Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial

Seung-Jung Park, Jung-Min Ahn*, Do-Yoon Kang, Sung-Cheol Yun, Young-Keun Ahn, Won-Jang Kim, Chang-Wook Nam, Jin-Ok Jeong, In-Ho Chae, Hiroki Shiomi, Hsien-Li Kao, Joo-Yong Hahn, Sung-Ho Her, Bong-Ki Lee, Tae Hoon Ahn, Ki-Yuk Chang, Jei Keon Chae, David Smyth, Gary S Mintz, Gregg W Stone, Duk-Woo Park, for the PREVENT Investigators†*

Summary

Background Acute coronary syndrome and sudden cardiac death are often caused by rupture and thrombosis of lipid-rich atherosclerotic coronary plaques (known as vulnerable plaques), many of which are non-flow-limiting. The safety and effectiveness of focal preventive therapy with percutaneous coronary intervention of vulnerable plaques in reducing adverse cardiac events are unknown. We aimed to assess whether preventive percutaneous coronary intervention of non-flow-limiting vulnerable plaques improves clinical outcomes compared with optimal medical therapy alone.

Methods PREVENT was a multicentre, open-label, randomised controlled trial done at 15 research hospitals in four countries (South Korea, Japan, Taiwan, and New Zealand). Patients aged 18 years or older with non-flow-limiting (fractional flow reserve >0·80) vulnerable coronary plaques identified by intracoronary imaging were randomly assigned (1:1) to either percutaneous coronary intervention plus optimal medical therapy or optimal medical therapy alone, in block sizes of 4 or 6, stratified by diabetes status and the performance of percutaneous coronary intervention in a non-study target vessel. Follow-up continued annually in all enrolled patients until the last enrolled patient reached 2 years after randomisation. The primary outcome was a composite of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina, assessed in the intention-to-treat population at 2 years. Time-to-first-event estimates were calculated with the Kaplan–Meier method and were compared with the log-rank test. This report is the principal analysis from the trial and includes all long-term analysed data. The trial is registered at ClinicalTrials.gov, NCT02316886, and is complete.

Findings Between Sept 23, 2015, and Sept 29, 2021, 5627 patients were screened for eligibility, 1606 of whom were enrolled and randomly assigned to percutaneous coronary intervention (n=803) or optimal medical therapy alone (n=803). 1177 (73%) patients were men and 429 (27%) were women. 2-year follow-up for the primary outcome assessment was completed in 1556 (97%) patients (percutaneous coronary intervention group n=780; optimal medical therapy group n=776). At 2 years, the primary outcome occurred in three (0·4%) patients in the percutaneous coronary intervention group and in 27 (3·4%) patients in the medical therapy group (absolute difference −3·0 percentage points [95% CI −4·4 to −1·8]; p=0·0003). The effect of preventive percutaneous coronary intervention was directionally consistent for each component of the primary composite outcome. Serious clinical or adverse events did not differ between the percutaneous coronary intervention group and the medical therapy group: at 2 years, four (0·5%) versus ten (1·3%) patients died (absolute difference −0·8 percentage points [95% CI −1·7 to 0·2]) and nine (1·1%) versus 13 (1·7%) patients had myocardial infarction (absolute difference −0·5 percentage points [−1·7 to 0·6]).

Interpretation In patients with non-flow-limiting vulnerable coronary plaques, preventive percutaneous coronary intervention reduced major adverse cardiac events arising from high-risk vulnerable plaques, compared with optimal medical therapy alone. Given that PREVENT is the first large trial to show the potential effect of the focal treatment for vulnerable plaques, these findings support consideration to expand indications for percutaneous coronary intervention to include non-flow-limiting, high-risk vulnerable plaques.

Funding The CardioVascular Research Foundation, Abbott, Yuhan Corp, CAH-Cordis, Philips, and Infraredx, a Nipro company.

Lancet 2024; 403; 1753–65

Published **Online** April 8, 2024 https://doi.org/10.1016/S0140-6736(24)00413-6

See **Comment** page 1724

*Contributed equally

†A full list of the investigators in the PREVENT trial is in the appendix (pp 3–4)

Division of Cardiology (Prof S-J Park MD, J-M Ahn MD, D-Y Kang MD, Prof D-W Park MD) **and Division of Biostatistics** (S-C Yun PhD), **Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Division of Cardiology, Chonnam National University Hospital, Gwangju, South Korea** (Prof Y-K Ahn MD); **Division of Cardiology, CHA University School of Medicine, CHA Ilsan Medical Center, Goyang, South Korea** (W-J Kim MD); **Division of Cardiology, Keimyung University Dongsan Hospital, Daegu, South Korea** (Prof C-W Nam MD); **Division of Cardiology, Chungnam National University Hospital, Daejeon, South Korea** (Prof J-O Jeong MD); **Division of Cardiology, Seoul National University Bundang Hospital, Sungnam, South Korea** (Prof I-H Chae MD); **Division of Cardiology, Kyoto University Hospital, Kyoto, Japan** (H Shiomi MD); **Division of Cardiology, National Taiwan University Hospital, Taipei, Taiwan** (Prof H-L Kao MD); **Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea** (Prof J-Y Hahn MD); **Department of Cardiology, Saint Vincent's Hospital, Suwon, South Korea** (Prof S-H Her MD); **Division of**

Cardiology, Kangwon National University Hospital, Chuncheon, South Korea (Prof B-K Lee MD); **Cardiovascular Center, Na-Eun Hospital, Incheon, South Korea** (T H Ahn MD); **Division of Cardiology, Seoul Saint Mary's Hospital, Catholic University of Korea, Seoul, South Korea** (Prof K-Y Chang MD); **Division of Cardiology, Jeonbuk National University Hospital, Jeonju, South Korea** (Prof J K Chae MD); **Department of Cardiology, Christchurch Hospital, Christchurch, New Zealand** (D Smyth MD); **Cardiovascular Research Foundation, New York, NY, USA** (G S Mintz MD); **The Zena and Michael A Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof G W Stone MD)

Correspondence to:
Dr Duk-Woo Park, Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, South Korea
dwpark@amc.seoul.kr

or
Dr Seung-Jung Park, Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, South Korea
sjpark@amc.seoul.kr

See Online for appendix

Research in context

Evidence before this study

Optimal medical therapy with pharmacological management is the standard approach to stabilise plaque vulnerability. Theoretically, preventive percutaneous coronary intervention might seal and passivate vulnerable plaques, potentially reducing future acute coronary events. However, the safety and efficacy of revascularisation by percutaneous coronary intervention of non-flow-limiting (non-ischaemic) vulnerable plaques remain uncertain. We searched PubMed and MEDLINE on June 11, 2015, for articles published in English, using the search terms: "coronary artery disease", "vulnerable plaque", "percutaneous coronary intervention", "fractional flow reserve", and "intravascular imaging". We found no randomised clinical trials that assessed the efficacy and safety of localised preventive therapy with percutaneous coronary intervention of non-flow-limiting vulnerable plaques.

Added value of this study

To our knowledge, PREVENT is the first large-scale, randomised controlled trial comparing preventive percutaneous coronary intervention plus optimal medical therapy versus optimal medical therapy alone for the treatment of patients with non-flow-limiting, high-risk, vulnerable plaques identified by intracoronary imaging. In this trial, preventive percutaneous coronary intervention reduced the composite risk of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina at 2 years, compared with optimal medical therapy alone. Preventive percutaneous coronary intervention also reduced the composite patient-oriented outcome of risk of all-cause death, any myocardial infarction, or any repeat revascularisation. This benefit was sustained throughout the 7-year follow-up period of the trial.

Implications of all the available evidence

The primary results of PREVENT provide clinical evidence that a preventive percutaneous coronary intervention strategy guided by intravascular imaging plus optimal medical therapy can reduce adverse cardiac events arising from high-risk coronary vulnerable plaques better than optimal medical therapy alone. These findings support an expansion of the indications for percutaneous coronary intervention to include non-flow-limiting, high-risk, vulnerable plaques.

