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CLINICAL RESEARCH
Interventional cardiology

Preventive percutaneous coronary intervention for non-flow-limiting vulnerable atherosclerotic coronary plaques in diabetes: the PREVENT trial

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Abstract

Background and Aims The efficacy and safety of preventive percutaneous coronary intervention (PCI) for treating vulnerable plaques in diabetic patients remain unclear.

Methods The PREVENT (Preventive Coronary Intervention on Stenosis with Functionally Insignificant Vulnerable Plaque) trial was a randomized clinical trial that compared preventive PCI plus optimal medical therapy with optimal medical therapy alone in patients with non-flow-limiting (fractional flow reserve >0.80) vulnerable plaques identified via intracoronary imaging. Randomization was stratified by diabetes status. The primary endpoint was a composite of cardiac death, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalization for unstable or progressive angina at 2 years.

Results Among 1606 randomized patients, 490 (30.5%) had diabetes. Diabetic patients underwent PCI for non-target lesions before randomization more frequently than non-diabetics (40.6% vs. 33.8%, $P = .009$). There were no significant differences in the incidence of the primary endpoint between diabetic and non-diabetic patients [1.8% vs. 1.9%; hazard ratio 0.98; 95% confidence interval 0.45–2.14); $P = .956$]. However, the primary endpoint at 2 years was less frequent with preventive PCI compared with optimal medical therapy alone in both diabetic (0% vs. 3.7%; $P = .004$) and non-diabetic patients (0.5% vs. 3.2%; hazard ratio 0.16; 95% confidence interval 0.05–0.55; $P = .004$), without a significant interaction between diabetic status and randomized strategy.

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Conclusions The risk of adverse clinical events was similar between diabetic and non-diabetic patients with non-flow-limiting vulnerable coronary plaques. However, preventive PCI was associated with a lower incidence of the primary endpoint at 2 years, regardless of diabetes status.

Structured Graphical Abstract

Key Question

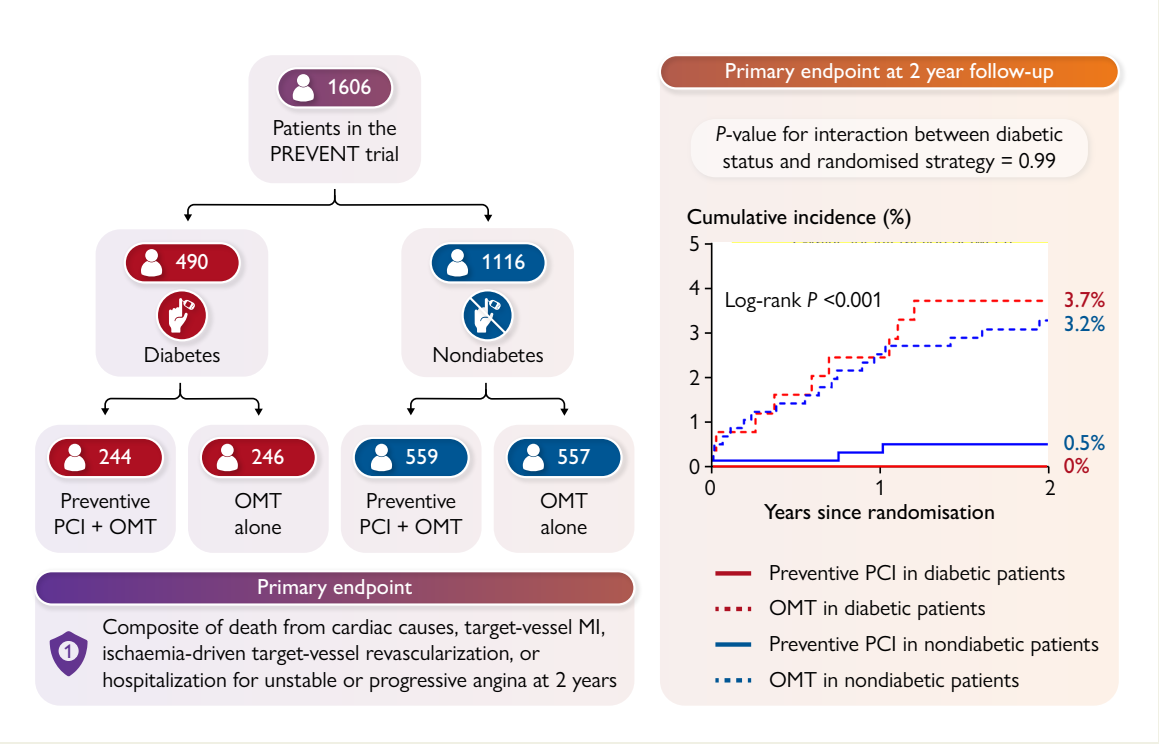
Is preventive percutaneous coronary intervention (PCI) effective for treating non-flow-limiting vulnerable coronary plaques compared to optimal medical treatment (OMT) alone in diabetic patients?

Key Finding

In this prespecified post hoc analysis of the PREVENT trial, there were no significant differences in the incidence of the primary endpoint between diabetic and nondiabetic patients. At 2-year follow up, the primary endpoint was less frequent with preventive PCI compared to OMT alone in both diabetic and nondiabetic patients.

Take Home Message

These finding support preventive PCI irrespective of diabetes status, in patients with non-flow-limiting vulnerable coronary plaques.



Keywords Diabetes mellitus • Percutaneous coronary intervention • Vulnerable coronary plaques • Fractional flow reserve

Introduction

Diabetes mellitus is a major risk factor for ischaemic heart disease, and adverse cardiovascular events, such as acute coronary syndrome (ACS), represent a leading cause of mortality among patients with diabetes.[1–3] Compared with non-diabetic patients, individuals with diabetes exhibit more complex coronary artery disease and a higher prevalence of vulnerable coronary plaques.[4–7] Vulnerable plaques, characterized by a large lipid core and a thin fibrous cap, serve as precursors to plaque rupture and thrombosis formation, which are the most common causes of ACS and sudden cardiac death.[8,9] However, many vulnerable plaques are non-flow-limiting (non-ischaemic), and current clinical guidelines recommend revascularization only for flow-limiting coronary lesions.[10–13] Despite the higher prevalence of vulnerable plaques in diabetic patients compared with non-diabetic individuals, the effectiveness and safety of preventive percutaneous coronary intervention (PCI) for non-flow-limiting vulnerable plaques in diabetic patients remain uncertain. Although one small randomized controlled trial demonstrated that preventive PCI could effectively enlarge lumen size in mild coronary lesions with large plaque burden

compared with optimal medical therapy (OMT), the study did not specifically evaluate diabetic patients.[14]

Given the pivotal role of vulnerable plaques in the occurrence of adverse cardiac events in diabetic patients, even in the absence of flow limitation, establishing an optimal treatment strategy for non-flow-limiting vulnerable plaques in this population is critical.[11,15–18] To address this gap, we analysed data from the Preventive Coronary Intervention on Stenosis with Functionally Insignificant Vulnerable Plaque (PREVENT) trial, a randomized clinical trial that compared preventive PCI plus OMT vs. OMT alone in patients with non-flow-limiting vulnerable plaques.[19] Randomization in the PREVENT trial was stratified based on the presence of diabetes. This study evaluated clinical outcomes of preventive PCI combined with OMT vs. OMT alone in patients with and without diabetes.

Methods

Study design and patients

The PREVENT trial was an investigator-initiated, multicentre, open-label, randomized controlled trial conducted at 15 hospitals across four countries (South Korea, Japan, Taiwan, and New Zealand) between September 2015 and September 2021. The trial design and primary results have previously been published.[19,20] In total, 1606 patients with non-flow-limiting vulnerable plaques were randomly assigned in a 1:1 ratio to receive preventive PCI plus OMT ($n = 803$) or OMT alone ($n = 803$).

