Commentary on "Preventive percutaneous coronary intervention *versus* optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicenter, open-label, randomized controlled trial"

Ottavia Borghese, Claudio Vincenzoni

Unit of Vascular Surgery, IRCCS "A. Gemelli" University Hospital, Università Cattolica del Sacro Cuore, Rome, Italy

To address the potential risk of acute coronary syndrome, the current clinical guidelines on coronary artery diseases recommend revascularization in significant and flow-limiting lesions,[1-3] but emerging data depict vulnerable atherosclerotic coronary plaques as possibly at risk of adverse cardiac events, compared to fibroatheromous or calcific plaques.[4-6]

Hence, in the light of this recent evidence, in a multicenter open label, randomized controlled trial, the authors investigated if preventive percutaneous coronary intervention of non-hemodynamically significant but vulnerable plaques could possibly be justified to improve clinical outcomes when compared to optimal medical therapy alone.[7]

Fifteen research hospitals in four different countries were included totaling 1608 adult patients with vulnerable coronary plaque detected at the intravascular ultrasonography or optical coherence tomography.

The population in the study was assigned 1:1 to preventive revascularization (n=803 patients) with bioresorbable vascular scaffolds (BVS) or cobalt-chromium everolimus-eluting metallic stents or to medical treatment alone (n=803 patients) and followed up annually. A composite outcome of mortality and coronary syndrome (target-vessel myocardial infarction, ischemia-driven target-vessel revascularization, and hospitalization for unstable or progressive angina) was analyzed and stratified by risk factors and performance of percutaneous coronary intervention between the two groups that were non-statistically different.

The authors concluded that indications for percutaneous coronary intervention should be extended to high-risk vulnerable plaques. Indeed, during a mean follow-up of two years, a significantly lower rate of all-cause mortality [absolute difference -1.1 percentage points; 95% confidence interval (CI) -2.0 to -0.2] was reported with preventive percutaneous coronary intervention versus optimal therapy alone and no statistical differences between serious clinical or adverse events was noted neither in terms of mortality (absolute difference -0.8 percentage points; 95% CI -1.7 to 0.2) nor in terms of myocardial infarction [absolute difference -0.5 percentage points (-1.7 to 0.6)].

Despite these promising results, we believe some considerations should be undertaken before the wider application of such approach could be suggested.

To start with, the decision to treat non-hemodynamic lesions is controversial as previous studies demonstrated that vulnerable lesions may lose their *vulnerable characteristics* over time possibly via subclinical rupture and healing.[8]

Additionally, the authors reported that numbers-needed-to-treat with preventive percutaneous coronary intervention was quite high (45.4 to prevent one primary outcome event over two years and 87.7 to prevent one cardiac death or target-vessel myocardial infarction over two years).

Finally, as suggested by Zimmerman *et al.*, the *target vessel revascularization* that was included in the composite endpoint of the study might represent an inappropriate choice. Indeed, patients with vulnerable plaques are asymptomatic by definition, and *if a patient develops medically refractory or unstable angina, then urgent percutaneous coronary intervention can be performed without loss of life or myocardial tissue.*[9]

Theoretically, despite the interventional treatment of vulnerable plaque might potentially prevent adverse cardiac events or

Correspondence: Claudio Vincenzoni, Unit of Vascular Surgery, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, 00168, Italy.
Tel.: +39.0630151.
E-mail: claudio.vincenzoni@policlinicogemelli.it

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received: 13 June 2024.
Accepted: 14 June 2024.

Bleeding, Thrombosis and Vascular Biology 2024; 3:141
doi:10.4081/btvb.2024.141

mortality, the safety and efficacy of revascularization of non-flow-limiting vulnerable plaques remains uncertain. To the best of our knowledge, two other similar randomized controlled trials (the PROSPECT ADSORB and PECTUS trials) have been conducted so far.[10,11]

The PROSPECT ADSORB trial was conducted on patients with angiographically non-obstructive stenosis but with intravascular ultrasound plaque burden ≥65% who were randomized to treat the lesion with either a BVS plus guideline-directed medical therapy (GDMT) or GDMT alone. In this study, the authors concluded that percutaneous coronary intervention of angiographically mild lesions with large plaque burden was safe and led to favorable long-term clinical outcomes.

The PECTUS trial stopped the treatment arm in 2018 because of the concerns with BVS and continued as a non-randomized observational cohort. In this study, the pre-emptive stenting of vulnerable plaques was not shown to be superior or more beneficial than conservative treatment.

In light of this contrasting evidence, several questions remain, including the uncertainty over which artery is the culprit of preventive coronary revascularization and if in an asymptomatic population, the risk of a preventive angioplasty outweighs the potential benefit.

Further research is needed to investigate the answers and to understand the underlying causes of plaque vulnerability and rupture with the aim to improve preventive medical strategies and diagnostic means in this setting.

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