Introduction

Rupture and thrombosis of lipid-rich atherosclerotic coronary artery lesions (known as vulnerable plaques) is the most frequent cause of acute coronary syndrome and sudden cardiac death.[1] Vulnerable plaques often appear mild on angiography and are often non-flow-limiting on haemodynamic assessment,[2,3] but can be identified with intravascular imaging as thin-capped fibroatheromas containing a large plaque and a lipid-rich necrotic core that is separated from the lumen by a thin fibrous cap.[4–6] Prospective studies have shown that imaging-detected vulnerable plaques increase the risk of adverse cardiac events compared with plaques without these vulnerable features.[4,5,7]

Current clinical guidelines recommend revascularisation by percutaneous coronary intervention only for coronary lesions that are haemodynamically flow-limiting or have caused an acute coronary syndrome.[8–10] As such, whether revascularising non-flow-limiting (ie, non-ischaemic) vulnerable plaques is safe and effective is uncertain. Theoretically, percutaneous coronary intervention might seal and passivate vulnerable plaques, potentially reducing the risk of acute coronary events.[11–14] A single randomised trial has shown that percutaneous coronary intervention for vulnerable plaques might safely enlarge the coronary lumen and thicken the fibrous cap at 2 years, but this study was not powered for clinical outcomes.[14] We therefore aimed to evaluate the effects of preventive percutaneous coronary intervention on major adverse cardiovascular events in patients with non-flow-limiting, high-risk, vulnerable plaques identified by intracoronary imaging.[15]

Methods

Study design and participants

The Preventive Coronary Intervention on Stenosis with Functionally Insignificant Vulnerable Plaque (PREVENT) trial was an investigator-initiated, multicentre, open-label, randomised controlled trial. The trial was conducted at 15 research hospitals in four countries (South Korea, Japan, Taiwan, and New Zealand). Details regarding the participating investigators and the organisation of the trial are in the appendix (pp 3–7). The trial design and methods have been published previously.[15] The study protocol was approved by the institutional review board (number 2015–1040) and ethics committee at each participating site. An independent data safety and monitoring board approved the initial trial protocol and subsequent amendments and monitored patient safety periodically (appendix pp 6, 113). All patients provided written informed consent. The original and final protocol and a summary of changes are in the appendix (pp 53–137).

Patients aged 18 years or older with stable coronary disease or acute coronary syndromes undergoing cardiac catheterisation were assessed for eligibility. Flow-limiting lesions with a fractional flow reserve of 0·80 or less and lesions causing acute coronary syndrome were treated with percutaneous coronary intervention with metallic drug-eluting stents before randomisation. All untreated, non-culprit lesions (ie, those that were clearly not responsible for the presenting clinical syndrome) with an angiographic diameter stenosis of 50% or more by site visual estimation were functionally assessed by

fractional flow reserve. Any intermediate, non-flow-limiting (fractional flow reserve >0·80), non-culprit lesions were then assessed by intracoronary imaging with either grey-scale intravascular ultrasonography, radiofrequency intravascular ultrasonography, a combination of grey-scale intravascular ultrasonography and near-infrared spectroscopy, or optical coherence tomography, at the discretion of the trained interventional cardiologists. Vulnerable plaques were defined as lesions possessing at least two of the following four characteristics: a minimal lumen area of less than 4·0 mm² by intravascular ultrasonography or optical coherence tomography; a plaque burden of more than 70% by intravascular ultrasonography; a lipid-rich plaque by near-infrared spectroscopy (defined as maximum lipid core burden index within any 4 mm pullback length [$maxLCBI_{4mm}$] >315); or a thin-cap fibroatheroma detected by radiofrequency intravascular ultrasonography or optical coherence tomography (defined as a ≥10% confluent necrotic core with >30° abutting the lumen in three consecutive frames on radiofrequency intravascular ultrasonography or as a lipid plaque with arc >90° and fibrous cap thickness <65 μm on optical coherence tomography). Major exclusion criteria included previous coronary-artery bypass grafting, target-lesions previously stented, patients with three and more target lesions or two target lesions in the same coronary artery, heavily calcified or angulated lesions, or bifurcation lesions requiring two-stent techniques. Full inclusion and exclusion criteria are listed in the appendix (pp 8–9); further details regarding fractional flow reserve and imaging assessments are also provided in the appendix (pp 10–12). During patient enrolment, baseline coronary angiograms, fractional flow reserve, and intracoronary imaging criteria were assessed at the time of the enrolment visit by investigators at each participating centre; final eligibility was based on these local determinations. After completion of enrolment, imaging data were centrally assessed at the independent core laboratory of the CardioVascular Research Foundation (Seoul, South Korea) in accordance with the established study protocol (appendix pp 10–12). Although most participating centres were experienced in the use of both coronary physiological assessment and intravascular imaging, feedback was occasionally necessary in the early period of trial, which was conducted by on-site training by key investigators in Asan Medical Center (Seoul, South Korea) in communication with the core laboratory (appendix p 12). Patient sex data were collected from medical records.

Randomisation and masking

Eligible patients with one or two non-flow-limiting vulnerable plaques were randomly assigned (1:1) to a strategy of percutaneous coronary intervention plus optimal medical therapy or optimal medical therapy alone. Randomisation was performed with a web-based system with permutated block sizes of 4 or 6, stratified by the presence or absence of diabetes and the presence or absence of concomitant percutaneous coronary intervention in a non-study target vessel. A computer-generated randomisation sequence was used and a non-sponsor affiliated independent statistician generated the randomisation list. The participating physicians or research personnel at each site enrolled the participants and assigned them to the trial groups after accessing a computerised interactive web-based response system. The independent clinical events committee was masked to the group assignment.

Procedures

During the initial recruitment period of the trial, percutaneous coronary intervention of vulnerable plaques was performed with bioresorbable vascular scaffolds (Absorb; Abbott, Santa Clara, CA, USA). Following the withdrawal of bioresorbable vascular scaffolds from the market, cobalt–chromium everolimus-eluting metallic stents (Xience; Abbott, Santa Clara, CA, USA) were used for the default device of percutaneous coronary intervention. The executive and steering committees decided on this change and an independent data safety and monitoring board approved it on July 23, 2017. Intravascular imaging of all target lesions in enrolled patients was performed to guide percutaneous coronary intervention. After percutaneous coronary intervention, patients received dual antiplatelet therapy for at least 6 or 12 months according to clinical presentation and anatomical complexity (appendix p 13). Optimal medical therapy in both groups consisted of adequate lifestyle modification and intensive pharmacological interventions, according to contemporary guideline-directed medical therapy for secondary prevention.[16–18] High-dose statin therapy was strongly recommended but was left at the discretion of local investigators. Additional details of the optimal medical therapy are in the trial protocol (appendix pp 106–107).

Clinical follow-up was done at 1, 6, 12, and 24 months after randomisation and every year thereafter. Follow-up continued annually in all enrolled patients until the last enrolled patient reached 2 years after randomisation. All information on adverse clinical events, risk factor control, and concomitant cardiovascular medications were systematically collected at each visit. The final clinical assessment for all trial participants was on Sept 30, 2023. Cross-validation of survival status was done using the Korean National Health Insurance database.[19]

Outcomes

The primary outcome was a composite of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina, all at 2 years after randomisation. Secondary outcomes were the individual components of the primary composite

outcome, death from any cause, any myocardial infarctions, any revascularisation, definite stent or scaffold thrombosis, stroke, bleeding events, angina status, procedural complications, and the patient-oriented composite of all-cause death, all myocardial infarctions, or any repeat revascularisation. Full lists and definitions of all trial outcomes are in the appendix (pp 14–24). A detailed list of procedural safety outcomes and serious adverse events are also reported. Safety was investigated by recording adverse events, vital signs, clinical laboratory assessments, and electrocardiogram parameters. Clinical outcomes were periodically adjudicated by the masked independent clinical events committee. Positive event adjudication was based on prespecified definitions requiring verification of the event from collected source documents.