Eligible patients had coronary lesions meeting all of the following criteria: angiographic diameter stenosis ≥50% by visual estimation, non-flow limitation with fractional flow reserve (FFR) > 0.80, and vulnerable plaques identified by intracoronary imaging, and all lesions with flow limitation (FFR ≤ 0.80). Lesions causing ACS were treated with PCI using drug-eluting stents prior to randomization. Vulnerable plaques were defined as lesions exhibiting at least two of the following characteristics: minimal lumen area (MLA) ≤ 4.0 mm^2 assessed by intravascular ultrasound (IVUS) or optical coherence tomography (OCT), plaque burden ≥70% by IVUS, lipid-rich plaques identified by near-infrared spectroscopy (NIRS) with a maximum lipid core burden index within any 4 mm pullback length ($maxLCBI_{4\ mm}$) > 315, and thin-cap fibroatheroma (TCFA) detected via radiofrequency IVUS (RF-IVUS) or OCT defined as either ≥10% confluent necrotic core with >30° abutting the lumen in three consecutive frames in RF-IVUS or as lipid plaques with an arc >90° and fibrous cap thickness <65 μm in OCT. The key exclusion criteria were previous coronary artery bypass grafting, in-stent restenosis lesions, ≥3 target lesions, two target lesions in the same coronary artery, heavily calcified or angulated lesions, or bifurcation lesions requiring a two-stent technique.

Randomization was stratified based on the presence of diabetes and concurrent PCI in non-study target vessels. Percutaneous coronary intervention was permitted in vessels containing lesions that did not meet criteria for vulnerable plaques (non-target vessels). Percutaneous coronary intervention of these non-target lesions had to be performed and be successful before randomization of the vulnerable plaque lesions in the target vessels. For this pre-specified subgroup analysis, clinical outcomes were compared between preventive PCI with OMT and OMT alone in patients with and without diabetes.

Trial procedures

Detailed trial procedures have previously been described.[20] For patients randomized to the preventive PCI group, bioresorbable vascular scaffolds (BVS; Absorb, Abbott Vascular) or durable polymer-coated everolimus-eluting stents (EES; Xience, Abbott Vascular) were used to treat vulnerable target lesions. Following the market withdrawal of BVS during the enrolment period, metallic EES became the default PCI device starting in September 2017. Intravascular imaging guidance was employed for all target lesion PCI procedures. After PCI, patients received dual antiplatelet therapy for 6–12 months based on clinical presentation and anatomical complexity. Optimal medical therapy in both groups included lifestyle modifications and pharmacological treatments as recommended by current guidelines.[21–23]

Clinical follow-up visits were conducted 1, 6, 12, and 24 months after randomization and annually, thereafter. Follow-up continued until the last enrolled patient completed a 2-year follow-up after randomization. Vital status was cross-referenced with the Korean National Health Insurance database.[19]

Study endpoints

The study endpoints have previously been described in detail.[20] The primary endpoint was a composite of cardiac death, target-vessel myocardial infarction (MI), ischaemia-driven target-vessel revascularisation (TVR), or hospitalization for unstable or progressive angina at 2 years post-randomization. The secondary endpoints were individual components of the primary composite endpoint, all-cause mortality, non-cardiac mortality, all MIs and non-target-vessel MIs, any revascularisation and non-TVR, definite stent or scaffold thrombosis, stroke, major bleeding events, composite outcomes of all-cause mortality or target-vessel MI, and patient-oriented composite outcomes of all-cause mortality, all MI, or any repeat revascularisation.

Follow-up data were obtained through patient visits or telephone interviews with patients or their family members. All study outcomes were adjudicated independently by a clinical events committee blinded to group assignments.

Statistical analysis

Continuous variables are presented as means ± standard deviation or medians (inter-quartile range), as appropriate. The Kolmogorov–Smirnov test was used to assess normality. Normally distributed variables were compared using an unpaired *t*-test, whereas non-normally distributed variables were compared using the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 or Fisher's exact test and are presented as counts (percentages). Time-to-event outcomes were analysed using Kaplan–Meier curves, and treatment effects were assessed using Cox proportional hazard regression models. Results are reported as hazard ratios (HRs) with 95% confidence interval (CI). Additional analysis was performed for comparison between preventive PCI and OMT with the use of the methods of Fine and Gray to adjust for the potential competing risk of death from non-cardiac causes. The proportional hazards assumption was verified using Schoenfeld residuals and was satisfied for all study endpoints. Interactions between treatment groups and diabetes status were tested using a formal interaction test.

All analyses were two-tailed, with statistical significance set at $P < .05$ without adjustment for multiple comparisons. Study endpoints were analysed on an intention-to-treat basis. Statistical analyses were performed using SPSS software version 27 (IBM Corp., Armonk, NY, USA).

Results

Study population and baseline characteristics

Among the 1606 patients enrolled in the PREVENT trial, 490 (30.5%) had diabetes. Within this subgroup, 244 patients (49.8%) and 246 (50.2%) were randomized to the preventive PCI and OMT groups, respectively. In the non-diabetic cohort ($n = 1116$), 559 (50.1%) were assigned to the preventive PCI group and 557 (49.9%) to the OMT group (*Figure 1*).

Baseline characteristics were balanced between treatment groups in both diabetic and non-diabetic cohorts due to stratified randomization (*Table 1*). The mean baseline glycated haemoglobin (HbA1c) level in the diabetic cohort was 7.1% in the preventive PCI group and 7.4% in the OMT group ($P = .074$). A comparison of baseline characteristics

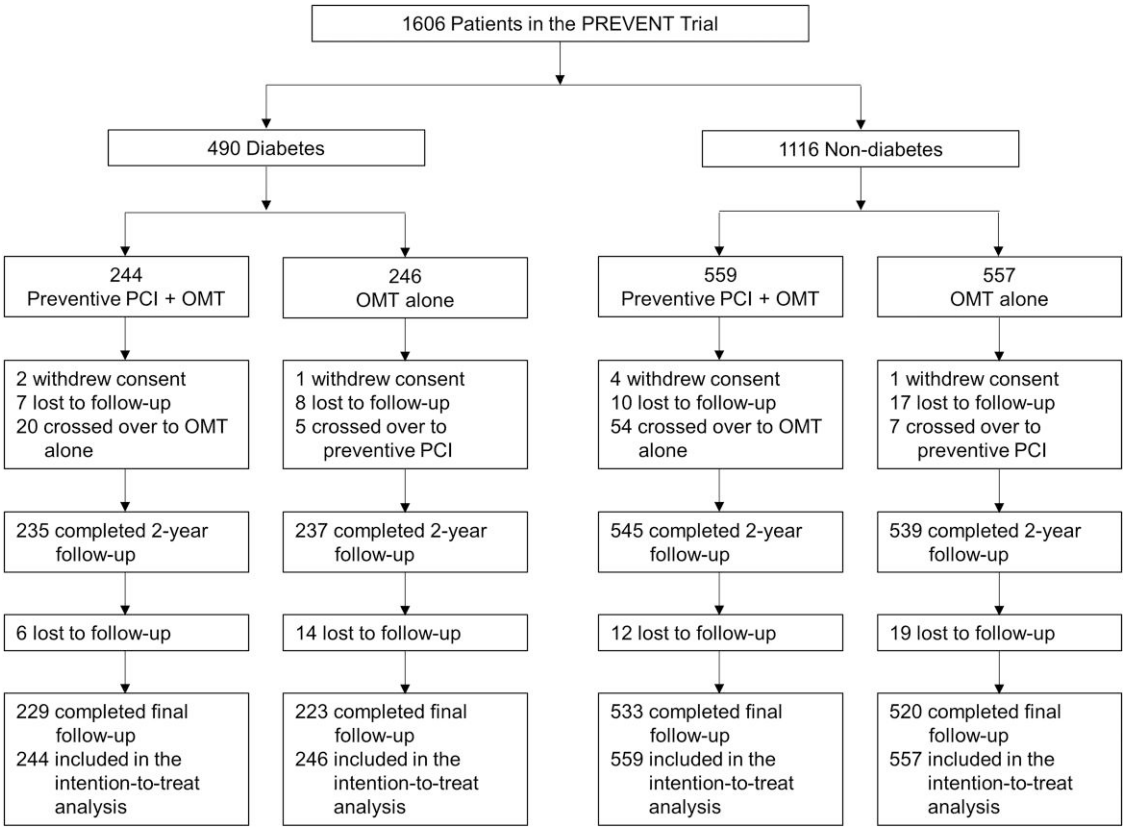


Figure 1 Study flow. OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PREVENT, Preventive Coronary Intervention on Stenosis with Functionally Insignificant Vulnerable Plaque

between diabetic and non-diabetic cohorts is presented in Supplementary data online, *Table S1*. Among the diabetic patients, 37 (7.6%) required insulin. Compared with non-diabetic patients, diabetic patients had higher rates of hypertension and chronic renal insufficiency. Key intracoronary imaging criteria for vulnerable target lesions were evenly distributed between treatment arms. Diabetic patients were more likely to undergo PCI for non-target lesions before randomization than non-diabetic patients (40.6% vs. 33.8%, $P = .009$).

