

# Intravascular ultrasound-guided versus angiography-guided percutaneous coronary intervention in acute coronary syndromes (IVUS-ACS): a two-stage, multicentre, randomised trial



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## Summary

**Background** Intravascular ultrasound-guided percutaneous coronary intervention has been shown to result in superior clinical outcomes compared with angiography-guided percutaneous coronary intervention. However, insufficient data are available concerning the advantages of intravascular ultrasound guidance for patients with an acute coronary syndrome. This trial aimed to investigate whether the use of intravascular ultrasound guidance, as compared with angiography guidance, improves the outcomes of percutaneous coronary intervention with contemporary drug-eluting stents in patients presenting with an acute coronary syndrome.

**Methods** In this two-stage, multicentre, randomised trial, patients aged 18 years or older and presenting with an acute coronary syndrome at 58 centres in China, Italy, Pakistan, and the UK were randomly assigned to intravascular ultrasound-guided percutaneous coronary intervention or angiography-guided percutaneous coronary intervention. Patients, follow-up health-care providers, and assessors were masked to random assignment; however, staff in the catheterisation laboratory were not. The primary endpoint was target vessel failure, a composite of cardiac death, target vessel myocardial infarction, or clinically driven target vessel revascularisation at 1 year after randomisation. This trial is registered at ClinicalTrials.gov, NCT03971500, and is completed.

**Findings** Between Aug 20, 2019 and Oct 27, 2022, 3505 patients with an acute coronary syndrome were randomly assigned to intravascular ultrasound-guided percutaneous coronary intervention (n=1753) or angiography-guided percutaneous coronary intervention (n=1752). 1-year follow-up was completed in 3504 (>99·9%) patients. The primary endpoint occurred in 70 patients in the intravascular ultrasound group and 128 patients in the angiography group (Kaplan-Meier rate 4·0% vs 7·3%; hazard ratio 0·55 [95% CI 0·41–0·74]; p=0·0001), driven by reductions in target vessel myocardial infarction or target vessel revascularisation. There were no significant differences in all-cause death or stent thrombosis between groups. Safety endpoints were also similar in the two groups.

**Interpretation** In patients with an acute coronary syndrome, intravascular ultrasound-guided implantation of contemporary drug-eluting stents resulted in a lower 1-year rate of the composite outcome of cardiac death, target vessel myocardial infarction, or clinically driven revascularisation compared with angiography guidance alone.

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## Introduction

Most percutaneous coronary interventions in the USA and Europe are guided by angiography. The low resolution of angiography and its inability to provide insight beyond the coronary artery lumen<sup>1</sup> led to the development of intravascular ultrasound and optical coherence tomography to provide more precise lesion assessment, stent size selection, and evaluation of stent expansion, vessel wall apposition, and lesion coverage.<sup>2–5</sup> Randomised trials and meta-analyses have shown reductions in composite adverse outcomes with intravascular imaging-guided percutaneous coronary

intervention compared with angiography-guided intervention.<sup>2–5</sup>

Most patients with an acute coronary syndrome present with coronary thrombosis after disruption of a lipid-rich plaque,<sup>6</sup> and stenting such lesions entails greater procedural risks compared with chronic stable lesions.<sup>7</sup> Although the prognosis of patients with an acute coronary syndrome is improved by percutaneous coronary intervention,<sup>7</sup> adverse outcomes from the intervention, including death, myocardial infarction, and stent thrombosis, are higher in patients with an acute coronary syndrome than in patients with chronic coronary

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For the Mandarin translation of the abstract see Online for appendix 1

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See Online for appendix 2

## Research in context

### Evidence before this study

We searched PubMed using the search terms “intravascular ultrasound”, “angiography”, and “percutaneous coronary intervention” using MeSH terms and appropriate variations from Jan 1, 2010, to March 11, 2019, with no language restrictions, before designing our study. We found no previous randomised controlled trials that compared intravascular ultrasound-guided percutaneous coronary intervention with angiography-guided percutaneous coronary intervention for either an acute procedural success or clinical outcomes exclusively in patients with an acute coronary syndrome. Some, but not all, registry studies have suggested that major adverse cardiac events in patients with an acute coronary syndrome could be reduced with contemporary drug-eluting stents implanted with intravascular ultrasound guidance. Three small randomised trials of optical coherence tomography guidance compared with angiography guidance were previously done, but their results were inconclusive due to their small sample size.