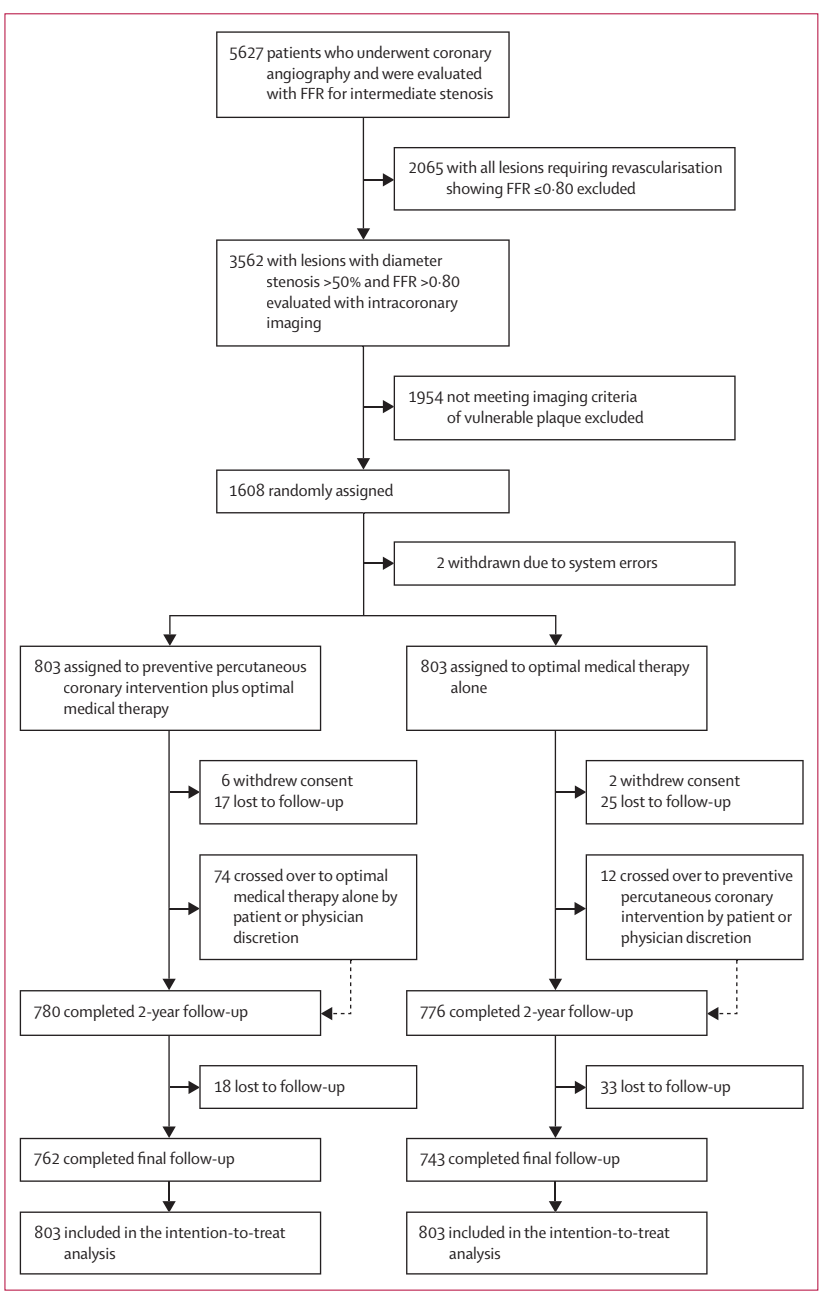


Figure 1: **Trial profile**
FFR=fractional flow reserve.

Statistical analysis

From previous studies,[4,20] we assumed an incidence of the primary outcome at 2 years of 8·5% for the preventive percutaneous coronary intervention group and 12·0% for the medical therapy alone group, which corresponds to a 30% relative risk reduction. A sample size of 1600 patients provided 80% power at a two-sided significance level of 5%, assuming a 7% loss to follow-up and crossover rate. Further details regarding the sample-size estimation are in the appendix (p 25). Detailed statistical methods are in the appendix (pp 26–27).

All principal analyses were done in the intention-to-treat population. Sensitivity analyses were done in the as-treated population (patients analysed by the treatment they actually received) and in the per-protocol population (patients analysed according to their assigned treatment group only if they actually received their assigned treatment). Time-to-first-event estimates were calculated with Kaplan–Meier methodology and were compared with the log-rank test. Treatment effects were estimated with Cox proportional-hazards regression and are presented as hazard ratios (HRs) with 95% CIs. The proportional-hazards assumption was confirmed using Schoenfeld residuals and visual assessment of log(–log) plots. Absolute differences and 95% CIs for the primary and secondary outcomes were calculated with Kaplan–Meier estimates and Greenwood standard errors[21] at 2 years (primary outcome), 4 years (median follow-up), and 7 years (maximum follow-up). The CIs were not adjusted for multiple comparisons, so these intervals should not be used to infer definitive treatment effects. Prespecified subgroup analyses (age, sex, diabetes, acute coronary syndrome, percutaneous coronary intervention of non-target vessel, median value of diameter stenosis, median value of fractional flow reserve, intracoronary imaging screening tools, and preventive percutaneous coronary intervention modalities) were done with models incorporating an interaction term. All comparisons were done with two-sided tests. As a post-hoc analysis, we evaluated hard clinical endpoints including composites of death from any cause or target-vessel myocardial infarction and death from cardiac causes or target-vessel myocardial infarction. We also compared the primary outcome in the as-treated population according to the type of device used for preventive percutaneous coronary intervention versus optimal medical therapy alone. Statistical analyses were done with SAS (version 9.4). The original and final statistical analysis plan and a summary of changes are in the appendix (pp 138–157). The trial was registered with ClinicalTrials.gov, NCT02316886, and is now completed.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Sept 23, 2015, and Sept 29, 2021, 5627 patients were screened for eligibility; 3562 patients had non-flow-limiting (fractional flow reserve >0·80) intermediate lesions that were evaluated with intracoronary imaging (figure 1). Vulnerable plaques were found in 1608 (45%) patients, all of whom were randomly assigned, but two (<1%) patients were withdrawn due to system errors. 1606 randomly assigned patients with 1672 qualifying lesions were included in the study; 803 patients (with 831 lesions) were assigned to the preventive percutaneous coronary intervention plus optimal medical therapy group and 803 patients (with 841 lesions) were assigned to the optimal medical therapy alone group.

The baseline characteristics were well balanced between the groups (table 1). Median age was 65 years (IQR 58–71). 1177 (73%) patients were men and 429 (27%) were women. 490 (31%) patients had diabetes. Data on race or ethnicity were not collected. 1347 (84%) patients had stable coronary artery disease, 197 (12%) had unstable angina, and 62 (4%) had had a recent (within 1 week) myocardial infarction. Percutaneous coronary intervention of non-target lesions was performed in 576 (36%) enrolled patients (1030 [64%] had only target lesions).

Vulnerable plaques were assessed by grey-scale intravascular ultrasonography in 1519 (95%) patients (1141 [71%] also had radiofrequency intravascular ultrasonography and 679 [42%] had near-infrared spectroscopy assessments), and by optical coherence tomography in 87 (5%) patients (appendix p 30). Anatomical characteristics and core-laboratory assessed angiographic and imaging data are summarised in table 1 and the appendix (pp 31–33). The median fractional flow reserve of the 1672 target lesions was 0·86 (IQR 0·83–0·90) and their mean diameter stenosis was 54·5% (SD 9·7). For the predefined criteria for plaque vulnerability per patient, 1562 (97%) of 1606 patients qualified with minimal luminal area less than 4·0 mm², 1533 (96%) qualified with plaque burden greater than 70%, 186 (11%) qualified with $maxLCBI_{4mm}$ greater than 315, and 77 (5%) qualified as thin-cap fibroatheromas. 1496 (89%) of 1672 operator-identified and enrolled lesions had at least two imaging-defined prespecified vulnerable plaque features as assessed by the imaging core laboratory (appendix pp 31–33).

Percutaneous coronary intervention of non-flow-limiting lesions was performed in 729 (91%) of the 803 patients assigned to preventive percutaneous coronary intervention, with bioresorbable vascular scaffolds (in 237 [33%] of 729 patients) or

	Preventive percutaneous coronary intervention plus optimal medical therapy (n=803 [831 lesions])	Optimal medical therapy alone (n=803 [841 lesions])
Age, years	64 (58–71)	65 (59–71)
Sex		
Male	606 (76%)	571 (71%)
Female	197 (25%)	232 (29%)
BMI, kg/m²	24·6 (22·9–26·5)	24·7 (22·9–26·4)
Diabetes		
Any	244 (30%)	246 (31%)
Requiring insulin	16 (2%)	21 (3%)
Hypertension	519 (65%)	536 (67%)
Hyperlipidaemia	721 (90%)	709 (88%)
Current smoker	136 (17%)	139 (17%)
Family history of premature coronary artery disease	95 (12%)	80 (10%)
Previous myocardial infarction	47 (6%)	41 (5%)
Previous percutaneous coronary intervention	109 (14%)	85 (11%)
History of heart failure	5 (1%)	10 (1%)
History of cerebrovascular disease	52 (6%)	50 (6%)
History of peripheral artery disease	21 (3%)	20 (2%)
Atrial fibrillation or atrial flutter	15 (2%)	7 (1%)
Chronic renal insufficiency*	9 (1%)	10 (1%)
Clinical presentation		
Stable angina or silent ischaemia	670 (83%)	677 (84%)
Unstable angina	106 (13%)	91 (11%)
Non-ST-elevation myocardial infarction	18 (2%)	28 (3%)
ST-elevation myocardial infarction	9 (1%)	7 (1%)
Left ventricular ejection fraction†	63 (60–66)	63 (60–66)
Serum cholesterol, mg/dL		
Total cholesterol‡	148 (40)	154 (40)
LDL cholesterol§	88 (34)	93 (34)
HDL cholesterol¶	46 (12)	47 (12)
Triglycerides, mg/dL‖	138 (116)	139 (99)
High-sensitivity C-reactive protein, mg/dL**	0·07 (0·04–0·19)	0·07 (0·04–0·18)
Number of diseased epicardial coronary arteries		
One vessel	327 (41%)	330 (41%)
Two vessels	302 (38%)	307 (38%)
Three vessels	174 (22%)	166 (21%)
Number of target lesions (vulnerable plaques) per patient	1 (1–1)	1 (1–1)
Qualifying criteria for target lesions††		
Minimal luminal area <4·0 mm² by grey-scale IVUS or OCT	809/831 (97%)	817/841 (97%)
Plaque burden >70% by grey-scale IVUS	792/815 (97%)	805/831 (97%)
Large lipid-rich plaque by NIRS ($maxLCBI_{4mm}$ >315)	99/348 (28%)	94/369 (26%)
Thin-cap fibroatheroma defined by OCT or radiofrequency IVUS	39/571 (7%)	40/679 (6%)
Target lesion location		
Left anterior descending artery	416/831 (50%)	400/841 (48%)
Left circumflex artery	170/831 (20%)	147/841 (17%)
Right coronary artery	245/831 (29%)	294/841 (35%)