Angiographic and intracoronary imaging analysis of target lesions

Baseline angiographic and intracoronary imaging analyses of vulnerable target lesions were comparable between treatment arms in both diabetic and non-diabetic patients (*Table 2*). Thin-cap fibroatheromas were detected via RF-IVUS or OCT in 12.0% of the preventive PCI group and 11.2% of the OMT group in diabetic patients ($P = .827$), and in 14.4% and 14.6%, respectively, in non-diabetic patients ($P = .944$). The number of high-risk plaque features was similarly distributed across treatment arms in both cohorts.

When comparing diabetic and non-diabetic patients (see Supplementary data online, *Table S2*), diabetic patients exhibited smaller reference vessel diameters, longer lesion lengths, larger plaque burdens, and greater dense calcium volumes. However, the incidence of TCFAs and the distribution of high-risk plaque features were similar between the two groups.

Study outcomes

Of the 1606 enrolled patients, 1556 (96.9%) completed the 2-year follow-up, including 472 diabetic patients (96.3%) and 1084 non-diabetic patients (97.1%). Final follow-up data were obtained for 1505 patients (93.7%) (*Figure 1*). The median follow-up duration was 4.3 years, with a maximum of 7.9 years.

Table 3 summarizes the primary and secondary outcomes across treatment arms in diabetic and non-diabetic cohorts. At 2 years, the incidence of the primary endpoint was significantly lower in the preventive PCI group than in the OMT group for both diabetic patients (0% vs. 3.7%, log-rank $P = .003$) (*Figure 2*) and non-diabetic patients (0.5% vs. 3.2%; HR 0.16; 95% CI 0.05–0.55; log-rank $P < .001$) (*Figure 3*). There was no significant interaction between diabetic status and treatment strategy for the primary endpoint at 2 years and maximal follow-up ($P = .990$ and $P = .338$, respectively) (*Structured Graphical Abstract*). In both diabetic and non-diabetic patients, the reduction in the primary endpoint with preventive PCI was primarily driven by lower rates of ischaemia-driven TVR and hospitalizations for unstable or progressive angina (see Supplementary data online, *Figures S1* and *S2*). There were no significant interactions between diabetic status and treatment strategy for secondary endpoints (*Table 3*). Although 2-year incidence of patient-oriented composite outcome was significantly lower with preventive PCI compared with OMT alone in only diabetic patients (*Figs 2* and *3*), there was also no interaction between diabetic status and randomized strategy ($P = .179$) (*Table 3*). In the analysis of primary and secondary outcomes adjusted for the competing risk of death from

Table 1 Baseline characteristics according to diabetes status and randomization group

Characteristic	Diabetes			Non-diabetes		
	Preventive PCI ($n = 244$) (251 lesions)	OMT ($n = 246$) (255 lesions)	*P*-value	Preventive PCI ($n = 559$) (580 lesions)	OMT ($n = 557$) (586 lesions)	*P*-value
Age—years, median (IQR)	65 (59–71)	66 (60–71)	.227	64 (57–71)	64 (58–70)	.887
Male sex—no. (%)	181 (74.2)	174 (70.7)	.393	425 (76.0)	397 (71.3)	.071
Body mass index—kg/m^2, median (IQR)	24.3 (22.9–26.8)	25.1 (23.2–27.0)	.059	24.8 (22.9–26.5)	24.5 (22.8–26.2)	.302
Medical history—no. (%)						
Diabetes requiring insulin	16 (6.6)	21 (8.5)	.407			
Hypertension	183 (75.0)	194 (78.9)	.310	336 (60.1)	342 (61.4)	.658
Hyperlipidaemia	223 (91.4)	223 (90.7)	.774	498 (89.1)	486 (87.3)	.343
Current smoker	43 (17.6)	44 (17.9)	.939	93 (16.6)	95 (17.1)	.852
Familial history of premature coronary artery disease	26 (10.7)	21 (8.5)	.426	69 (12.3)	59 (10.6)	.359
Previous myocardial infarction	12 (4.9)	10 (4.1)	.648	35 (6.3)	31 (5.6)	.622
Previous PCI	41 (16.8)	29 (11.8)	.113	68 (12.2)	56 (10.1)	.262
History of cerebrovascular disease	16 (6.6)	20 (8.1)	.505	36 (6.4)	30 (5.4)	.455
History of peripheral artery disease	9 (3.7)	8 (3.3)	.792	12 (2.1)	12 (2.2)	.993
Atrial fibrillation or atrial flutter	5 (2.0)	0 (0)	.030	10 (1.8)	7 (1.3)	.468
Chronic renal insufficiency[a]	4 (1.6)	10 (4.1)	.173	5 (0.9)	0 (0)	.025
Clinical presentation—no. (%)			.508			.410
Stable angina or silent ischaemia	199 (81.6)	208 (84.6)		471 (84.3)	469 (84.2)	
Unstable angina	38 (15.6)	28 (11.4)		68 (12.2)	63 (11.3)	
Non-ST-elevation myocardial infarction	6 (2.5)	8 (3.3)		12 (2.1)	20 (3.6)	
ST-elevation myocardial infarction	1 (0.4)	2 (0.8)		8 (1.4)	5 (0.9)	
Left ventricular ejection fraction—%, median (IQR)[b]	62 (60–65)	64 (61–67)	.032	63 (59–66)	63 (60–66)	.289
Serum cholesterol—mg/dL, mean ± SD						
Total cholesterol[c]	140 ± 38	140 ± 38	.955	152 ± 40	160 ± 39	.001
LDL cholesterol[d]	82 ± 31	83 ± 32	.781	90 ± 35	98 ± 34	<.001
HDL cholesterol[e]	44 ± 12	44 ± 10	.875	47 ± 12	48 ± 13	.304
Triglyceride—mg/dL, mean ± SD[f]	149 ± 172	140 ± 91	.470	132 ± 80	139 ± 103	.279
High-sensitivity C-reactive protein—mg/dL, mean ± SD[g]	0.2 ± 0.5	0.5 ± 2.9	.249	0.6 ± 3.3	0.5 ± 3.1	.682