### Added value of this study

The present study is the first randomised controlled trial to compare intravascular ultrasound-guided versus angiography-guided percutaneous coronary intervention in a population composed exclusively of patients with an acute coronary syndrome. The study was conducted at 58 hospitals in four countries. The results show that implantation of

contemporary drug-eluting stents with intravascular ultrasound guidance reduces the 1-year risk of target vessel failure compared with angiography guidance alone in these patients. The improvement was driven by fewer target vessel myocardial infarctions (especially during the follow-up period) and fewer repeat revascularisations with intravascular ultrasound guidance, with rates of survival and stent thrombosis similar between groups. Intravascular ultrasound guidance was safe, although the procedures were longer and slightly more contrast material was required—acceptable trade-offs for the lower risk of early and late major adverse cardiac events.

### Implications of all the available evidence

The findings from the IVUS-ACS trial are consistent with those of previous studies in patients with a chronic coronary syndrome. Collectively, these data show that intravascular ultrasound-guided percutaneous coronary intervention improves clinical outcomes, including measures of both safety and effectiveness, across the spectrum of coronary artery disease and patient presentations (acute or non-acute coronary syndrome). Adverse events during follow-up are especially reduced in patients for whom prespecified intravascular ultrasound criteria for optimal stent implantation are achieved, including optimal stent expansion, lesion coverage, and freedom from major edge dissections.

syndrome.<sup>8</sup> Some registry studies have suggested that major adverse cardiac events in patients with an acute coronary syndrome could be reduced by implantation of contemporary drug-eluting stents guided by intravascular ultrasound.<sup>9–13</sup> To date, only three small randomised trials have compared intravascular imaging-guided percutaneous coronary intervention with optical coherence tomography-guided versus angiography-guided percutaneous coronary intervention for patients with an acute coronary syndrome, all with inconclusive results;<sup>14–16</sup> no dedicated randomised trial of intravascular ultrasound-guided percutaneous coronary intervention has been reported in this patient population. Consequently, international guidelines do not currently recommend intravascular imaging guidance during percutaneous coronary intervention for patients with an acute coronary syndrome.<sup>17,18</sup> We therefore conducted this large-scale randomised trial to compare intravascular ultrasound-guided percutaneous coronary intervention versus angiography-guided intervention in this patient population.

## Methods

### Study design and participants

The integrated IVUS-ACS and ULTIMATE-DAPT study programme (comparison of 1-month vs 12-month dual antiplatelet therapy after implantation of drug-eluting

stents guided by either intravascular ultrasound or angiography in patients with an acute coronary syndrome) was a two-stage randomised, masked, multicentre trial conducted at 58 centres in China (n=52), Pakistan (n=4), the UK (n=1), and Italy (n=1), in patients presenting to emergency care settings with an acute coronary syndrome and treated with implantation of a second-generation drug-eluting stent within 30 days (appendix 2 pp 5–7). Participation of study centres required an annual volume of more than 1000 percutaneous coronary intervention procedures (except for the UK site, as percutaneous coronary interventions are less common by site in the UK) and more than 200 procedures per operator. The original protocol specified patients present with an acute coronary syndrome just before the stenting procedure, but was amended on March 28, 2021, to allow inclusion of patients presenting with an acute coronary syndrome event up to 30 days before randomisation because of strict quarantine policies during the COVID-19 pandemic; this protocol amendment was approved by the institutional review board or ethics committee at each participating centre. The background and study design have been previously reported.<sup>19</sup> The trial complied with the Declaration of Helsinki, and the protocol was approved by the institutional review board or ethics committee at each participating centre. A data and safety

monitoring board oversaw the trial, and an independent adjudication committee masked to treatment allocation assessed all clinical events.

Patients were eligible for inclusion in the trial if they were aged 18 years or older; had an acute coronary syndrome (ie, unstable angina [angiography showing a severely narrowed or ruptured plaque or thrombotic lesion without cardiac biomarker elevation], non-ST-segment elevation myocardial infarction [NSTEMI], or ST-segment elevation myocardial infarction [STEMI]) caused by a culprit lesion in an untreated coronary artery segment, up to 30 days before randomisation; and had an indication for percutaneous coronary intervention with a second-generation drug-eluting stent (appendix 2 p 8). Exclusion criteria were stroke within 3 months or any permanent neurological deficit; any previous intracranial bleed or intracranial disease (eg, aneurysm or fistula); previous coronary artery bypass graft surgery; any planned surgery within 12 months; any reason for which antiplatelet therapy might need to be discontinued within 12 months; severe chronic kidney disease (defined as an estimated glomerular filtration rate  $<20$  mL/min per  $1.73$  m<sup>2</sup>); need for chronic oral anticoagulation (ie, warfarin or coumadin or direct oral anticoagulants); a platelet count of less than  $100\,000$  mm<sup>3</sup>; contraindication to aspirin or ticagrelor; liver cirrhosis; people intending to become pregnant; a life expectancy of less than 1 year; and any condition likely to interfere with study processes, including medication compliance or follow-up visits (eg, dementia, alcohol abuse, severe frailty, or required to travel a long distance for follow-up visits). All patients or their family members provided written informed consent before random assignment; for patients with unstable angina or NSTEMI, there was sufficient time to introduce the percutaneous coronary intervention procedure and this study to patients; for patients with STEMI, research staff briefly explained the details to patients and their families immediately after wiring and thrombolysis in myocardial infarction (TIMI) flow restoration. Sex data were collected according to physical examination.