(Table 1 continues on next page)

	Preventive percutaneous coronary intervention plus optimal medical therapy (n=803 [831 lesions])	Optimal medical therapy alone (n=803 [841 lesions])
(Continued from previous page)		
Median FFR values of target lesions	0·87 (0·83–0·90)	0·86 (0·83–0·90)
Quantitative coronary angiography of target lesions		
Diameter stenosis	56·6% (9·2)	52·6% (9·8)
Minimal lumen diameter, mm	1·3 (0·3)	1·5 (0·4)
Reference vessel diameter, mm	3·1 (0·4)	3·1 (0·5)
Lesion length, mm	23·6 (8·5)	19·3 (8·3)
Any percutaneous coronary intervention of target lesion, per patient‡‡	729/803 (91%)	12/803 (1%)
Drug-eluting stent implantation	491/729 (67%)	7/12 (58%)
Bioabsorbable scaffold implantation	237/729 (33%)	5/12 (42%)
Number of stents or scaffolds implanted	1 (1–1)	0 (0–0)
Stent or scaffold diameter, mm	3·5 (3·0–3·5)	3·3 (3·0–3·5)
Total stent or scaffold length, mm	23 (18–28)	23 (18–28)
Intravascular imaging used to optimise stent or scaffold implantation	729/729 (100%)	12/12 (100%)
Any percutaneous coronary intervention of non-target lesions, per patient	290/803 (36%)	286/803 (36%)
Number of lesions treated	0 (0–1)	0 (0–1)
Number of stents implanted	0 (0–1)	0 (0–1)
Stent diameter, mm	3·3 (3·0–3·5)	3·3 (3·0–3·5)
Total stent length, mm	38 (23–51)	38 (28–51)

Data are median (IQR), n (%), mean (SD), or n/N (%). FFR=fractional flow reserve. IVUS=intravascular ultrasonography. $maxLCBI_{4mm}$=maximal lipid core burden index in a 4 mm segment. NIRS=near-infrared spectroscopy. OCT=optical coherence tomography. *Defined as serum creatinine ≥2·0 mg/dL or dependence on chronic haemodialysis. †Preventive percutaneous coronary intervention group n=485; optimal medical therapy group n=358. ‡Preventive percutaneous coronary intervention group n=773; optimal medical therapy group n=760. §Preventive percutaneous coronary intervention group n=733; optimal medical therapy group n=725. ¶Preventive percutaneous coronary intervention group n=732; optimal medical therapy group n=727. ||Preventive percutaneous coronary intervention group n=732; optimal medical therapy group n=728. **Preventive percutaneous coronary intervention group n=392; optimal medical therapy group n=326. ††The denominators represent the number of lesions that were assessed for these characteristics by one or more of the imaging tests. ‡‡One patient underwent balloon angioplasty only.

Table 1: **Baseline characteristics**

	Preventive percutaneous coronary intervention plus optimal medical therapy (n=803)	Optimal medical therapy alone (n=803)	Difference in event rates, percentage points (95% CI)	Hazard ratio (95% CI)*
Primary composite outcome†	..	..	..	0·54 (0·33 to 0·87)
At 2 years (primary timepoint)	3 (0·4%)	27 (3·4%)	−3·0 (−4·4 to −1·8)	0·11 (0·03 to 0·36), p=0·0003
At 4 years	17 (2·8%)	37 (5·4%)	−2·6 (−4·7 to 0·4)	..
At 7 years	26 (6·5%)	47 (9·4%)	−2·9 (−7·3 to 1·5)	..
Death from any cause	..	..	..	0·61 (0·35 to 1·06)
At 2 years	4 (0·5%)	10 (1·3%)	−0·8 (−1·7 to 0·2)	..
At 4 years	11 (1·8%)	17 (2·6%)	−0·8 (−2·4 to 0·8)	..
At 7 years	20 (5·2%)	32 (7·4%)	−2·3 (−6·0 to 1·5)	..

(Table 2 continues on next page)

cobalt–chromium everolimus-eluting metallic stents (in 491 [67%]; figure 1 and table 1). In the preventive percutaneous coronary intervention group, 74 (9%) patients crossed over to medical therapy alone. In the medical therapy group, 791 (99%) received medical therapy alone and 12 (1%) patients crossed over to percutaneous coronary intervention. The most common reason for cross-over was patient or physician preference.

Medication use and risk-factor control over time are shown in the appendix (pp 48–50). Use of dual antiplatelet therapy was greater in the percutaneous coronary intervention group than the optimal medical therapy alone group. More than half of patients in both groups were taking high-intensity statins or moderate-intensity statins plus ezetimibe during the entire follow-up period (appendix p 49). Mean LDL cholesterol was 64 mg/dL (SD 21) in both groups at last follow-up. Angina during follow-up was infrequent in both groups (appendix p 51).

2-year follow-up for the primary outcome assessment was completed in 1556 (97%) patients (figure 1). The median follow-up duration was 4·3 years (IQR 2·6–6·1) in the percutaneous coronary intervention group and 4·4 years (2·6–6·2) in the optimal medical therapy alone group. The maximum follow-up duration was 7·9 years in both groups.

At 2 years, the primary outcome occurred in three (0·4%) patients in the preventive percutaneous coronary intervention group and in 27 (3·4%) patients in the optimal medical therapy group (absolute difference −3·0 percentage points [95% CI −4·4 to −1·8]; p=0·0003; table 2 and figure 2). The effect of preventive percutaneous coronary intervention was directionally consistent for each component of the primary composite outcome. In addition, in the post-hoc analysis, the composite rate of death from any cause or target-vessel myocardial infarction was consistently lower at 2 years with preventive percutaneous coronary intervention than with optimal therapy alone, as was the composite rate of death from cardiac causes or target-vessel myocardial infarction (two [0·3%] patients *vs* eleven [1·4%] patients; absolute difference −1·1 percentage points [95% CI −2·0 to −0·2]). During the entire follow-up period, the risk of the primary outcome remained lower in the preventive percutaneous coronary intervention group than in the optimal medical therapy alone group (table 2). The risk of the composite patient-oriented outcome of all-cause death, all myocardial infarction, or any revascularisation was also lower in the preventive percutaneous coronary intervention group than the optimal medical therapy group (table 2 and figure 2). Numbers-needed-to-treat with preventive percutaneous coronary intervention were 45·4 to prevent one primary outcome event over 2 years and 87·7 to prevent one cardiac death or target-vessel myocardial infarction over 2 years. During the entire follow-up, two scaffold thromboses occurred in target lesions in the

percutaneous coronary intervention group and three stent thromboses occurred in non-target lesions in the optimal medical therapy group (appendix pp 35–37). Stroke and bleeding events did not differ between the two groups (appendix pp 35–37).

The procedural safety outcomes and percutaneous coronary intervention-related adverse events are shown in table 3. Four (<1%) of 741 patients had a total of five preventive percutaneous coronary intervention-related acute adverse events. Core-laboratory measured quantitative coronary angiography on preventive percutaneous coronary intervention is summarised in the appendix (p 34).

The risk of a primary outcome event was lower in the preventive percutaneous coronary intervention group than the optimal medical therapy group in the as-treated and per-protocol populations (appendix pp 38–47). At 2 years and during the entire follow-up, the treatment effect of preventive percutaneous coronary intervention was consistently reduced in most subgroups (figure 3). In addition, in the post-hoc as-treated analysis, the durability of preventive percutaneous coronary intervention appeared to be more sustained with cobalt–chromium everolimus-eluting metallic stents than with bioresorbable vascular scaffolds (appendix p 52).