Continued

Table 1 *Continued*

Characteristic	Diabetes			Non-diabetes		
	Preventive PCI (*n* = 244) (251 lesions)	OMT (*n* = 246) (255 lesions)	*P*-value	Preventive PCI (*n* = 559) (580 lesions)	OMT (*n* = 557) (586 lesions)	*P*-value
HbA1c—%, mean ± SD[h]	7.1 ± 1.0	7.4 ± 1.4	.074	5.8 ± 0.4	5.8 ± 0.5	.797
Number of diseased epicardial coronary arteries—no. (%)			.110			.178
One vessel	102 (41.8)	82 (33.3)		225 (40.3)	248 (44.5)	
Two vessels	93 (38.1)	100 (40.7)		209 (37.4)	207 (37.2)	
Three vessels	49 (20.1)	64 (26.0)		125 (22.4)	102 (18.3)	
Number of target lesions per patient—median (IQR)	1 (1–1)	1 (1–1)	.623	1 (1–1)	1 (1–1)	.242
Qualifying criteria for target lesions—no. (%)						
Minimal luminal area <4.0 mm^2 by Gray-scale IVUS or OCT	236/248 (95.2)	242/253 (95.7)	.793	546/563 (97.0)	552/577 (95.7)	.239
Plaque burden >70% by Gray-scale IVUS	225/248 (90.7)	236/253 (93.3)	.291	495/563 (87.9)	518/577 (89.8)	.320
Large lipid-rich plaque by NIRS ($maxLCBI_{4\ mm}$ > 315)	41/95 (43.2)	40/109 (36.7)	.347	103/253 (40.7)	98/260 (37.7)	.484
Thin-cap fibroatheroma defined by OCT or radiofrequency IVUS	17/142 (12.0)	19/170 (11.2)	.827	51/353 (14.4)	61/417 (14.6)	.944
Target lesion location—no. (%)			.544			.054
Left anterior descending artery	122/251 (48.6)	114/255 (44.7)		294/580 (50.7)	186/586 (48.8)	
Left circumflex artery	48/251 (19.1)	47/255 (18.4)		122/580 (21.0)	100/586 (17.1)	
Right coronary artery	81/251 (32.3)	94/255 (36.9)		164/580 (28.3)	200/586 (34.1)	
Median FFR values of target lesions—median (IQR)	0.87 (0.84–0.91)	0.85 (0.83–0.90)	.009	0.86 (0.83–0.90)	0.86 (0.83–0.91)	.723
Quantitative coronary angiography of target lesions						
Diameter stenosis—%, mean ± SD	56.5 ± 9.7	51.9 ± 9.4	<.001	56.6 ± 8.8	52.6 ± 9.9	<.001
Minimal lumen diameter—mm, mean ± SD	1.3 ± 0.3	1.5 ± 0.4	<.001	1.3 ± 0.3	1.5 ± 0.4	<.001
Reference vessel diameter—mm, mean ± SD	2.9 ± 0.4	2.9 ± 0.5	.916	3.0 ± 0.4	3.1 ± 0.5	.085
Lesion length—mm, mean ± SD	23.5 ± 8.0	20.0 ± 9.1	<.001	23.6 ± 8.7	18.9 ± 7.9	<.001
Any PCI of target lesion, per patient—no. (%)[i]	224 (91.8)	5 (2.0)	<.001	505 (90.3)	7 (1.3)	<.001
Drug-eluting stent implantation—no. (%)	158/224 (70.5)	3/5 (60.0)	.610	333/505 (65.9)	4/7 (57.1)	.626
Bioabsorbable scaffold implantation—no. (%)	66/224 (29.5)	2/5 (40.0)	.610	171/505 (33.9)	3/7 (42.9)	.618
Number of stents or scaffolds implanted—median (IQR)	1 (1–1)	0 (0–0)	<.001	1 (1–1)	0 (0–0)	<.001
Stent or scaffold diameter—mm, median (IQR)	3.5 (3.0–3.5)	3.3 (3.0–3.5)	.634	3.5 (3.0–3.5)	3.3 (3.0–3.5)	.697
Total stent or scaffold length—mm, median (IQR)	23 (18–28)	23 (15–28)	.330	23 (18–28)	23 (18–30)	.997

Continued

Table 1 *Continued*

Characteristic	Diabetes			Non-diabetes		
	Preventive PCI ($n = 244$) (251 lesions)	OMT ($n = 246$) (255 lesions)	*P*-value	Preventive PCI ($n = 559$) (580 lesions)	OMT ($n = 557$) (586 lesions)	*P*-value
Intravascular imaging used to optimise—no. (%)	224/224 (100)	5/5 (100)				
Any PCI of non-target lesions, per patient—no. (%)	94 (38.5)	105 (42.7)	.349	196 (35.1)	181 (32.5)	.365
Number of lesions treated—median (IQR)	0 (0–1)	0 (0–1)	.491	0 (0–1)	0 (0–1)	.263
Number of stents implanted—median (IQR)	0 (0–1)	0 (0–1)	.291	0 (0–1)	0 (0–1)	.432
Stent diameter—mm, median (IQR)	3.1 (3.0–3.5)	3.3 (3.0–3.5)	.450	3.3 (3.0–3.5)	3.3 (3.0–3.5)	.992
Total stent length—mm, median (IQR)	38 (23–55)	38 (28–61)	.383	38 (23–51)	38 (28–51)	.912

FFR, fractional flow reserve; IVUS, intravascular ultrasound; HDL, high-density lipoprotein; IQR, inter-quartile range; LDL, low-density lipoprotein; $maxLCBI_{4\ mm}$, maximal lipid core burden in a 4 mm segment; NIRS, near-infrared spectroscopy; OCT, optical coherence tomography; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

[a]Defined as serum creatinine ≥2.0 mg/dL or dependence on chronic haemodialysis.

[b]Preventive percutaneous coronary intervention group $n = 136$ and optimal medical therapy group $n = 118$ in diabetes; preventive percutaneous coronary intervention group $n = 349$ and optimal medical therapy group $n = 240$ in non-diabetes.

[c]Preventive percutaneous coronary intervention group $n = 237$ and optimal medical therapy group $n = 233$ in diabetes; preventive percutaneous coronary intervention group $n = 536$ and optimal medical therapy group $n = 527$ in non-diabetes.

[d]Preventive percutaneous coronary intervention group $n = 227$ and optimal medical therapy group $n = 222$ in diabetes; preventive percutaneous coronary intervention group $n = 506$ and optimal medical therapy group $n = 503$ in non-diabetes.

[e]Preventive percutaneous coronary intervention group $n = 226$ and optimal medical therapy group $n = 222$ in diabetes; preventive percutaneous coronary intervention group $n = 506$ and optimal medical therapy group $n = 505$ in non-diabetes.

[f]Preventive percutaneous coronary intervention group $n = 227$ and optimal medical therapy group $n = 224$ in diabetes; preventive percutaneous coronary intervention group $n = 505$ and optimal medical therapy group $n = 504$ in non-diabetes.

[g]Preventive percutaneous coronary intervention group $n = 126$ and optimal medical therapy group $n = 107$ in diabetes; preventive percutaneous coronary intervention group $n = 266$ and optimal medical therapy group $n = 219$ in non-diabetes.

[h]Preventive percutaneous coronary intervention group $n = 106$ and optimal medical therapy group $n = 128$ in diabetes; preventive percutaneous coronary intervention group $n = 98$ and optimal medical therapy group $n = 98$ in non-diabetes.

[i]One patient underwent balloon angioplasty only.

Table 2 Baseline core-laboratory angiographic and intracoronary imaging analysis of vulnerable plaque target lesions according to diabetes status and randomization group

Characteristic	Diabetes			Non-diabetes		
	Preventive PCI (*n* = 244) (251 lesions)	OMT (*n* = 246) (255 lesions)	*P*-value	Preventive PCI (*n* = 559) (580 lesions)	OMT (*n* = 557) (586 lesions)	*P*-value
Fractional flow reserve—median (IQR)	0.86 (0.83–0.90)	0.86 (0.83–0.90)	.902	0.86 (0.83–0.90)	0.87 (0.83–0.91)	.139
QCA analysis						
Diameter stenosis—%, mean ± SD	56.5 ± 9.7	52.0 ± 9.5	<.001	56.6 ± 8.9	52.8 ± 9.9	<.001
Diameter stenosis <50%—no. (%)	39 (15.7)	91 (35.8)	<.001	96 (16.6)	179 (30.7)	<.001
Minimal lumen diameter—mm, mean ± SD	1.32 ± 0.34	1.46 ± 0.35	<.001	1.33 ± 0.33	1.50 ± 0.37	<.001
Reference vessel diameter—mm, mean ± SD	3.03 ± 0.43	3.06 ± 0.51	.499	3.07 ± 0.45	3.18 ± 0.53	<.001
Lesion length—mm, mean ± SD	23.6 ± 8.0	20.0 ± 9.1	<.001	23.6 ± 8.7	19.0 ± 7.9	<.001
IVUS measurements	*n* = 248	*n* = 253		*n* = 563	*n* = 577	
Lesion length—mm, mean ± SD	24.0 ± 8.3	23.8 ± 9.8	.795	23.7 ± 8.8	22.0 ± 8.8	<.002
MLA—mm^2, mean ± SD	2.8 ± 1.0	2.8 ± 0.9	.604	2.8 ± 0.8	2.9 ± 0.9	.075
MLA ≤ 4.0 mm^2—no. (%)	236/248 (95.2)	242/253 (95.7)	.793	546/563 (97.0)	552/577 (95.7)	.239
EEM at MLA site—mm^2, mean ± SD	12.6 ± 4.3	13.2 ± 4.8	.156	12.0 ± 4.1	12.4 ± 4.2	.104
Plaque burden—%, mean ± SD	76.6 ± 6.7	77.7 ± 6.7	.070	75.7 ± 6.3	75.9 ± 6.6	.759
Plaque burden >70%—no. (%)	225/248 (90.7)	236/253 (93.3)	.291	495/563 (87.9)	518/577 (89.8)	.320
Remodelling index—mean ± SD	0.89 ± 0.18	0.88 ± 0.18	.816	0.85 ± 0.20	0.87 ± 0.19	.356
Attenuated plaque—no. (%)	172/248 (69.4)	178/253 (70.4)	.807	383/563 (68.0)	424/577 (73.5)	.043
Calcification present—no. (%)	225/248 (90.7)	231/253 (91.3)	.821	488/563 (86.7)	480/577 (83.2)	.100
Maximal calcium arc—°, median (IQR)	120 (67–199)	127 (81–227)	.232	97 (56–147)	97 (55–149)	.780
Superficial calcium present—no. (%)	211/248 (85.1)	218/253 (86.2)	.729	458/563 (81.3)	442/577 (76.6)	.049
Calcium nodule present—no. (%)	18/248 (7.3)	14/253 (5.5)	.430	26/563 (4.6)	32/577 (5.5)	.476
Plaque rupture present—no. (%)	11/248 (4.4)	12/253 (4.7)	.869	30/563 (5.3)	45/577 (7.8)	.093
RF-IVUS measurements	*n* = 131	*n* = 168		*n* = 327	*n* = 408	
Target lesion segmental data—%, mean ± SD						
Fibrous volume	58.1 ± 19.2	62.3 ± 28.9	.137	61.7 ± 23.4	62.5 ± 26.7	.696
Fibrofatty volume	25.1 ± 10.9	28.2 ± 15.7	.046	26.5 ± 24.0	26.1 ± 13.2	.750
Necrotic core volume	14.2 ± 8.0	15.4 ± 10.9	.262	14.5 ± 9.0	13.5 ± 8.6	.127