### Randomisation and masking

Patients indicated for percutaneous coronary intervention underwent a first randomisation, by means of an interactive web-based system, to undergo either intravascular ultrasound-guided percutaneous coronary intervention or angiography-guided percutaneous coronary intervention in a 1:1 ratio stratified by diabetes status (yes vs no), sex, and site using dynamic minimisation.<sup>20</sup> 30 days after the first-stage randomisation, surviving patients free from major ischaemic or bleeding events underwent a second randomisation to receive either ticagrelor plus oral enteric aspirin or ticagrelor plus a matching placebo for an additional 11 months (ie, second-stage randomisation).

By necessity, random assignment was not masked for the physicians and staff in the cardiac catheterisation

laboratory. However, patients and all personnel interacting with the patient after catheterisation (including researchers, treating physicians, and health outcomes assessors) were masked to random assignment.

The first randomisation was done by an interventional nurse in the catheterisation laboratory and the second randomisation was done by the research coordinator in each centre; these individuals did not have involvement in the rest of study. Investigators were responsible for enrolment of participants.

We herein describe the outcomes of the first-stage randomisation (IVUS-ACS trial). The results of the second-stage randomisation (ULTIMATE-DAPT trial) are discussed in a separate publication.<sup>21</sup>

### Procedures

Percutaneous coronary intervention for lesions responsible for the acute coronary syndrome (culprit lesions) was performed during the index procedure using standard techniques as per the discretion of the operator. If other non-culprit lesions were present, their treatment was also recommended during the same procedure. If percutaneous coronary intervention for non-culprit lesions could not be completed during the index procedure, a second percutaneous coronary intervention procedure was allowed 2–3 days before discharge and followed the originally assigned intravascular ultrasound versus angiography guidance strategy.

In the group assigned to intravascular ultrasound-guided guidance, intravascular ultrasound was done with the Opticross catheter (Boston Scientific, Marlborough, MA, USA) and was recommended before percutaneous coronary intervention and mandatory after percutaneous coronary intervention for assessment of whether criteria for optimal stent implantation were achieved.<sup>2,3,5</sup> For lesions with a TIMI flow of 0–1 or patients with critical (ie,  $>90\%$  of diameter stenosis but TIMI flow 2–3) disease and tenuous haemodynamics (ie, large infarct with hypotension), pre-dilation using a small balloon (usually  $1.5$ – $2.0$  mm) was mandatory before the pre-percutaneous coronary intervention intravascular ultrasound. The target criteria for non-left main lesions were minimal stent area of more than  $5.0$  mm<sup>2</sup> or more than  $90\%$  of the minimal lumen area at the distal reference segment; plaque burden of less than  $55\%$  within  $5$  mm proximal or distal to the stent edge; and absence of medial dissection over  $3$  mm in length. For left main lesions, the target minimal stent area was more than  $10$  mm<sup>2</sup> for the left main segment, more than  $7$  mm<sup>2</sup> for the ostial or proximal left anterior descending artery and more than  $6$  mm<sup>2</sup> for the ostial or proximal left circumflex artery (if stented).<sup>5</sup> For both non-left main and left main lesions, all criteria had to be present to declare optimal stent implantation. Intravascular ultrasound use was not permitted in patients assigned to angiography guidance unless the operator