Discussion

In the PREVENT trial, treatment of vulnerable plaques with a preventive percutaneous coronary intervention strategy reduced the composite risk of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina at 2 years, compared with optimal medical therapy alone. This difference was driven by a reduction in each individual component of the composite outcome and was sustained throughout the 7-year follow-up period. Preventive percutaneous coronary intervention also reduced the composite patient-oriented risk of all-cause death, all myocardial infarctions, or any repeat revascularisation. The treatment effect of preventive percutaneous coronary intervention was consistent across multiple prespecified patient and anatomical subgroups.

Vulnerable plaques, whether flow-limiting or non-flow-limiting, are at risk for future adverse cardiac events, even with optimal medical therapy.[1–5,7,22] The concept of preventive percutaneous coronary intervention to passivate high-risk vulnerable plaques has been proposed;[11–14] the potential mechanism is that the obligate amount of neointima that develops over the stent or scaffold would functionally thicken the fibrous cap, reducing its risk of rupture. This mechanism was shown in a previous randomised trial in which preventive percutaneous coronary intervention of vulnerable plaques safely enlarged the coronary artery lumen at 2-year follow-up, reduced the lipid content of the

	Preventive percutaneous coronary intervention plus optimal medical therapy (n=803)	Optimal medical therapy alone (n=803)	Difference in event rates, percentage points (95% CI)	Hazard ratio (95% CI)*
(Continued from previous page)				
Death from cardiac causes	..	..	..	0·87 (0·31 to 2·39)
At 2 years	1 (0·1%)	6 (0·8%)	–0·6 (–1·3 to 0·02)	..
At 4 years	5 (0·8%)	7 (0·9%)	–0·1 (–1·1 to 0·9)	..
At 7 years	7 (1·4%)	8 (1·3%)	0·1 (–1·4 to 1·5)	..
All myocardial infarctions	..	..	..	0·79 (0·40 to 1·55)
At 2 years	9 (1·1%)	13 (1·7%)	–0·5 (–1·7 to 0·6)	..
At 4 years	14 (2·0%)	15 (2·0%)	–0·1 (–1·5 to 1·4)	..
At 7 years	15 (2·4%)	19 (3·5%)	–1·2 (–3·4 to 1·0)	..
Target-vessel-related myocardial infarction	..	..	..	0·62 (0·20 to 1·90)
At 2 years	1 (0·1%)	6 (0·8%)	–0·6 (–1·3 to 0·02)	..
At 4 years	4 (0·6%)	7 (10%)	–0·3 (–1·3 to 0·6)	..
At 7 years	5 (1·0%)	8 (1·4%)	–0·3 (–1·7 to 1·1)	..
Any revascularisation	..	..	..	0·66 (0·44 to 0·98)
At 2 years	14 (1·8%)	29 (3·7%)	–1·9 (–3·6 to –0·3)	..
At 4 years	31 (4·6%)	42 (6·1%)	–1·5 (–4·0 to 0·9)	..
At 7 years	39 (8·5%)	58 (12·4%)	–3·9 (–8·9 to 1·2)	..
Ischaemia-driven target-vessel revascularisation	..	..	..	0·44 (0·25 to 0·77)
At 2 years	1 (0·1%)	19 (2·4%)	–2·3 (–3·4 to –1·2)	..
At 4 years	10 (1·7%)	29 (4·4%)	–2·7 (–4·6 to –0·8)	..
At 7 years	17 (4·9%)	38 (8·0%)	–3·2 (–7·4 to 1·1)	..
Hospitalisation for unstable or progressive angina	..	..	..	0·19 (0·06 to 0·54)
At 2 years	1 (0·1%)	12 (1·5%)	–1·4 (–2·3 to –0·5)	..
At 4 years	4 (0·7%)	16 (2·4%)	–1·7 (–3·0 to –0·4)	..
At 7 years	4 (0·7%)	21 (4·9%)	–4·2 (–7·2 to –1·4)	..
Death from any cause or target-vessel myocardial infarction	..	..	..	0·62 (0·38 to 1·03)
At 2 years	5 (0·6%)	15 (1·9%)	–1·3 (–2·4 to –0·2)	..
At 4 years	15 (2·4%)	23 (3·4%)	–1·0 (–2·8 to 0·9)	..
At 7 years	25 (6·2%)	39 (8·6%)	–2·4 (–6·4 to 1·6)	..
The composite of death from any cause, all myocardial infarctions, or any revascularisation	..	..	..	0·69 (0·50 to 0·95)
At 2 years	24 (3·0%)	41 (5·2%)	–2·2 (–4·1 to –0·2)	..
At 4 years	48 (7·1%)	61 (8·9%)	–1·8 (–4·7 to 1·2)	..
At 7 years	65 (14·4%)	92 (19·3%)	–4·9 (–10·8 to 1·1)	..

Estimated differences were tabulated at a prespecified timepoint of primary-outcome assessment (2 years), at median follow-up time (4 years), and at maximum follow-up time (7 years). *Hazard ratios are for preventive percutaneous coronary intervention compared with optimal medical therapy alone during the entire follow-up period, other than for the primary composite outcome at 2 years. 95% CIs have not been adjusted for multiple comparisons, and therefore these intervals should not be used to infer definitive treatment effects. †Death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina at 2 years.

Table 2: **Primary composite outcome and key secondary composite outcomes in the intention-to-treat population**

plaque, and thickened the neointima by approximately 210 µm compared with optimal medical therapy alone.[14] However, this previous trial was not powered for clinical outcomes. PREVENT has now shown that preventive percutaneous coronary intervention might reduce the 2-year and long-term risks of major cardiac events arising from vessels containing vulnerable plaques compared with optimal medical therapy alone. The risk of all adverse events (the patient-oriented composite outcome) was also reduced with preventive percutaneous coronary intervention compared with optimal medical therapy alone. Importantly, patients in both groups were treated with optimal medical therapy and stringent risk-factor control, with the achievement of low LDL concentrations. These findings suggest that the focal treatment of high-risk vulnerable plaques might