Continued

Table 2 *Continued*

Characteristic	Diabetes			Non-diabetes		
	Preventive PCI ($n = 244$) (251 lesions)	OMT ($n = 246$) (255 lesions)	*P*-value	Preventive PCI ($n = 559$) (580 lesions)	OMT ($n = 557$) (586 lesions)	*P*-value
Dense calcium volume	7.1 ± 6.1	8.1 ± 9.7	.296	6.3 ± 5.9	5.5 ± 5.0	.035
Index lesion data—%, mean ± SD						
Fibrous tissue	48.9 ± 11.4	50.1 ± 11.9	.390	51.7 ± 11.1	52.5 ± 11.3	.360
Fibrofatty tissue	13.3 ± 9.2	13.9 ± 9.3	.610	12.8 ± 9.1	13.5 ± 8.9	.316
Necrotic core	25.1 ± 8.4	24.2 ± 7.8	.348	25.0 ± 9.0	23.9 ± 8.7	.078
Dense calcium	12.7 ± 9.3	11.9 ± 9.6	.419	10.4 ± 8.8	10.1 ± 8.5	.669
Lesion classification—no. (%)						
TCFA	15/131 (11.5)	18/168 (10.7)	.840	42/327 (12.8)	55/408 (13.5)	.800
Thick-cap fibroatheroma	113/131 (86.3)	148/168 (88.1)	.636	269/327 (82.3)	334/408 (81.9)	.888
Pathological intimal thickening	3/131 (2.3)	1/168 (0.6)	.322	12/327 (3.7)	17/408 (4.2)	.731
Fibrotic plaque	0/131 (0)	1/168 (0.6)	>.999	2/327 (0.6)	1/408 (0.2)	.588
NIRS measurements	$n = 95$	$n = 109$		$n = 253$	$n = 260$	
Plaque-level maxLCBI$_{4\ mm}$—median (IQR)	264 (121–409)	241 (123–425)	.948	266 (69–373)	251 (99–383)	.832
Plaque-level maxLCBI$_{4\ mm} > 315$—no. (%)	41/95 (43.2)	40/109 (36.7)	.347	103/253 (40.7)	98/260 (37.7)	.484
OCT measurements	$n = 16$	$n = 4$		$n = 47$	$n = 17$	
Lesion length—mm, mean ± SD	23.6 ± 4.6	21.1 ± 8.3	.594	23.4 ± 7.5	19.7 ± 6.7	.066
MLA—mm^2, mean ± SD	2.5 ± 0.9	2.4 ± 0.8	.901	2.2 ± 0.7	2.2 ± 0.8	.998
Lipid core—no. (%)	16/16 (100)	4/4 (100)	>.999	47/47 (100)	16/17 (94.1)	.094
Maximal lipid core arc—°, mean ± SD	224.2 ± 84.6	254.2 ± 101.8	.614	220.7 ± 84.3	243.5 ± 73.3	.313
Maximal lipid core arc >90°—no. (%)	16/16/(100)	4/4 (100)	>.999	45/47 (95.7)	16/17 (94.1)	.786
Calcium present—no. (%)	12/16 (75.0)	4/4 (100)	.538	33/47 (70.2)	12/17 (70.6)	.977
Maximal calcium arc—°, mean ± SD	135.1 ± 79.5	146.2 ± 81.6	.822	82.1 ± 47.8	129.8 ± 64.8	.034
Calcium thickness—mm, mean ± SD	0.97 ± 0.20	0.84 ± 0.11	.144	0.70 ± 0.26	0.76 ± 0.29	.532
Plaque rupture—no. (%)	2/16 (12.5)	0/16 (0)	>.999	1/47 (2.1)	3/17 (17.6)	.054
TCFA defined by OCT—no. (%)	2/16 (12.5)	1/4 (25.0)	.509	9/47 (19.1)	6/17 (35.3)	.178
TCFA defined by RF-IVUS or OCT—no. (%)	17/142 (12.0)	19/170 (11.2)	.827	51/353 (14.4)	61/417 (14.6)	.944

Continued

Table 2 *Continued*

Characteristic	Diabetes			Non-diabetes		
	Preventive PCI ($n = 244$) (251 lesions)	OMT ($n = 246$) (255 lesions)	*P*-value	Preventive PCI ($n = 559$) (580 lesions)	OMT ($n = 557$) (586 lesions)	*P*-value
Number of high-risk plaque feature—no. (%)[a]						
Lesions with ≥1 of 4 high-risk features	244 (97.2)	250 (98.0)	.541	559 (96.4)	566 (96.6)	.847
Lesions with ≥2 of 4 high-risk features	229 (91.2)	233 (91.4)	.956	507 (87.4)	527 (89.9)	.175
Lesions with ≥3 of 4 high-risk features	44 (17.5)	51 (20.0)	.477	119 (20.5)	126 (21.5)	.680
Lesions with 4 of 4 high-risk features	2 (0.8)	3 (1.2)	>.999	10 (1.7)	10 (1.7)	.981

EEM, external elastic membrane; IVUS, intravascular ultrasound; $MaxLCBI_{4\ mm}$, maximal lipid core burden in a 4 mm segment; MLA, minimal lumen area; NIRS, near-infrared spectroscopy; OCT, optical coherence tomography; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; RF, radiofrequency; TCFA; thin-cap fibroatheroma.
[a]High-risk plaque features were the following derived from intracoronary imaging; (i) MLA < 4.0 mm^2 by IVUS or OCT, (ii) plaque burden >70% by IVUS, (iii) lipid-rich plaque by NIRS (defined as $maxLCBI_{4\ mm} > 315$), and (iv) TCFA by RF-IVUS (≥10% confluent necrotic core with >30° abutting to the lumen in 3 consecutive slices) or OCT (fibrous cap thickness <65 μm and lipid arc > 90°).