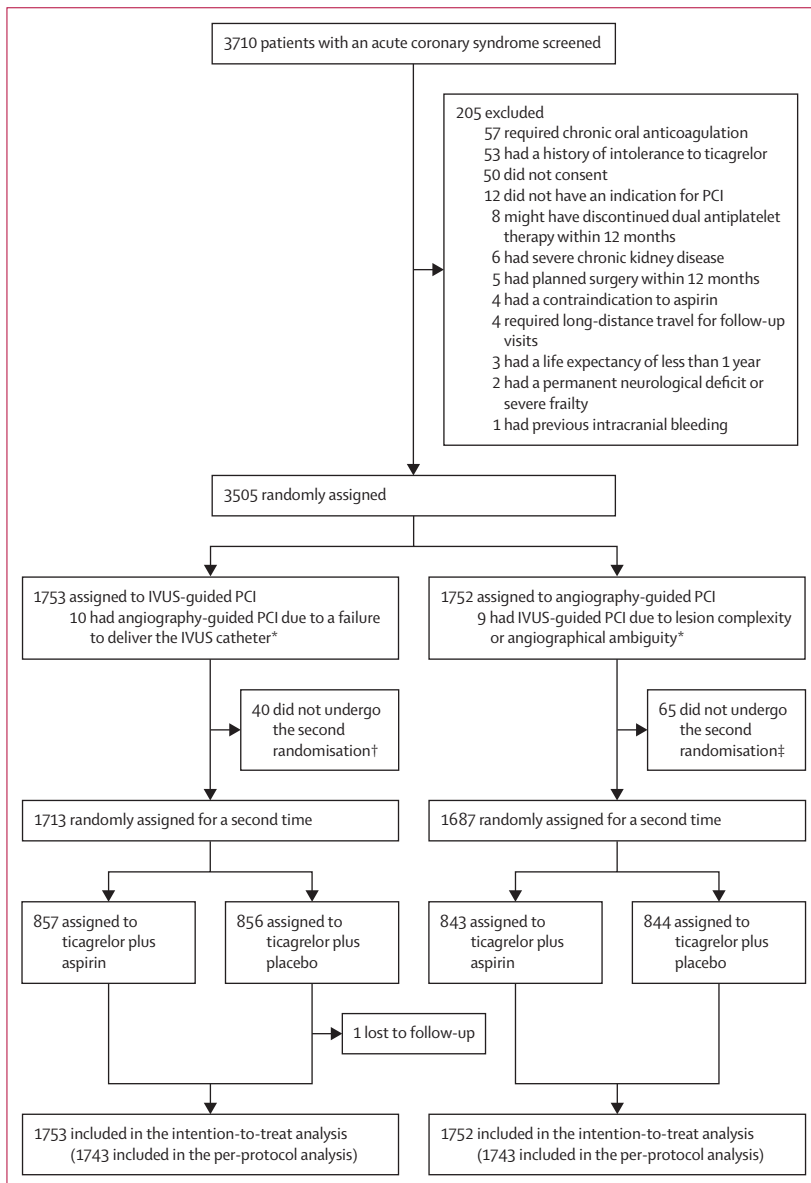
believed it was essential for lesion selection, in which case intravascular ultrasound was used only before percutaneous coronary intervention. Use of optical coherence tomography was not permitted in either group unless the IVUS catheter could not cross the lesion. All

patients received dual antiplatelet therapy consisting of oral aspirin (100 mg daily) plus oral ticagrelor (90 mg, twice daily) for 30 days after percutaneous coronary intervention and before the second-stage randomisation for the ULTIMATE-DAPT trial.

Angiograms and intravascular ultrasounds before and after percutaneous coronary intervention procedures were analysed by independent core laboratories. Measurements were assessed in the target lesion responsible for the acute coronary syndrome as assessed by the operator (appendix 2 pp 9–10). Follow-up visits were scheduled for 1, 4, 6, and 12 months after discharge. Angiographic follow-up was done only for clinical indications.

### Outcomes

The primary endpoint was target vessel failure, a composite of cardiac death, target vessel myocardial infarction, or clinically driven target vessel revascularisation, assessed at 12 months after the first randomisation. Secondary endpoints consisted of the individual components of the primary endpoint (ie, cardiac death, target vessel myocardial infarction, clinically driven target vessel revascularisation), target vessel failure without procedural myocardial infarction, target lesion revascularisation, Bleeding Academic Research Consortium (BARC)-defined types 3 or 5 bleeding, and Academic Research Consortium (ARC)-defined definite or probable stent thrombosis (appendix 2 pp 11–14). In brief, cardiac death was defined as any death due to a proximate cardiac cause (eg, myocardial infarction, low-output failure, or fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths including those related to concomitant treatment. Target vessel myocardial infarction consisted of procedural and spontaneous myocardial infarction; procedural myocardial infarction was defined as myocardial infarction within 48 h of the index procedure according to the Society of Cardiac Angiography and Interventions definition, and spontaneous myocardial infarction (beyond 48 h after the index procedure) was defined according to the third Universal Definition of Myocardial Infarction. Clinically driven revascularisation included repeat percutaneous coronary intervention or coronary artery bypass graft surgery and was defined according to its relationship to the target vessels and target lesions treated during the index percutaneous coronary intervention. BARC type 3 bleeding was defined as clinical, laboratory, or imaging evidence of severe bleeding with specific health-care provider responses (appendix 2 p 11); BARC type 5 bleeding was defined as fatal bleeding (ie, death for which the primary cause was bleeding). ARC definite stent thrombosis was defined as angiographical or pathological confirmation of stent thrombosis in or within 5 mm of the stent, in the setting of at least one of the following criteria with a 48-h time window: acute ischaemic symptoms at rest, new ischaemic changes on electrocardiogram, and typical rise and fall in troponin or CK-MB (appendix 2 p 12). ARC