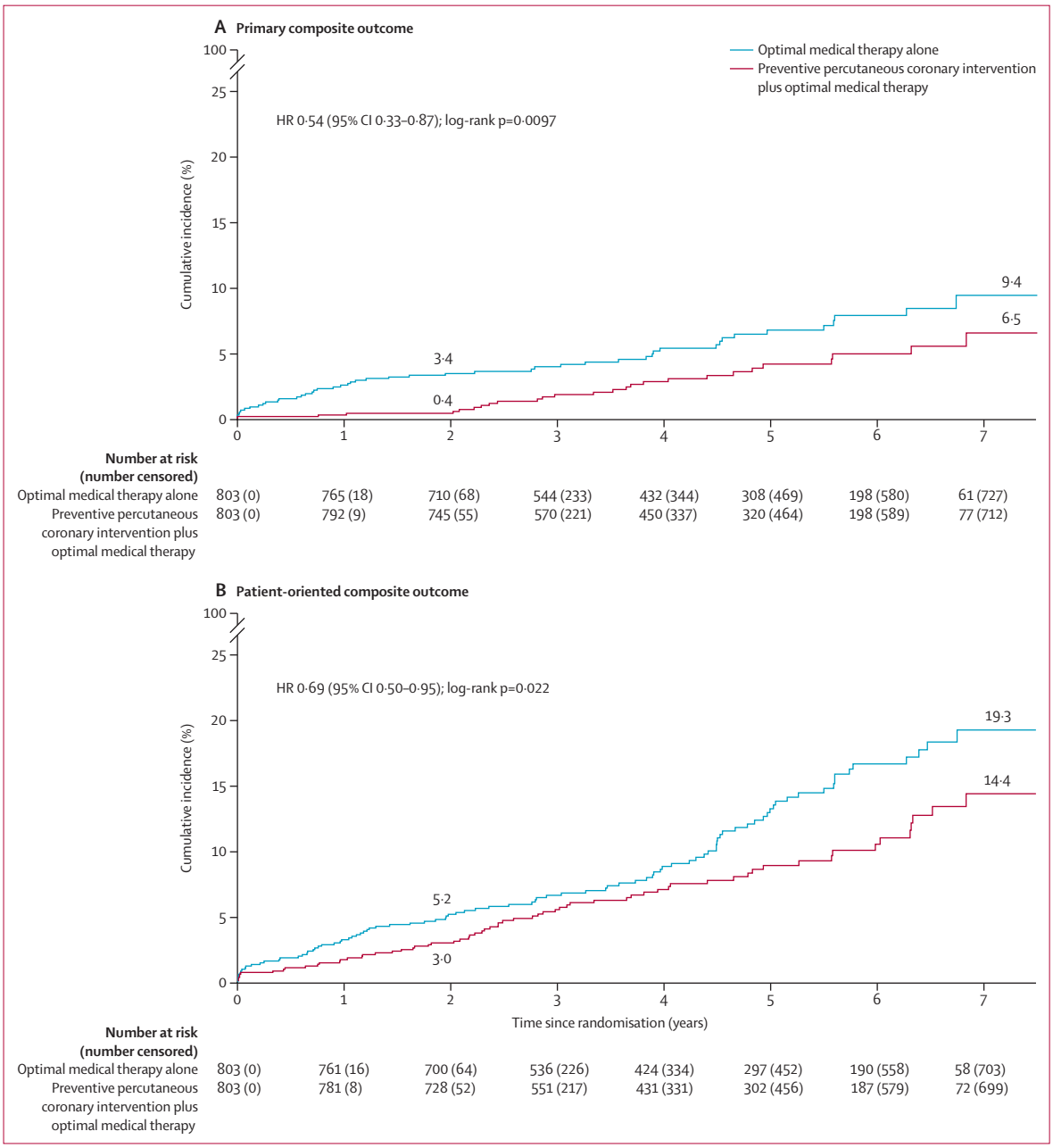


Figure 2: **Time-to-event curves for the primary composite outcome and key secondary patient-oriented composite outcome**
(A) Cumulative incidence of the primary composite outcome of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina during the entire follow-up period. (B) Cumulative incidence of the secondary patient-oriented composite outcome of death from any cause, any myocardial infarction, or any repeat revascularisation. Event rates are noted at 2 years (the time of the primary endpoint) and at 7 years (maximum follow-up). HR=hazard ratio.

improve patient prognosis beyond optimal medical therapy alone.

Previous natural history studies have shown that large plaque burden, small minimal lumen area, high lipid content, and a thin fibrous cap are all associated with future lesion-specific cardiac events, with the risk increasing with the number of adverse features present.[4–6] In this study, at least two high-risk features were required because we believed that criterion would identify lesions at sufficient long-term risk to justify focal treatment and outweigh the potential procedural risks associated with preventive percutaneous coronary intervention. Furthermore, stent or scaffold implantation was guided by intravascular imaging to minimise procedure-related complications and optimise long-term outcomes.[23] This practice might further improve the results of preventive percutaneous coronary intervention beyond medical therapy alone.

Clinical guidelines currently recommend percutaneous coronary intervention only for flow-limiting lesions or those that are responsible for acute coronary syndromes.[8–10] However, studies have shown that cardiovascular events arise from vulnerable plaques whether or not they are flow-limiting, despite optimal medical therapy.[2,3,5] In this context, the major findings from PREVENT support considerations to expand indications for percutaneous coronary intervention to non-flow-limiting, high-risk vulnerable plaques.

The primary endpoint hazard curves favouring percutaneous coronary intervention diverged through 2 years of follow-up and were thereafter parallel. Several explanations might underlie this observation. First, new vulnerable plaques might develop over time in each group and become clinically manifest, contributing events equally to both the preventive percutaneous coronary intervention group and control group. Second, bioresorbable vascular scaffolds were initially used in the trial until they were withdrawn by the manufacturer, after which metallic cobalt–chromium everolimus-eluting metallic stents were used. In the as-treated population (appendix p 52), the long-term benefit of preventive percutaneous coronary intervention appeared to be greater with cobalt–chromium everolimus-eluting metallic stents than with bioresorbable vascular scaffolds because of the higher occurrence of scaffold thrombosis and target-lesion revascularisation during late (but not early) follow-up. This might explain some of the late events beyond 2 years in the percutaneous coronary intervention group in the intention-to-treat analysis. Conversely, the hazard curves continued to spread during 7-year follow-up in patients treated with cobalt–chromium everolimus-eluting metallic stents versus medical therapy alone. However, as the selection of scaffolds versus stents was not randomly assigned, and the optimal technique for scaffold implantation evolved during the trial,[24] these results should be considered hypothesis-generating. Nevertheless, it is reassuring that the long-term outcomes after preventive percutaneous coronary intervention with cobalt–chromium everolimus-eluting metallic stents were excellent, and the differences favouring preventive percutaneous coronary intervention remained significant even during 7 years of follow-up.

	Preventive percutaneous coronary intervention plus optimal medical therapy (n=741)	Optimal medical therapy alone (n=865)
Patients without non-target-vessel preventive percutaneous coronary intervention*		
Total percutaneous coronary intervention time, min	29 (18–45)	0
Total amount of contrast media used, mL	150 (120–200)	0
Patients with non-target-vessel percutaneous coronary intervention†		
Total percutaneous coronary intervention time, min	57 (40–73)	46 (25–65)
Total amount of contrast media used, mL	250 (200–300)	200 (150–250)
Any percutaneous coronary intervention-related acute adverse events		
Total	7 (<1%)	3 (<1%)
Acute stent or scaffold thrombosis	1 (<1%)	1 (<1%)
Distal dissection of at least type B	1 (<1%)	0
Side branch occlusion	3 (<1%)	2 (<1%)
Distal embolisation	1 (<1%)	0
Coronary perforation	1 (<1%)	0
Preventive percutaneous coronary intervention-related acute adverse events		
Total	4 (<1%)‡	0
Acute stent or scaffold thrombosis	1 (<1%)	0
Distal dissection of at least type B	1 (<1%)	0
Side branch occlusion	2 (<1%)	0
Distal embolisation	1 (<1%)	0
Coronary perforation	0	0

Data are median (IQR) or n (%). *Preventive percutaneous coronary intervention group n=461; optimal medical therapy group n=569. †Preventive percutaneous coronary intervention group n=280; optimal medical therapy group n=296. ‡One patient has two events.

Table 3: **Procedural safety outcomes in the as-treated population**

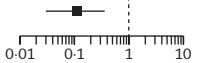
Some investigators have suggested that the presence of a vulnerable plaque might be a better biomarker of a patient at high risk than identifying a specific focal lesion at risk for future plaque rupture.[22] In addition, plaque vulnerability might be a dynamic condition—some vulnerable plaques might stabilise without events, whereas stable plaques might transition and become vulnerable later—and plaques of differing maturity frequently co-exist. Up to three-quarters of vulnerable plaques might evolve to a more stable phenotype while the patient is treated with high-intensity statin therapy,[25] putting the necessity for (and effectiveness of) focal preventive treatments targeting

vulnerable plaques into question. Nevertheless, this study showed a significant benefit of preventive percutaneous coronary intervention of vulnerable plaques beyond intensive lipid-lowering therapy. Further studies are needed to evaluate the role of preventive percutaneous coronary intervention in concert with more potent pharmacotherapies, such as PCSK9 inhibitors.

Our trial has several limitations. First, the study was open-label, introducing the risks of placebo effects and ascertainment bias. However, the fact that preventive percutaneous coronary intervention reduced the incidence of objective events, such as cardiac death and myocardial infarction, suggests the present findings are valid. Second, the observed rates of the primary outcome were substantially lower than expected in both groups, especially after preventive percutaneous coronary intervention. Several explanations might underlie this finding: (1) most patients presented with chronic coronary syndromes, and study target lesions were relatively short and had a large reference vessel diameter; (2) intravascular imaging was used to guide preventive percutaneous coronary intervention procedures, which might reduce event rates by approximately 50%, including death and myocardial infarction;[26] (3) ongoing improvements in percutaneous coronary intervention equipment and technique and medical therapy;[19,27] and (4) excellent risk-factor control, especially of LDL risk. Nonetheless, the number of randomly assigned patients was sufficient to show the benefit of preventive percutaneous coronary intervention given the risk difference observed. However, although only 50 (3%) patients were lost to follow-up within 2 years, given the low event rate, we cannot exclude

