous blood sampling for labs, Genome-Wide Association Study, and biobanking for future multi-omics evaluations, scanning of the retina to obtain a noninvasive map of its vascular pattern, body silhouette, and face imaging will be performed. Lifestyle patterns (exercise, sleep, diet, psychological aspects, and other metrics) will be obtained through questionnaires and by the use of smartwatches in a subpopulation. The serial longitudinal atherosclerosis screening will allow us to determine trajectories of silent disease in different age and sex groups and its association with other data obtained

### Scope of the project

REACT’s overarching goal is to set a renewed paradigm of precision ASCVD prevention: Screening for silent atherosclerosis from early adulthood to initiate strict risk factors control by pharmacological and/or non-pharmacological interventions upon visualization of the disease. This personalized early preventive intervention should have higher odds of abrogating atherosclerosis progression and even its regression (cure).

The development of a new risk score (using clinically available data) determining the odds of having atherosclerosis at a given age/sex (silent atherosclerosis calculator) should serve as a gatekeeper for undergoing screening by imaging. Imaging should be universally available and, technically, VUS seems to be the obvious choice but needs to be refined to be portable, applied by non-experts, and to have fully automated readings.

Artificial intelligence (AI) plays a critical role in several aspects of REACT such as VUS equipment refinement to allow an AI-assisted acquisition by non-experts and to refine AI-based fully automatic analysis of images obtained. An atherosclerosis calculator will be developed by using AI with data sets obtained from REACT and similar previous projects.<sup>11</sup> AI will be applied to study retina, body silhouettes, and face images, as well as for processing data from digital biomarkers collected in real-time from wearables.

Implementation of such a revolutionary approach for population screening needs intense advocacy directed toward the population, healthcare providers, and policymakers. It is reassuring that interventions in the early stages of other conditions like diabetes [intervention upon the presence of a biomarker (i.e. high glucose)] are well accepted also in asymptomatic subjects.

## Phases of the project

In phase 1 (July 2024–December 2026), 16 000 individuals (half in each country) without clinical ASCVD will be enrolled and undergo screening to determine the age- and sex-specific prevalence of silent atherosclerosis by a complete set of tests (Figure 1), including different imaging modalities, combined with examinations for the broad range of risk factors known or suspected to be associated with ASCVD. Dominant drivers of atherosclerosis in different vascular territories at different age and sex groups will be determined by advanced AI risk models.

In phase 2 (January 2027–June 2032), a randomized clinical trial will test an imaging-guided approach (intervening on risk factors) upon the presence of VUS-detected atherosclerosis as compared to standard of care. The primary outcome of the trial will be atherosclerosis progression, a surrogate for all-cause mortality.<sup>8</sup> The target age for inclusion will depend on age- and sex-associated findings in phase 1. A second examination of the entire population at the end of the 8-year project will allow us to determine trajectories of silent atherosclerosis progression.

## Project logistics

Data will be stored in a single database located in Computerome II in Copenhagen. A total of 16 000 subjects will be enrolled, distributed as follows: 2000 aged 18–29 years, 4000 in each of the following age groups (30–39, 40–49, and 50–59 years), and 2000 aged 60–69 years. Each age group will have an equal gender distribution (50% female). Central readings for VUS and computed tomography angiography (CTA) are located in CNIC and Rigshospitalet, respectively. Samples are stored in duplicated biobanks in Copenhagen and Madrid.

REACT has a scientific committee that will organize scientific dissemination with fair access to scientists from any part of the world making sound proposals in any field. REACT counted with an expert group that provided feedback during the preparation<sup>12</sup> and that will be engaged during the entire 8-year span of the project.

## REACT consortium

REACT consortium is composed of ample teams in Denmark and Spain. The scientific and operational leaders are the authors of this article. Enrolling centres in Denmark are Rigshospitalet (Professor Klaus Kofoed, cardiologist and expert in CTA, local Principal Investigator (PI) and head of CTA corelab for both countries; Professor Ruth Frikke-Schmidt, specialist in clinical biochemistry, head of biochemistry), Glostrup Hospital (Chief Physician in Radiology Martin Lundsgaard, local PI and head of corelab for incidental findings on CT in Denmark), Herlev Hospital (Professor Kasper Iversen, cardiologist, local PI) and Gødstrup Hospital (Professor Morten Bøtcher, cardiologist, local PI). Enrolment in Spain will take place in Madrid at CNIC (headed by Professor Valentín Fuster) and at the Bank of Santander headquarters in Boadilla, Madrid. Other Spanish key members are Jose J. Fuster (professor and head of mechanistic studies using biobank samples), Inés García-Lunar (assistant health scientist, cardiologist, and head of the VUS corelab for both countries), Javier Sánchez-González (scientist from Philips) leads the new VUS portable and AI-assisted solution hardware and software developments, and Alfredo Castillo (professor, responsible for the ophthalmic protocols and evaluation). Fátima Sánchez-Cabo (assistant professor, head of the Computational Systems Biomedicine lab) will lead the AI-based risk calculator development.

## Impact of REACT on future CV risk

Upon meeting its goals, REACT will demonstrate that primary prevention of ASCVD should be initiated much earlier in life by universal imaging-guided screening for silent atherosclerosis and treatment of risk factors. Early precision prevention directed at individual risk factors for those with early atherosclerosis will have a drastic long-term impact in ASCVD consequences and will be cost-effective.

## Declarations

### Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

### Funding

REACT is funded by the Novo Nordisk Foundation and counts with the collaboration of companies providing in-kind contribution (Philips Healthcare, Zeiss, Bank of Santander). Other companies will be incorporated into the initiative through an in-kind contribution scheme. AI developments are funded through competitive grants from the Spanish Ministry of Digital Transformation and Public Function (NEXTGENERATION EU 'AI-POCVUS-REACT' and 'ENPESA'). The initiative is designed, directed, and managed solely by the research team. Researchers have no conflicts of interest to declare related to the initiative.

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