**Figure 1: Trial profile of the integrated IVUS-ACS and ULTIMATE-DAPT study programme**

All randomly assigned patients (n=3505) received open-label dual antiplatelet therapy (ticagrelor plus aspirin) for 30 days after PCI and before the second randomisation. BARC=Bleeding Academic Research Consortium. IVUS=intravascular ultrasound. PCI=percutaneous coronary intervention. \*Ten patients in the intravascular ultrasound-guided percutaneous coronary intervention group had angiography-guided PCI instead, and nine patients in the angiography-guided percutaneous coronary intervention group had intravascular ultrasound-guided percutaneous coronary intervention instead; these 19 patients were included in the intention-to-treat population (all patients who underwent first randomisation) but were excluded from the per-protocol population. †40 patients did not undergo the second random assignment (two stopped DAPT for  $\geq 48$  h, nine had clinical events, five had BARC types 3 or 5 bleeding, five refused, 17 had dyspnea, one was allergic to ticagrelor, and one was lost to follow-up). ‡65 patients did not undergo the second random assignment (six stopped DAPT for  $\geq 48$  h, ten had clinical events, nine had BARC types 3 or 5 bleeding, 12 refused, 23 had dyspnea, one was allergic to ticagrelor, and four needed chronic oral anticoagulation).



probable stent thrombosis was defined as any unexplained death within the first 30 days after percutaneous coronary intervention or any myocardial infarction at any time after percutaneous coronary intervention that was related to documented acute ischaemia in the territory of the implanted stent, in the absence of angiographical or pathological confirmation of stent thrombosis and with no other obvious cause. Intraprocedural complications included coronary artery perforation, cardiac tamponade, type B coronary artery dissection, abrupt vessel closure, no reflow or slow flow, occlusion of a large side branch (diameter >2.5 mm), and contrast allergy.

### Statistical analysis

On the basis of previous studies,<sup>2,3,10,21</sup> we estimated a 1-year rate of target vessel failure with angiography-guided percutaneous coronary intervention of 10.0% (appendix 2 p 15). Randomisation of 3486 patients provided 80% power to demonstrate a 28% risk reduction in target vessel failure with intravascular ultrasound-guided percutaneous coronary intervention, assuming a two-sided *p* value of 0.05 and a dropout rate of 5%.

Categorical variables are reported as numbers and percentages and were compared using the  $\chi^2$  test or Fisher's exact test. Continuous variables are reported as mean (SD) or median (IQR) if not normally distributed and were compared using the *t* test or the Mann-Whitney *U* test, respectively. Event rates were estimated using the Kaplan-Meier method and were compared using the log-rank test. Treatment effects were estimated using Cox proportional hazards regression, with results presented as hazard ratios (HR) and corresponding 95% CIs. Target vessel failure with and without periprocedural myocardial infarction were analysed with the subdistribution method of Fine and Gray to account for the competing risk of non-cardiac death. The treatment effects for the primary analyses were adjusted for type of acute coronary syndrome (ie, unstable angina *vs* NSTEMI *vs* STEMI), second-stage randomisation (treatment with single *vs* dual antiplatelet therapy after 30 days), diabetes, and geographical region (Pakistan, UK, Italy, western China, eastern China, southern China, or northern China). Adjustment for multiplicity was not done for any secondary endpoints, and these should therefore be considered hypothesis-generating only. The relative treatment effects of the primary endpoint in prespecified subgroups (appendix 2 p 138), including according to the second randomisation, were assessed using interaction terms in the Cox proportional hazard model. Missing data were not imputed or otherwise replaced.

All principal analyses were done in the intention-to-treat population, regardless of inclusion in the second-stage randomisation. As a sensitivity analysis, the primary endpoint was assessed in the per-protocol population, defined as all patients in whom intravascular ultrasound-guided and angiography-guided percutaneous coronary intervention were performed as assigned. All tests were two-sided and *p*<0.05 was considered

significant. Statistical analyses were done using SAS version 9.4. This trial is registered at ClinicalTrials.gov, NCT03971500, and is completed.