A

	Number of events/number of patients (cumulative 2-year incidence)		HR (95% CI)	$P_{interaction}$
	Preventive percutaneous coronary intervention plus optimal medical therapy	Optimal medical therapy alone		
Age (years)				
<65 years	1/408 (0·3%)	15/394 (3·9%)	0·06 (0·01–0·47)	0·44
≥65 years	2/395 (0·5%)	12/409 (3·0%)	0·17 (0·04–0·76)	
Sex				
Male	2/606 (0·3%)	17/571 (3·0%)	0·11 (0·03–0·47)	0·97
Female	1/197 (0·5%)	10/232 (4·4%)	0·11 (0·02–0·89)	
Diabetes				
Yes	0/244 (0%)	9/246 (3·7%)	NC	0·99
No	3/559 (1·2%)	18/557 (3·3%)	0·16 (0·05–0·56)	
Acute coronary syndrome				
Yes	0/133 (0%)	8/126 (6·7%)	NC	0·99
No	3/670 (0·5%)	19/677 (2·8%)	0·16 (0·05–0·53)	
Percutaneous coronary intervention of non-target vessel				
Yes	0/290 (0%)	13/286 (4·6%)	NC	0·99
No	3/513 (0·6%)	14/517 (2·8%)	0·21 (0·06–0·74)	
Median diameter stenosis by QCA				
≥55%	1/491 (0·2%)	14/316 (4·5%)	0·04 (0·01–0·34)	0·18
<55%	2/308 (0·7%)	13/484 (2·7%)	0·24 (0·05–1·07)	
Median fractional flow reserve value				
≤0·86	3/412 (0·7%)	14/395 (3·6%)	0·20 (0·06–0·71)	0·92
>0·86	0/389 (0%)	13/405 (3·3%)	NC	
Intracoronary imaging screening tools				
Grey-scale IVUS only	3/303 (1·0%)	6/261 (2·3%)	0·41 (0·10–1·66)	NA
Radiofrequency IVUS	0/506 (0%)	18/635 (2·9%)	NC	
Near-infrared spectroscopy	1/333 (0·3%)	12/346 (3·5%)	0·09 (0·01–0·66)	
OCT	1/67 (1·5%)	1/20 (5·0%)	0·30 (0·02–4·76)	
Type of stent used for preventive coronary intervention				
BVS	1/265 (0·4%)	12/281 (4·3%)	0·09 (0·01–0·67)	0·77
CoCr-EES	2/538 (0·4%)	15/522 (2·9%)	0·13 (0·03–0·55)	
Overall population	**3/803 (0·4%)**	**27/803 (3·4%)**	**0·11 (0·03–0·36)**	



Favours preventive percutaneous coronary intervention plus optimal medical therapy Favours optimal medical therapy alone

(Figure 3 continues on next page)

B

	Number of events/number of patients (incidence)		HR (95% CI)	$p_{interaction}$
	Preventive percutaneous coronary intervention plus optimal medical therapy	Optimal medical therapy alone		
Age (years)				0·62
<65 years	13/408 (3·2%)	25/394 (6·4%)	0·48 (0·25 to 0·94)	
≥65 years	13/395 (3·3%)	22/409 (5·4%)	0·61 (0·31 to 1·20)	
Sex				1·00
Male	19/606 (3·1%)	32/571 (5·6%)	0·54 (0·31 to 0·96)	
Female	7/197 (3·6%)	15/232 (6·5%)	0·53 (0·22 to 1·31)	
Diabetes				0·70
Yes	8/244 (3·3%)	13/246 (5·3%)	0·62 (0·26 to 1·50)	
No	18/559 (3·2%)	34/557 (6·1%)	0·51 (0·29 to 0·89)	
Acute coronary syndrome				0·38
Yes	4/133 (3·0%)	11/126 (8·7%)	0·33 (0·11 to 1·05)	
No	22/670 (3·3%)	36/677 (5·3%)	0·60 (0·35 to 1·01)	
Percutaneous coronary intervention of non-target vessel				0·0074
Yes	5/290 (1·7%)	24/286 (8·4%)	0·19 (0·07 to 0·51)	
No	21/513 (4·1%)	23/517 (4·4%)	0·91 (0·50 to 1·64)	
Median diameter stenosis by QCA				0·014
≥55%	11/491 (2·2%)	23/316 (7·3%)	0·28 (0·14 to 0·58)	
<55%	15/308 (4·9%)	24/484 (5·0%)	0·95 (0·50 to 1·81)	
Median fractional flow reserve value				0·77
≤0·86	16/412 (3·9%)	25/395 (6·3%)	0·59 (0·32 to 1·11)	
>0·86	10/389 (2·6%)	22/405 (5·4%)	0·46 (0·22 to 0·97)	
Intracoronary imaging screening tools				NA
Grey-scale IVUS only	10/306 (3·3%)	14/261 (5·4%)	0·50 (0·22 to 1·12)	
Radiofrequency IVUS	15/506 (3·0%)	31/635 (4·9%)	0·55 (0·29 to 1·01)	
Near-infrared spectroscopy	15/333 (4·5%)	24/346 (6·9%)	0·63 (0·33 to 1·20)	
OCT	5/67 (7·5%)	3/20 (15·0%)	0·41 (0·10 to 1·71)	
Type of stent used for preventive coronary intervention				0·018
BVS	19/265 (7·2%)	22/281 (7·8%)	0·89 (0·48 to 1·65)	
CoCr-EES	7/538 (1·3%)	25/522 (4·8%)	0·25 (0·11 to 0·59)	
Overall population	**26/803 (3·2%)**	**47/803 (5·9%)**	**0·54 (0·33 to 0·87)**	

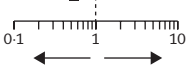


Figure 3: **Subgroup analyses of the primary composite outcome at 2-year follow-up and maximal follow-up**
(A) Subgroup analysis for the primary composite outcome (composite of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalisation for unstable or progressive angina) at 2 years. (B) Subgroup analysis for the primary composite outcome at maximal follow-up. HRs are for the preventive percutaneous coronary intervention group compared with the optimal medical therapy alone group. CIs have not been adjusted for multiplicity and should not be used to reject or not reject treatment effects. BVS=bioresorbable vascular scaffolds. CoCr-EES=cobalt–chromium everolimus-eluting metallic stents. HR=hazard ratio. NA=not available. NC=not calculated. OCT=optical coherence tomography. QCA=quantitative coronary angiography.

some effect that this missing data might have had on the primary results of the study. Third, the selection of imaging modality to assess plaque vulnerability was left to operator discretion and was not randomly assigned. In this regard, the principal determinants of a vulnerable plaque in this trial were a minimal luminal area of less than 4 mm² and a plaque burden of more than 70% as assessed by intravascular ultrasonography. Studies are needed to determine the optimal imaging technique and high-risk feature criteria for vulnerable plaque identification. Moreover, operators at all participating sites were experienced with both physiology assessment and intracoronary imaging; 1496 (89%) of 1672 operator-identified and enrolled lesions had at least two imaging-defined prespecified vulnerable plaque features as assessed by the imaging core laboratory (appendix pp 31–33). This low discrepancy rate (11%), representing potential over-treatment, is unlikely to have had a major effect on the overall results, given the excellent safety profile of contemporary drug-eluting stents, although 100% accuracy should be the objective. However, a potential generalisability issue is that use of intracoronary

imaging for vulnerable plaque detection is not yet a global standard, so operators not accustomed to the use of intracoronary imaging for real-time vulnerable plaque detection would need a brief period of dedicated training before adoption of this technique. Fourth, 74 (9%) of 803 patients in the treatment group did not undergo preventive PCI, and PCI was performed in 12 (1%) of 803 patients in the optimal medical therapy group. However, outcomes in the as-treated and per-protocol populations were consistent with those from the intention-to-treat analysis. Fifth, subgroup interaction testing suggests that the long-term outcomes of preventive percutaneous coronary intervention for the primary endpoint might be better in patients with a median site-assessed target lesion diameter stenosis of more than 55%, those who had a percutaneous coronary intervention of a non-target vessel, and with use of cobalt–chromium everolimus-eluting metallic stents rather than bioresorbable vascular scaffolds. However, these subgroup observations were not present at 2 years (the timing of the primary endpoint) and were not adjusted for more than 20 multiple comparisons, and should therefore be considered hypothesis-generating only. Sixth, the present study did not collect data to examine the cost-effectiveness of a preventive percutaneous coronary intervention strategy. Seventh, dual antiplatelet therapy use was greater in the preventive percutaneous coronary intervention group than in the optimal medical therapy group. Prolonged dual antiplatelet therapy beyond 6 months has not been shown to be beneficial after percutaneous coronary intervention in troponin-negative acute or chronic coronary syndromes[10,28] (representing the vast majority of patients enrolled in this trial), and is thus unlikely to have contributed to the differences between groups. In addition, although no cases of acute vessel closure or identifiable plaque disruption caused by intracoronary imaging occurred, we cannot exclude the possibility that intracoronary imaging in the control group might have resulted in endothelial denudation and late events in some patients. However, such events might also occur after instrumentation of untreated atherosclerotic segments in the preventive percutaneous coronary intervention group. Eighth, we only enrolled patients with imaging-detected vulnerable plaques that had a site-assessed visual angiographic diameter stenosis of 50% or more and were fractional flow reserve-negative. The present trial does not inform the outcomes of preventive percutaneous coronary intervention in vulnerable plaques with a site-assessed visual angiographic diameter stenosis of less than 50%. However, the mean core laboratory-assessed diameter stenosis of plaques that cause future events has been reported to be approximately 47%,[5] correlating with a site-assessed diameter stenosis of approximately 55–60% (as sites routinely over-estimate lesion severity compared with core laboratory reads). Thus, it is likely that participating operators identified most lesions to treat that were likely to cause cardiovascular events in the intermediate term, as further evidenced by the fact that the 2-year target vessel failure rate was only 0·4% in the preventive percutaneous coronary intervention group. Finally, the study population was enrolled only from South Korea, Japan, Taiwan, and New Zealand, and only 27% of patients were women, which might limit the generalisability of the trial. Ongoing trials of preventive percutaneous coronary intervention of vulnerable plaques are being performed in different geographies (eg, NCT05333068, NCT05027984, NCT05669222, and NCT05599061), and are necessary to confirm or refute our findings. In addition, most patients in this trial presented with chronic coronary syndromes. Vulnerable plaques might be more frequent and biologically more active in patients with troponin-positive acute coronary syndromes. Ongoing studies are also addressing the role of preventive percutaneous coronary intervention in patients presenting with recent myocardial infarction (eg, NCT05027984, NCT05669222, and NCT05599061).