Table 3 **Primary and secondary outcomes according to diabetes status and randomization group**

Outcome	Diabetes			Non-diabetes			*P* for interaction
	Preventive PCI ($n = 244$)	OMT ($n = 246$)	Hazard ratio (95% CI)[a]	Preventive PCI ($n = 559$)	OMT ($n = 557$)	Hazard ratio (95% CI)[a]	
Primary composite outcome[b]			0.62 (0.26–1.50)			0.51 (0.29–0.89)	.338
At 2 years (primary time point)	0 (0)	9 (3.7)	NA[c]	3 (0.5)	18 (3.2)	0.16 (0.05–0.55)	.990
At 4 years (median follow-up)	6 (2.5)	13 (5.3)		11 (2.0)	24 (4.3)		
At 7 years (maximum follow-up)	8 (3.3)	13 (5.3)		18 (3.2)	34 (6.1)		
Death from any cause			0.28 (0.09–0.84)			0.87 (0.45–1.71)	.152
At 2 years	1 (0.4)	4 (1.6)		3 (0.5)	6 (1.1)		
At 4 years	3 (1.2)	8 (3.3)		8 (1.4)	9 (1.6)		
At 7 years	4 (1.6)	15 (6.1)		16 (2.9)	17 (3.1)		
Death from cardiac causes			NA			1.14 (0.38–3.39)	NA
At 2 years	0 (0)	2 (0.8)		1 (0.2)	4 (0.7)		

Continued

Table 3 *Continued*

Outcome	Diabetes			Non-diabetes			*P* for interaction
	Preventive PCI (*n* = 244)	OMT (*n* = 246)	Hazard ratio (95% CI)[a]	Preventive PCI (*n* = 559)	OMT (*n* = 557)	Hazard ratio (95% CI)[a]	
At 4 years	0 (0)	2 (0.8)		5 (0.9)	5 (0.9)		
At 7 years	0 (0)	2 (0.8)		7 (1.3)	6 (1.1)		
Death from non-cardiac causes			0.32 (0.11–0.99)			0.74 (0.31–1.75)	.489
At 2 years	1 (0.4)	2 (0.8)		2 (0.4)	2 (0.4)		
At 4 years	3 (1.2)	6 (2.4)		3 (0.5)	4 (0.7)		
At 7 years	4 (1.6)	13 (5.3)		9 (1.6)	11 (2.0)		
All myocardial infarctions			0.80 (0.22–2.98)			0.79 (0.36–1.73)	.580
At 2 years	2 (0.8)	5 (2.0)		7 (1.3)	8 (1.4)		
At 4 years	4 (1.6)	5 (2.0)		10 (1.8)	10 (1.8)		
At 7 years	4 (1.6)	5 (2.0)		11 (2.0)	14 (2.5)		
Target-vessel myocardial infarction			0.99 (0.14–7.08)			0.50 (0.12–1.98)	.981
At 2 years	0 (0)	2 (0.8)		1 (0.2)	4 (0.7)		
At 4 years	2 (0.8)	2 (0.8)		2 (0.4)	5 (0.9)		
At 7 years	2 (0.8)	2 (0.8)		3 (0.5)	6 (1.1)		
Non-target-vessel myocardial infarction			0.67 (0.11–4.00)			1.00 (0.38–2.68)	.476
At 2 years	2 (0.8)	3 (1.2)		6 (1.1)	4 (0.7)		
At 4 years	2 (0.8)	3 (1.2)		8 (1.4)	5 (0.9)		
At 7 years	2 (0.8)	3 (1.2)		8 (1.4)	8 (1.4)		
Any revascularisation			0.78 (0.39–1.58)			0.60 (0.37–0.99)	.865
At 2 years	3 (1.2)	11 (4.5)		11 (2.0)	18 (3.2)		
At 4 years	12 (4.9)	16 (6.5)		19 (3.4)	26 (4.7)		
At 7 years	14 (5.7)	18 (7.3)		25 (4.5)	40 (7.2)		
Ischaemia-driven target-vessel revascularization			0.71 (0.27–1.88)			0.34 (0.17–0.70)	.651
At 2 years	0 (0)	6 (2.4)		1 (0.2)	13 (2.3)		
At 4 years	5 (2.0)	10 (4.1)		5 (0.9)	19 (3.4)		
At 7 years	7 (2.9)	10 (4.1)		10 (1.8)	28 (5.0)		

Continued

Table 3 *Continued*

Outcome	Diabetes			Non-diabetes			*P* for interaction
	Preventive PCI ($n = 244$)	OMT ($n = 246$)	Hazard ratio (95% CI)[a]	Preventive PCI ($n = 559$)	OMT ($n = 557$)	Hazard ratio (95% CI)[a]	
Non-target-vessel revascularization			0.90 (0.35–2.33)			0.87 (0.44–1.70)	.910
At 2 years	3 (1.2)	6 (2.4)		10 (1.8)	7 (1.3)		
At 4 years	8 (3.3)	7 (2.8)		14 (2.5)	12 (2.2)		
At 7 years	8 (3.3)	9 (3.7)		16 (2.9)	18 (3.2)		
Hospitalization for unstable or progressive angina			0.34 (0.07–1.66)			0.13 (0.03–0.56)	.333
At 2 years	0 (0)	4 (1.6)		1 (0.2)	8 (1.4)		
At 4 years	2 (0.8)	6 (2.4)		2 (0.4)	10 (1.8)		
At 7 years	2 (0.8)	6 (2.4)		2 (0.4)	15 (2.7)		
Definite stent or scaffold thrombosis			NA			0.65 (0.11–3.90)	NA
At 2 years	0 (0)	0 (0)		1 (0.2)	3 (0.5)		
At 4 years	0 (0)	0 (0)		2 (0.4)	3 (0.5)		
At 7 years	0 (0)	0 (0)		2 (0.4)	3 (0.5)		
Stroke			0.34 (0.07–1.68)			1.79 (0.60–5.34)	.435
At 2 years	0 (0)	3 (1.2)		5 (0.9)	3 (0.5)		
At 4 years	2 (0.8)	6 (2.4)		8 (1.4)	3 (0.5)		
At 7 years	2 (0.8)	6 (2.4)		9 (1.6)	5 (0.9)		
Major bleeding events			0.50 (0.09–2.70)			1.12 (0.41–3.09)	.469
At 2 years	1 (0.4)	4 (1.6)		4 (0.7)	7 (1.3)		
At 4 years	2 (0.8)	4 (1.6)		6 (1.1)	7 (1.3)		
At 7 years	2 (0.8)	4 (1.6)		8 (1.4)	7 (1.3)		
Minor bleeding events			1.00 (0.06–16.09)			1.97 (0.68–5.78)	.306
At 2 years	0 (0)	1 (0.4)		7 (1.3)	3 (0.5)		
At 4 years	1 (0.4)	1 (0.4)		9 (1.6)	5 (0.9)		
At 7 years	1 (0.4)	1 (0.4)		10 (1.8)	5 (0.9)		
Death from any cause or target-vessel myocardial infarction			0.36 (0.14–0.92)			0.81 (0.44–1.49)	.217
At 2 years	1 (0.4)	6 (2.4)		4 (0.7)	9 (1.6)		
At 4 years	5 (2.0)	10 (4.1)		10 (1.8)	13 (2.3)		
At 7 years	6 (2.5)	17 (6.9)		19 (3.4)	22 (3.9)		

Continued

Table 3 *Continued*

Outcome	Diabetes			Non-diabetes			*P* for interaction
	Preventive PCI (*n* = 244)	OMT (*n* = 246)	Hazard ratio (95% CI)[a]	Preventive PCI (*n* = 559)	OMT (*n* = 557)	Hazard ratio (95% CI)[a]	
The composite of death from any cause, all myocardial infarctions, or any revascularization			0.60 (0.35–1.04)			0.75 (0.51–1.10)	.439
At 2 years	6 (2.5)	16 (6.5)	0.37 (0.14–0.94)	18 (3.2)	25 (4.5)	0.71 (0.39–1.30)	.179
At 4 years	17 (7.0)	25 (10.2)		31 (5.5)	36 (6.5)		
At 7 years	20 (8.2)	34 (13.8)		45 (8.1)	58 (10.4)		

Results reported as no. (%).
CI, confidence interval; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.
[a]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.
[b]Death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularization, or hospitalization for unstable or progressive angina at 2 years.
[c]Hazard ratio was not able to calculate using conventional Cox proportional hazard regression due to no event in the prevent PCI group.

non-cardiac cause according to diabetes status and randomization group, the results were not changed after adjustment for the competing risk of death from non-cardiac causes (see Supplementary data online, *Table S3*).

Medication status, including statin intensity and risk factor control status were comparable between treatment arms during follow-up in both diabetic and non-diabetic cohorts (see Supplementary data online, *Tables S4* and *S5*). In both strata, dual antiplatelet was more used in preventive PCI group than OMT group over time. Despite somewhat differences in usage rate of beta-blocker and statin between preventive PCI and OMT groups, the level of LDL cholesterol and blood pressure were similar between treatment arms during follow-up in both cohorts. Angina status, as assessed by the Canadian Cardiovascular Society class, was also similar across groups (see Supplementary data online, *Table S6*).