### Role of the funding source

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

	Intravascular ultrasound-guided percutaneous coronary intervention (n=1753)	Angiography-guided percutaneous coronary intervention (n=1752)
Age (years)	62 (54–69)	63 (54–69)
Sex		
Male	1285 (73.3%)	1299 (74.1%)
Female	468 (26.7%)	453 (25.9%)
Race		
Chinese	1550 (88.4%)	1545 (88.2%)
Other	203 (11.6%)	207 (11.8%)
Initial presentation		
Unstable angina	699 (39.9%)	726 (41.4%)
Non-STEMI	570 (32.5%)	537 (30.7%)
STEMI	484 (27.6%)	489 (27.9%)
Medical history		
Hypertension	1103 (62.9%)	1089 (62.2%)
Diabetes	554 (31.6%)	551 (31.5%)
On insulin treatment	148 (8.4%)	145 (8.3%)
Dyslipidaemia	1187 (67.7%)	1222 (69.8%)
Current smoking*	499 (28.5%)	487 (27.8%)
Chronic kidney disease	132 (7.5%)	127 (7.3%)
Previous PCI	179 (10.2%)	179 (10.2%)
Previous CABG	4 (0.2%)	4 (0.2%)
Previous myocardial infarction	152 (8.7%)	154 (8.8%)
Previous stroke	142 (8.1%)	169 (9.7%)
Peripheral arterial disease	82 (4.7%)	83 (4.7%)
Heart failure	111 (6.3%)	106 (6.1%)
Left ventricular ejection fraction, %	62% (55–65)	62% (55–65)
Medications at discharge after percutaneous coronary intervention		
Aspirin	1753 (100%)	1752 (100%)
Ticagrelor	1753 (100%)	1752 (100%)
$\beta$ blocker	857 (48.9%)	840 (48.0%)
ACEI or ARB	793 (45.2%)	812 (46.4%)
Calcium channel antagonist	468 (26.7%)	456 (26.0%)
Statin	1434 (81.8%)	1474 (84.1%)

Data are median (IQR), or n (%). ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. CABG=coronary artery bypass graft surgery. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. \*Defined as  $\geq 100$  lifetime cigarettes and still smoking at the time of enrolment; other tobacco products were not included.

**Table 1: Baseline characteristics and medications at discharge**

	Intravascular ultrasound-guided percutaneous coronary intervention (n=1753)	Angiography-guided percutaneous coronary intervention (n=1752)	Hazard ratio (95% CI)	p value
<b>Primary endpoint</b>				
Target vessel failure*	70 (4.0%)	128 (7.3%)	0.55 (0.41–0.74)	0.0001
<b>Secondary endpoints</b>				
Target vessel failure without procedural myocardial infarction*	38 (2.2%)	90 (5.1%)	0.45 (0.30–0.66)	<0.0001
Cardiac death*	9 (0.5%)	20 (1.1%)	0.56 (0.24–1.29)	0.17
Target vessel myocardial infarction*	44 (2.5%)†	67 (3.8%)†	0.63 (0.43–0.92)	0.018
Procedural myocardial infarction	34 (1.9%)	42 (2.4%)	0.78 (0.50–1.22)	0.28
Non-procedural myocardial infarction	11 (0.6%)	26 (1.5%)	0.41 (0.20–0.84)	0.014
Clinically driven target vessel revascularisation*	24 (1.4%)	56 (3.2%)	0.44 (0.27–0.72)	0.0010
Clinically driven target lesion revascularisation*	22 (1.3%)	44 (2.5%)	0.52 (0.31–0.88)	0.014
<b>Safety endpoints</b>				
Definite or probable stent thrombosis	10 (0.6%)	16 (0.9%)	0.82 (0.35–1.90)	0.64
Definite stent thrombosis	5 (0.3%)	11 (0.6%)	0.51 (0.18–1.46)	0.21
Probable stent thrombosis	5 (0.3%)	5 (0.3%)	1.77 (0.36–8.65)	0.48
All-cause death	14 (0.8%)	26 (1.5%)	0.64 (0.32–1.27)	0.20
Major bleeding (BARC types 3 or 5)	15 (0.9%)	26 (1.5%)	0.57 (0.30–1.08)	0.09

Data are number (%) of events (Kaplan–Meier estimated percentage at 1 year), unless otherwise specified. BARC=Bleeding Academic Research Consortium. \*Related to the acute coronary syndrome culprit lesion. †One patient in each group had both a procedure-related and non-procedure-related target vessel myocardial infarction.

