trials should move beyond assessing CT coronary angiography as compared with no CT coronary angiography and beyond stenosis detection alone. Contemporary CT coronary angiography assessments can quantify total plaque volume, determine plaque composition, identify high-risk plaque features, and analyze epicardial fat with measures that include the perivascular fat attenuation index, a measure of coronary inflammation. Artificial intelligence may allow these features to be quantified rapidly with high precision and to be combined into disease phenotypes. Whether assessment of such features on CT coronary angiography might have a role in guiding the selection of treatment or in monitoring response to established preventive medication or new antiinflammatory therapy warrants study.[8] Newer photon-counting CT technology, which is already in clinical use, offers a higher spatial resolution than previous generations of CT technology and most probably allows more accurate grading of coronary stenosis and assessment of coronary stents.[9,10] This technology was not used in the TARGET-CTCA trial; whether it would have altered clinical decision making or outcomes remains unclear.

The TARGET-CTCA trial provides important evidence against routinely performing CT coronary angiography solely on the basis of high-sensitivity cardiac troponin concentrations indicating an intermediate risk in patients with acute chest pain after myocardial infarction has been ruled out. These findings should not be generalized to the use of CT coronary angiography to stratify risk and guide care in other clinical settings. Whether new CT technology and more comprehensive CT coronary angiography strategies can identify actionable biologic features and thereby improve outcomes in patients with acute disease remains to be tested prospectively.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Atherosclerosis across the Adult Lifespan — A Call to Act from REACT

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In 1953, autopsy studies of soldiers killed in the Korean War (mean age, 22 years) revealed that 77% had "some gross evidence" of coronary atherosclerosis.[1] Nearly 75 years later, we are at the precipice of a paradigm shift with regard to the prevention of cardiovascular diseases, from treating advanced cardiovascular disease toward recognizing and modifying cardiovascular risk earlier across the life course.[2] The PREVENT (Predicting the Risk of Cardiovascular Disease Events) equations include 30-year risk prediction rather than only short-term 10-year risk, and the 2026 American College of Cardiology–American Heart Association multisociety dyslipidemia guidelines pro-

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mote the concept of earlier treatment to prevent future atherosclerotic cardiovascular disease.[3]

In this issue of the *Journal*, Bundgaard and colleagues describe the results of the REACT study, an observational study that included 16,808 adults from 18 to 70 years of age (88% White) in Denmark and Spain with no history of known clinical atherosclerotic cardiovascular disease.[4] Multimodal imaging for subclinical atherosclerosis was performed with three-dimensional vascular ultrasonography of the femoral and carotid arteries, noncontrast computed tomography (CT) measurement of coronary-artery calcium, and coronary CT angiography to measure noncalcified and calcified plaque volumes and stenosis; complete imaging data were available for 13,186 participants.

In a surprising finding, subclinical atherosclerosis was present in 6.7% of women and 8.7% of men 18 to 29 years of age and in 21.3% of women and 34.6% of men 30 to 39 years of age. There was an exponential increase in atherosclerosis plaque volume with age so that virtually all (>90%) participants from 60 to 70 years of age had some degree of subclinical atherosclerosis. The increase was particularly marked during the menopausal period for women. Men had more subclinical atherosclerosis than women, but women came close to catching up at older ages. The REACT study informs the yield of multiple imaging methods across age groups, which will lead to future precision prevention approaches for atherosclerosis.

The presence of subclinical atherosclerosis indicates established arterial disease, often decades before clinical events. Detection of atherosclerosis in asymptomatic persons signals future risk of atherosclerotic cardiovascular disease, including myocardial infarction. The presence of coronary-artery calcium can refine primary prevention decisions in cases in which treatment might be modified by adding prognostic information beyond traditional risk factors.[5] Whether routine coronary CT angiography adds meaningful prognostic information beyond coronary-artery calcium levels in asymptomatic patients for primary prevention remains unclear.[6] Carotid ultrasound also identifies early atherosclerotic risk,[7] whereas the prognostic significance of femoral plaque requires further study.[8] In MESA (Multi-Ethnic Study of Atherosclerosis), coronary-artery calcium levels far exceeded focal carotid-plaque levels with regard to predicting future risk,[7] and carotid intima-media thickness was not associated with risk.

Ultrasonography is portable, less costly than CT, and avoids radiation and the iodinated contrast needed for coronary CT angiography. In the REACT study, 87 participants who underwent CT angiography had mild to moderate allergic reactions, and 8 had severe allergic reactions. Although some participants had noncalcified plaque and no coronary-artery calcium, this finding was numerically very uncommon.

The REACT study shows that carotid and femoral plaque can be detected at younger ages, often before noncalcified and calcified coronary-artery plaque. This finding will have implications for screening strategies to identify younger people who are at risk for adverse cardiovascular events. We look forward to continued follow-up of the REACT study participants, with repeat imaging and ascertainment of clinical atherosclerotic disease–related events, and to a randomized clinical trial to assess an image-guided approach for risk-factor management as compared with usual care with regard to atherosclerosis progression.

The REACT study reinforces the observation that atherosclerosis begins early and becomes widespread across adulthood. The early appearance of atherosclerosis reflects the substantial burden of cardiovascular risk factors among young adults. Among ostensibly healthy men from 18 to 29 years of age in the REACT study, hypertension and dyslipidemia were each present in approximately 22%, including 5% with low-density lipoprotein cholesterol levels of 160 mg per deciliter or higher. Similarly, according to the National Health and Nutrition Examination Survey, approximately one in five adults from 18 to 39 years of age has hypertension,[9] and obesity and adverse lipid levels are common; risk factors early in life correlate with risk factors and cardiovascular events in later adulthood.[10]

The REACT study was performed in Europe, and Systematic Coronary Risk Evaluation 2 (SCORE2) 10-year risk scores were evaluated. This clinical risk score was an imperfect correlate of the presence of subclinical atherosclerosis. However, the SCORE2 framework only includes persons 40 to 69 years old. Likewise, although PREVENT risk-prediction equations include a broader age range, they are not applicable to persons who are younger than 30 years of age.

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Future studies are needed to provide an evidence-based strategy for risk assessment and precision-medicine approaches, possibly including genomics, to target younger persons for preventive therapies.

REACT delivers a clear message: start earlier to prevent atherosclerotic cardiovascular disease, which manifests as atherosclerosis early in life and becomes almost ubiquitous with age. These findings reinforce the imperative for primary prevention across the life course, with an emphasis on improved lifestyle habits for the entire population, including heart-healthy dietary patterns and weight, regular physical activity, and smoking cessation. This course of action is especially important in light of the epidemic of obesity, cardiovascular–kidney–metabolic syndrome, and diabetes that is affecting persons at younger ages than in the past. If seeing is believing, we cannot delay in reacting to the findings of this important study.

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