In conclusion, in the PREVENT trial of patients with non-flow-limiting vulnerable plaques, preventive percutaneous coronary intervention plus optimal medical therapy resulted in a lower incidence of major adverse cardiac events during long-term follow-up, compared with optimal medical therapy alone. Our key findings might provide novel insights on the potential effect of preventive percutaneous coronary intervention on non-flow-limiting high-risk vulnerable plaques.

Contributors

S-JP, J-MA, D-YK, GWS, and D-WP conceived and designed the study. S-JP, J-MA, and D-WP obtained research funding. S-JP, J-MA, D-YK, S-CY, Y-KA, W-JK, C-WN, J-OJ, I-HC, HS, H-LK, J-YH, S-HH, B-KL, THA, K-YC, JKC, DS, and D-WP acquired the data. S-JP, J-MA, D-YK, S-CY, GWS, and D-WP analysed and interpretated the data. S-CY did the statistical analysis. S-JP, J-MA, D-YK, S-CY, Y-KA, W-JK, C-WN, J-OJ, I-HC, HS, H-LK, J-YH, S-HH, B-KL, THA, K-YC, JKC, DS, and D-WP provided administrative, technical, or logistical support. S-JP, J-MA, D-YK, GWS, and D-WP drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content and approved the final version for submission. S-JP, J-MA, D-YK, and D-WP accessed and verified the data. All authors had access to all the included data in the study. All authors had final responsibility for the decision to submit to publication. All authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The principal investigator had unrestricted access to the data, maintained the database, and prepared the first draft of the manuscript.

Declaration of interests

S-JP reports research grants and speaker fees from Abbott Vascular, Medtronic, Daiichi-Sankyo, ChongKunDang Pharm, Daewoong Pharm, and Edwards. D-YK reports speaker fees from Abbott Vascular, Daiichi-Sankyo, Viatris, Boryoung, and Daewoong Pharm. Y-KA reports research grants from Boston Scientific, Medtronic, Abbott, and DioMedical. C-WN reports a research grant from Abbott. J-OJ reports speaker fees from Medtronic. HS reports speaker fees from Abbott Vascular and Boston Scientific. H-LK reports grants and speaker fees from Abbott Vascular and Boston Scientific. J-YH reports research grants and speaker fees from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. K-YC reports research grant from Biotronik and Medtronik. GSM reports honoraria from Boston Scientific, Abbott, SpectraWave, and Gentuity. GWS reports speaker fees from Medtronic, Pulnovo, Infraredx, Abiomed, Abbott, Amgen, and Boehringer Ingelheim; consultant fees from Daiichi Sankyo, Ablative Solutions, CorFlow, Apollo

Therapeutics, Cardiomech, Gore, Robocath, Miracor, Vectorious, Abiomed, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Elucid Bio, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, and Oxitope; equity or stock options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; and grants from Abbott, Abiomed, Bioventrix, Cardiovascular Systems, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave outside the submitted work; and GWS's daughter is an employee at IQVIA. D-WP reports research grants and speaker fees from Abbott Vascular, Medtronic, Daiichi-Sankyo, Edwards Lifescience, ChongKunDang Pharm, and Daewoong Pharm. All other authors declare no competing interests relevant to the contents of this paper.

Data sharing

De-identified individual participant data will be shared to investigators whose proposed use of the data has been approved by the trial leadership committee. Any relevant inquiries for the data sharing should be sent to the corresponding author via email.

Acknowledgments

This study was funded by the CardioVascular Research Foundation, Abbott, Yuhan Corp, CAH-Cordis, Philips, and Infraredx, a Nipro company. We thank the staff members of the PREVENT trial, the other members of the cardiac catheterisation laboratories at the participating centres, and the study coordinators for their efforts to collect clinical data and to ensure their accuracy and completeness.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims made in published text and institutional affiliations.

References

1 Gaba P, Gersh BJ, Muller J, Narula J, Stone GW. Evolving concepts of the vulnerable atherosclerotic plaque and the vulnerable patient: implications for patient care and future research. *Nat Rev Cardiol* 2023; **20:** 181–96.

2 Kedhi E, Berta B, Roleder T, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J* 2021; **42:** 4671–79.

3 Mol JQ, Volleberg RHJA, Belkacemi A, et al. Fractional flow reserve-negative high-risk plaques and clinical outcomes after myocardial infarction. *JAMA Cardiol* 2023; **8:** 1013–21.

4 Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364:** 226–35.

5 Erlinge D, Maehara A, Ben-Yehuda O, et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet* 2021; **397:** 985–95.

6 Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020; **41:** 383–91.

7 Gallone G, Bellettini M, Gatti M, et al. Coronary plaque characteristics associated with major adverse cardiovascular events in atherosclerotic patients and lesions: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2023; **16:** 1584–604.

8 Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019; **40:** 87–165.

9 Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022; **145:** e18–114.

10 Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2023; **148:** e9–119.

11 Rodés-Cabau J, Bertrand OF, Larose E, et al. Comparison of plaque sealing with paclitaxel-eluting stents versus medical therapy for the treatment of moderate nonsignificant saphenous vein graft lesions: the moderate vein graft lesion stenting with the taxus stent and intravascular ultrasound (VELETI) pilot trial. *Circulation* 2009; **120:** 1978–86.

12 Wykrzykowska JJ, Diletti R, Gutierrez-Chico JL, et al. Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield evaluated at cardiac hospital in Rotterdam for investigation and treatment of TCFA (SECRITT). *EuroIntervention* 2012; **8:** 945–54.

13 Mol JQ, Bom MJ, Damman P, Knaapen P, van Royen N. Pre-emptive OCT-guided angioplasty of vulnerable intermediate coronary lesions: results from the prematurely halted PECTUS-trial. *J Interv Cardiol* 2020; **2020:** 8821525.

14 Stone GW, Maehara A, Ali ZA, et al. Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J Am Coll Cardiol* 2020; **76:** 2289–301.

15 Ahn JM, Kang DY, Lee PH, et al. Preventive PCI or medical therapy alone for vulnerable atherosclerotic coronary plaque: rationale and design of the randomized, controlled PREVENT trial. *Am Heart J* 2023; **264:** 83–96.

16 Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2014; **130:** 1749–67.

17 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; **139:** e1082–143.

18 Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020; **41:** 407–77.

19 Park DW, Kang DY, Ahn JM, et al. Routine functional testing or standard care in high-risk patients after PCI. *N Engl J Med* 2022; **387:** 905–15.

20 Cheng JM, Garcia-Garcia HM, de Boer SP, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. *Eur Heart J* 2014; **35:** 639–47.

21 Com-Nougue C, Rodary C, Patte C. How to establish equivalence when data are censored: a randomized trial of treatments for B non-Hodgkin lymphoma. *Stat Med* 1993; **12:** 1353–64.

22 Tomaniak M, Katagiri Y, Modolo R, et al. Vulnerable plaques and patients: state-of-the-art. *Eur Heart J* 2020; **41:** 2997–3004.

23 Lee JM, Choi KH, Song YB, et al. Intravascular imaging-guided or angiography-guided complex PCI. *N Engl J Med* 2023; **388:** 1668–79.

24 Stone GW, Abizaid A, Onuma Y, et al. Effect of technique on outcomes following bioresorbable vascular scaffold implantation: analysis from the ABSORB trials. *J Am Coll Cardiol* 2017; **70:** 2863–74.

25 Räber L, Koskinas KC, Yamaji K, et al. Changes in coronary plaque composition in patients with acute myocardial infarction treated with high-intensity statin therapy (IBIS-4): a serial optical coherence tomography study. *JACC Cardiovasc Imaging* 2019; **12:** 1518–28.

26 Stone GW, Christiansen EH, Ali ZA, et al. Intravascular imaging-guided coronary drug-eluting stent implantation: an updated network meta-analysis. *Lancet* 2024; **403:** 824–37..

27 Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020; **382:** 1395–407.

28 Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018; **39:** 213–60.