**Table 2: Primary, secondary, and safety endpoints at 1 year**

## Results

Between Aug 20, 2019, and Oct 27, 2022, 3710 patients with an acute coronary syndrome were screened and 3505 were enrolled. 1753 (50.0%) patients were randomly assigned to intravascular ultrasound-guided percutaneous coronary intervention and 1752 (50.0%) to angiography-guided percutaneous coronary intervention (figure 1; appendix 2 p 16). 3382 (96.5%) patients were recruited upon presentation to the emergency room (1688 [96.3%] patients to the intravascular ultrasound-guided percutaneous coronary intervention group and 1694 [96.7%] to the angiography group). Intravascular ultrasound was not used for ten patients assigned to the treatment group due to a failure to deliver the intravascular ultrasound catheter. In the 1743 (99.4%) of 1753 patients who received intravascular ultrasound as per assignment, 1737 patients (99.7%) had pre-procedural intravascular ultrasound and 1743 patients (100.0%) had post-procedural intravascular ultrasound. In the angiography group, nine (0.5%) of 1752 patients required pre-procedural intravascular ultrasound for lesion selection, but no patients had post-procedural

percutaneous coronary intervention. No patient in either group had optical coherence tomography. 30 days after percutaneous coronary intervention, 1713 patients in the intravascular ultrasound group underwent a second randomisation (856 [50.0%] assigned to single antiplatelet therapy and 857 [50.0%] assigned to dual antiplatelet therapy), and 1687 patients in the angiography group underwent a second randomisation (844 [50.0%] assigned to single antiplatelet therapy and 843 [50.0%] assigned to dual antiplatelet therapy; figure 1; appendix 2 p 17).

Baseline characteristics were similar between the two groups (table 1; appendix 2 p 18). The median patient age was 62 years (IQR 54–69, 2584 (73.7%) were men, 921 (26.3%) were women, and 1105 (31.5%) had type 2 diabetes. The presenting clinical syndrome was unstable angina in 1425 patients (40.7%), NSTEMI in 1107 (31.6%) and STEMI in 973 (27.8%).

Baseline angiographic and percutaneous coronary intervention procedural characteristics were well matched between the groups (appendix 2 pp 19–20). Compared with patients in the angiography guidance group, patients who had intravascular ultrasound-guided percutaneous coronary intervention received longer and larger stents that were more frequently post-dilated (appendix 2 p 20). Quantitative coronary analysis after percutaneous coronary intervention showed that the median minimal lumen diameter was 2.76 mm (IQR 2.38–3.17) in the intravascular ultrasound-guided group and 2.70 mm (2.34–3.06) in the angiography-guided group ( $p=0.0007$ ). The median diameter stenosis was 12.9% (6.5–19.3) in the intravascular ultrasound-guided group and 14.0% (7.9–20.3) in the angiography-guided group ( $p=0.0005$ ; appendix 2 p 21). Complete revascularisation by angiographical criteria was reached in a similar proportion of patients in both groups (appendix 2 p 21). Contrast use was slightly greater (median difference 13.1 mL [95% CI 9.5–16.9]) and procedure duration was longer (19.6 min [95% CI 17.5–21.2]) with intravascular ultrasound guidance than with angiography guidance. 254 (7.2%) of 3505 patients had a second percutaneous coronary intervention (appendix 2 p 19).

In the intravascular ultrasound group, optimal post-intervention intravascular ultrasound criteria were met in 1392 (79.9%) of 1743 (10 patients in IVUS group did not undergo IVUS guidance) patients (appendix 2 pp 22–23, 26, 28). Of note, quantitative angiographical measurements were similar in patients who did and did not meet optimal intravascular ultrasound criteria, but both had a better minimal lumen diameter after percutaneous coronary intervention than patients in the angiography group.

1-year follow-up was completed by 3504 (>99.9%) patients, including 3399 of 3400 (>99.9%) patients who underwent the second-stage randomisation. The primary endpoint of target vessel failure at 1 year occurred in