Comparison of clinical outcomes by diabetes status

Clinical outcomes by diabetes status are presented in Supplementary data online, *Table S7*. The 2-year incidence of the primary endpoint was 1.8% in diabetic patients and 1.9% in non-diabetic patients (HR 0.98; 95% CI 0.45–2.14; *P* = .956). At maximal follow-up, the incidence of the primary endpoint was 4.3% in diabetic patients and 4.7% in non-diabetic patients (HR 0.94; 95% CI 0.56–1.55; *P* = .799). Secondary endpoints, including the patient-oriented composite outcome, occurred at similar rates between diabetic and non-diabetic patients (see Supplementary data online, *Figures S3* and *S4*).

Study outcomes according to randomization group and diabetes status at discharge and at 1 year

In the PREVENT trial, enrolled patients were stratified according to presence of diabetes at the time of randomization, and diabetes was determined by patients' self-report or case of taking antidiabetic medications or insulin. During initial hospitalization, HbA1c was checked in 196 patients (17.6%) of non-diabetic cohort. Among these, 12 patients (6.1%) were newly diagnosed as diabetes by HbA1c criteria (HbA1c ≥ 6.5%) at discharge. Forty-four patients [44/485 patients who were checked HbA1c at 1 year (9.1%)] were additionally diagnosed as diabetes by HbA1c criteria at 1-year follow-up. In the time-to-event curves for the primary composite outcome according to randomization group and diabetes status at discharge and at 1 year, the results were not altered (see Supplementary data online, *Figure S5*).

Discussion

In this pre-specified subgroup analysis of the PREVENT trial, we investigated the impact of preventive PCI on clinical outcomes in patients with diabetes who had non-flow-limiting vulnerable coronary plaques. There were no significant differences in the risk of the primary composite endpoint (death from cardiac causes, target-vessel MI, ischaemia-driven TVR, or hospitalization for unstable or progressive angina) at 2 years between patients with and without diabetes. However, preventive PCI reduced the risk of the primary composite endpoint irrespective of diabetes status, and this was primarily driven by the lower incidence of ischaemia-driven TVR and hospitalization for unstable or progressive angina, respectively.

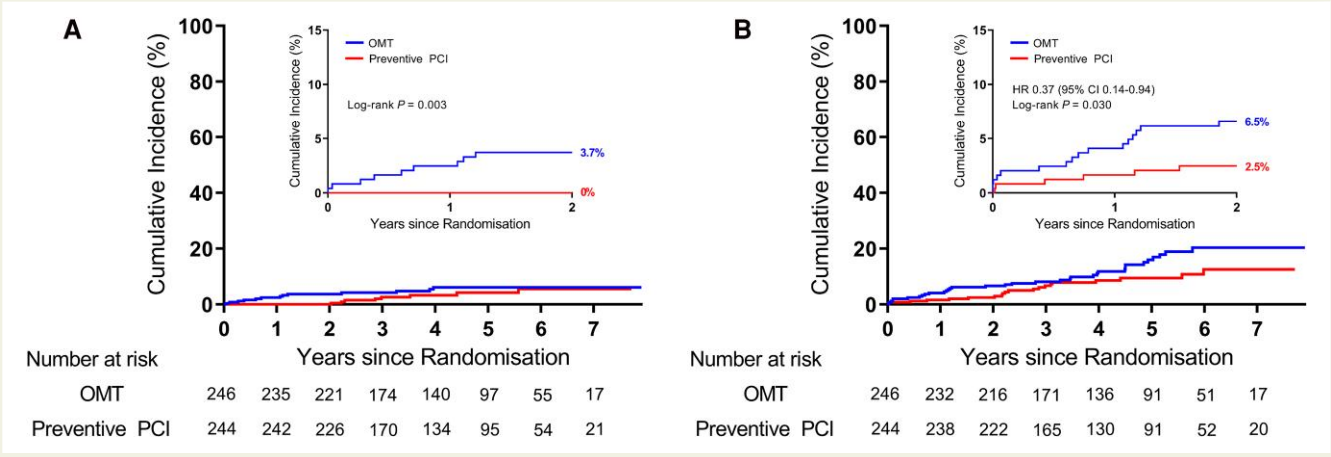


Figure 2 Time-to-event curves during maximal follow-up and through 2 years for clinical outcomes according to randomization group in patients with diabetes. Kaplan–Meier estimates of the cumulative incidence of (*A*) the primary endpoint, a composite of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalization for unstable or progressive angina, and (*B*) the patient-oriented composite endpoint of death from any cause, all myocardial infarctions, or any repeat revascularisation. CI, confidence interval; HR, hazard ration; OMT, optimal medical therapy; PCI, percutaneous coronary intervention

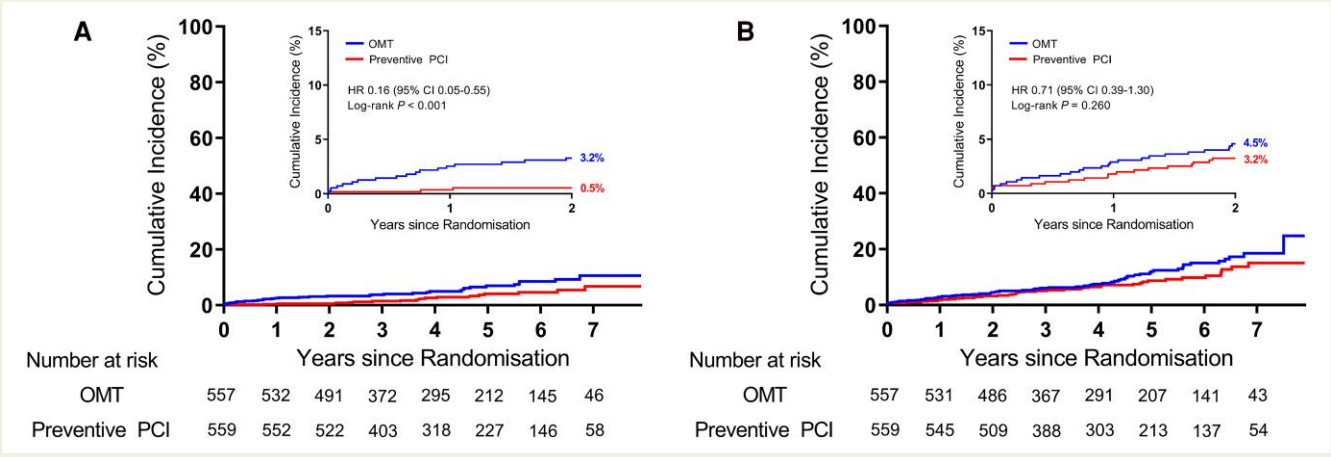


Figure 3 Time-to-event curves during maximal follow-up and through 2 years for clinical outcomes according to randomization group in patients without diabetes. Kaplan–Meier estimates of the cumulative incidence of (*A*) the primary endpoint, a composite of death from cardiac causes, target-vessel myocardial infarction, ischaemia-driven target-vessel revascularisation, or hospitalization for unstable or progressive angina, and (*B*) the patient-oriented composite endpoint of death from any cause, all myocardial infarctions, or any repeat revascularisation. CI, confidence interval; HR, hazard ration; OMT, optimal medical therapy; PCI, percutaneous coronary intervention

The PREVENT trial demonstrated that preventive PCI aimed at sealing vulnerable coronary plaques was effective for reducing adverse clinical outcomes compared with the OMT-alone strategy.[19] In a prior study that compared BVS with OMT in 182 patients with non-flow-limiting vulnerable plaques detected by IVUS, PCI for angiographically mild lesions with a large plaque burden significantly enlarged the MLA compared with OMT.[14] However, that study was limited in scope, focusing on angiographic outcomes rather than clinical endpoints, and did not include an analysis of diabetic patients. Whether preventive PCI benefits patients with diabetes remains unclear despite its potential clinical significance, as diabetic patients generally present with more vulnerable plaques than non-diabetic individuals.[4–7] In addition, vulnerable plaques are major determinants of adverse clinical events in diabetic patients.[11,15–18] For example, in the COMBINE OCT-FFR trial, diabetic patients with non-flow-limiting TCFA identified by OCT exhibited a higher risk of adverse clinical events than those without TCFA.[11,16] However, the study only assessed the natural history of non-flow-limiting vulnerable plaques, limiting its ability to conclude the effectiveness of preventive PCI. To the best of our knowledge, no randomized trials have directly compared preventive PCI with OMT for treating non-flow-limiting vulnerable plaques in diabetic patients, which makes the findings of the current study particularly relevant.

In our analysis, patients with diabetes had clinical outcomes comparable to those without diabetes. Diabetes is typically associated with worse clinical outcomes than those exhibited by non-diabetics but several factors may

explain this similarity in our study. First, the event rates for the primary endpoint were substantially lower than anticipated in the PREVENT trial,[19] raising the possibility of underestimating outcomes in both diabetic and non-diabetic groups. Second, all enrolled patients had at least one vulnerable target lesion, and the incidence of TCFA or plaque rupture detected via intracoronary imaging was not significantly different between diabetic and non-diabetic patients. Because TCFA is a critical determinant of adverse events in diabetes, its comparable incidence across groups may have contributed to the similar outcomes observed. Third, baseline HbA1c levels in diabetic patients were relatively low (mean: 7.3%), indicating well-controlled blood glucose. Furthermore, HbA1c levels remained stable during follow-up (mean: 7.2% at 2 years and 7.3% at maximal follow-up). As HbA1c is a well-established predictor of adverse events and plaque vulnerability in diabetes, effective glycaemic control may have mitigated risk in this population.[24–26]

Despite the similar risk for adverse cardiac events between patients with and without diabetes, preventive PCI significantly reduced the primary composite endpoint compared with OMT alone in both groups. As noted, the rate of PCI for vulnerable target lesions was similar, and the incidence of TCFA was also comparable between groups. The reduction in the primary composite endpoint with preventive PCI was primarily attributed to a lower incidence of ischaemia-driven TVR and hospitalization for unstable or progressive angina in both diabetic and non-diabetic patients. These results highlight the importance of addressing the progression of untreated vulnerable plaques and support the need for preventive PCI in managing such lesions. Although follow-up intravascular imaging was not routinely performed to assess changes in plaque composition, patient risk factors were well controlled across the study population. These findings highlight the clinical importance of preventive PCI, regardless of diabetes status. However, the incidence of target-vessel MI was comparable between preventive PCI and OMT in both diabetic and non-diabetic cohorts. The concept of preventive PCI has been proposed to reduce the risk of plaque rupture and development of MI.[14] We think that the explanations for similar risk of target-vessel MI between preventive PCI and OMT were as follows. First, the number of patients with a TCFA as qualifying criterion for study inclusion was low, and it is similarly distributed between preventive PCI and OMT groups in both diabetic and non-diabetic cohorts in the current study. Although the principal determinants of vulnerable plaque in the current study were a MLA of <4 mm^2 and a plaque burden of more than 70% as assessed by IVUS, it could not fully reflect high-risk feature criteria for vulnerable plaque identification. Second, the incidence of target-vessel MI in this study was too low. However, its incidence might be low with updated PCI techniques, new PCI devices and potent medications in the current PCI era. In the IVUS-guided vs. angiography-guided PCI in ACS (IVUS–ACS) trial, the incidence of non-procedural-related target-vessel MI was also low (1.06% in overall population).[27] Finally, risk factors including LDL cholesterol were well controlled during follow-up in all study population of the PREVENT trial. These factors might be associated with a lack of benefit of preventive PCI in the hard clinical endpoints such as target-vessel MI.

Interestingly, the benefit of preventive PCI diminished beyond 2 years in terms of the primary composite endpoint in diabetic patients. However, no significant interaction was observed in the primary composite endpoint at 2 years or during maximal follow-up between patients with and without diabetes. Thus, further large-scale studies are required to confirm the long-term benefits of preventive PCI in diabetic patients with non-flow-limiting vulnerable plaques.

Study limitations

This study had several limitations. First, the clinical outcomes presented were exploratory, as the PREVENT trial was powered for the primary endpoint: a composite of death from cardiac causes, target-vessel MI, ischaemia-driven TVR, or hospitalization for unstable or progressive angina at 2 years after randomization. In addition, the event rate for the primary endpoint was lower than anticipated, indicating the need to interpret the findings of this subgroup analysis as hypothesis-generating. Explanations for low incidence of the primary endpoint were as follows: (i) most patients in the PREVENT trial were presented with chronic coronary syndrome and study target lesions were relatively short and had a large reference diameter, (ii) intravascular imaging was routinely used to guide prevent PCI, which was associated with lower incidence of adverse cardiac events,[27,28] (iii) risk factors such as lipid profile, blood pressure, glycaemic control, and smoking status were relatively well controlled, and (iv) 51 patients were lost to follow-up within 2 years. Given that low event rate in the PREVENT trial, there is a possibility that this missing data have had on the primary results Second, detailed information on diabetes status, such as duration of diabetes, was unavailable. A prolonged duration of diabetes correlates with adverse cardiovascular outcomes and aggressive plaque morphology.[29] However, baseline characteristics, intravascular imaging findings, cardiovascular medication use, and the status of risk factor control were well-balanced between the preventive PCI and OMT groups, regardless of diabetes status. Third, only a small number of patients were treated with insulin, and the differentiation between type 1 and type 2 diabetes was not recorded, potentially limiting the generalisability of the findings to specific diabetes subtypes. Although insulin use is a well-known predictor of adverse cardiac events in diabetic patients with ischaemic heart disease, formal statistical analysis was difficult due to the low number of patients with insulin-treated diabetes and the low number of event rate (primary endpoint) in the PREVENT trial. Fourth, follow-up intravascular imaging was not routinely performed. Because the observed differences in the primary endpoint between treatment groups were primarily driven by the progression of untreated vulnerable plaques, changes in plaque composition, particularly in the OMT group, might have influenced clinical outcomes. Fifth, death from any cause less occurred with preventive PCI in diabetics but not in the non-diabetics. However, the difference was not statistically significant at 2-year and 4-year follow-up, respectively. Death from any cause was mainly driven by death from non-cardiac causes. Although the difference was evident at maximal follow-up, we could not evaluate the individual cause of death in study population. Therefore, we think that there is a possibility of a play of chance in this finding. Sixth, the data for exact time from ACS to study-specific coronary intervention are unavailable. The rate of ACS was 16.1% ($n = 259$) in the current study (see Supplementary data online, *Table S1*): ST-segment elevation myocardial infarction (STEMI) 1.0% ($n = 16$), non-STEMI (NSTEMI) 2.9% ($n = 46$), and unstable angina 12.3% ($n = 197$). We think that time from ACS to the study-specific coronary intervention is important in patients with MI rather than unstable angina. In patients with STEMI and NSTEMI, most patients were enrolled in the study after PCI for culprit lesion [STEMI 15/16 (93.8%) and NSTEMI 37/46 (80.4%)]. If patients with MI were clinically unstable after PCI for culprit, they were not entered into study. All patients with MI enrolled to the study were clinically stable, therefore, the impact of time from ACS to study-specific intervention might be minimized in these patients. Finally, enrolled patients in the PREVENT trial were stratified according to presence of diabetes at the time of randomization. Although we checked HbA1c during initial

hospitalization and during follow-up, it was not checked in all patients. However, the primary result was not changed in *post hoc* analysis including patients with newly diagnosed diabetes at discharge and at 1 year.

Conclusions

In this pre-specified subgroup analysis of the PREVENT trial, there was a similar risk of the primary composite endpoint between diabetic and non-diabetic patients with non-flow-limiting vulnerable coronary plaques. Although there was a lack of benefit of preventive PCI in hard clinical endpoints such as cardiac mortality or target-vessel MI, it was associated with a lower rate of the primary composite endpoint, driven by a reduced incidence of ischaemia-driven TVR or hospitalization for unstable or progressive angina, at 2 years in both groups. These findings support that preventive PCI appears to be beneficial irrespective of diabetes status, in patients with non-flow-limiting vulnerable coronary plaques.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

Data will be shared on reasonable request to the corresponding author.

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Ethical Approval

The study protocol was approved by the institutional review board or Ethics Committee at each participating centre, and written informed consent was obtained from all patients prior to randomization.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT02316886.

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