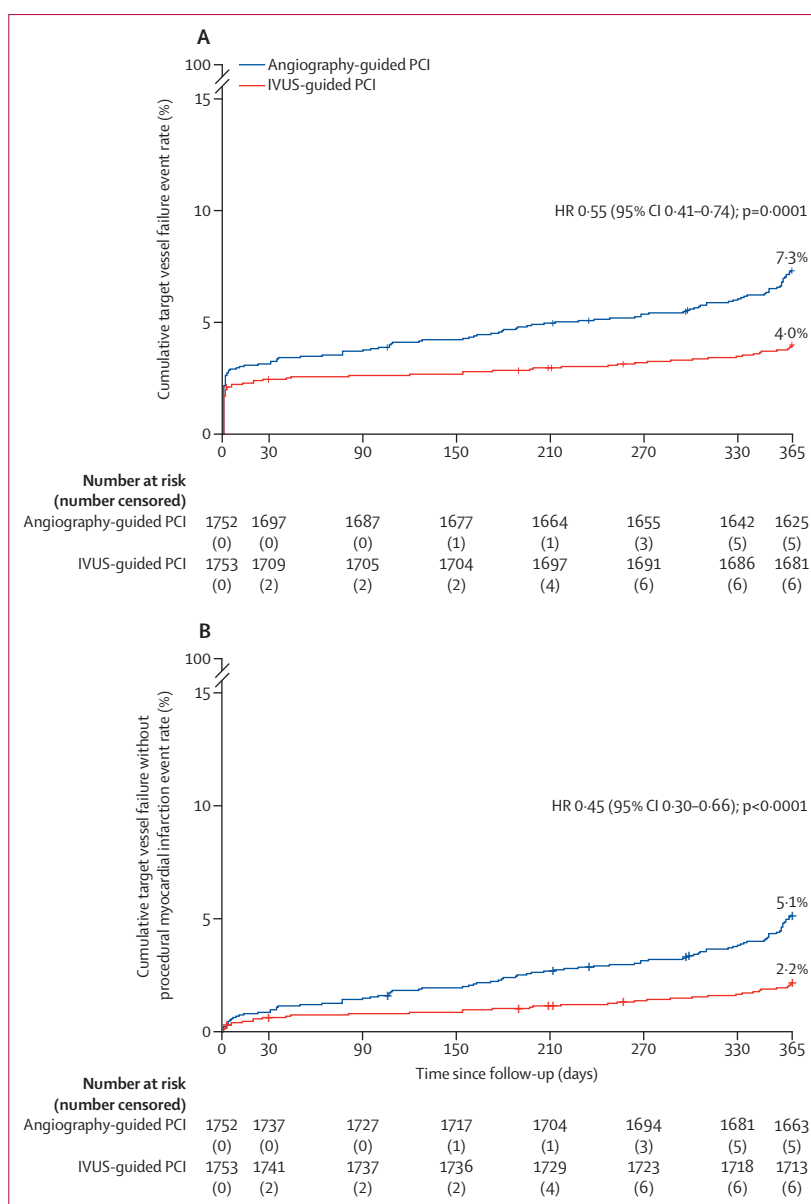
70 patients in the intravascular ultrasound-guided group and in 128 patients in the angiography group (Kaplan-Meier rate 4.0% vs 7.3%; HR 0.55 [95% CI 0.41–0.74];  $p=0.0001$ ; table 2, figure 2A). The risk of target vessel failure without procedural myocardial infarction was also lower in the intravascular ultrasound group than in the angiography group (HR 0.45 [95% CI 0.30–0.66];  $p<0.0001$ ; table 2, figure 2B). An interaction effect between all randomly assigned patients and those who underwent the second randomisation was ruled out (HR 0.79 [95% CI 0.43–1.49];  $p_{\text{interaction}}=0.48$ ).

Fewer target vessel myocardial infarctions and clinically driven target vessel revascularisations occurred after intravascular ultrasound-guided percutaneous coronary intervention compared with angiography-guided percutaneous coronary intervention (table 2). We observed no significant differences in the secondary outcomes of cardiac death or procedural myocardial infarction between the groups. Angiographical follow-up within 365 days for clinical indications was done for 73 (4.2%) of the 1753 patients in the intravascular ultrasound-guided group and in 90 (5.1%) of the 1752 patients in the angiography-guided group ( $p=0.31$ ).

The relative risks of target vessel failure between the two groups were similar in analyses that were not covariate adjusted (appendix 2 p 24) and in the per-protocol cohort (appendix 2 p 25). The hazard ratios for the primary endpoint were consistent across 12 prespecified subgroups in each trial group, including acute coronary syndrome type and single versus dual antiplatelet therapy after the second randomisation (figure 3). The rate of the primary endpoint was 3.2% (45 of 1392) in patients in the intravascular ultrasound group who met optimal stent implantation criteria, 7.1% (25 of 351) in patients in the intravascular ultrasound group with suboptimal criteria, and 7.3% (128 of 1752) in patients in the angiography group. No significant differences in safety endpoints were seen at 1 year of follow-up (table 2; appendix 2 p 27).

## Discussion

In the IVUS-ACS trial, intravascular ultrasound-guided percutaneous coronary intervention resulted in a lower incidence of target vessel failure at 1-year of follow-up than did angiography-guided percutaneous coronary intervention in patients with an acute coronary syndrome. This difference was driven by fewer target vessel myocardial infarctions (especially non-procedural infarctions after hospital discharge) and repeat revascularisation procedures in the intravascular ultrasound compared with the angiography-guided group. The results of the primary (intention-to-treat) analysis were consistent with those of the per-protocol analysis and across prespecified subgroups. Both intravascular ultrasound guidance and angiography guidance were safe and few procedural complications were noted. No significant differences in cardiac death, all-cause death, or stent thrombosis were

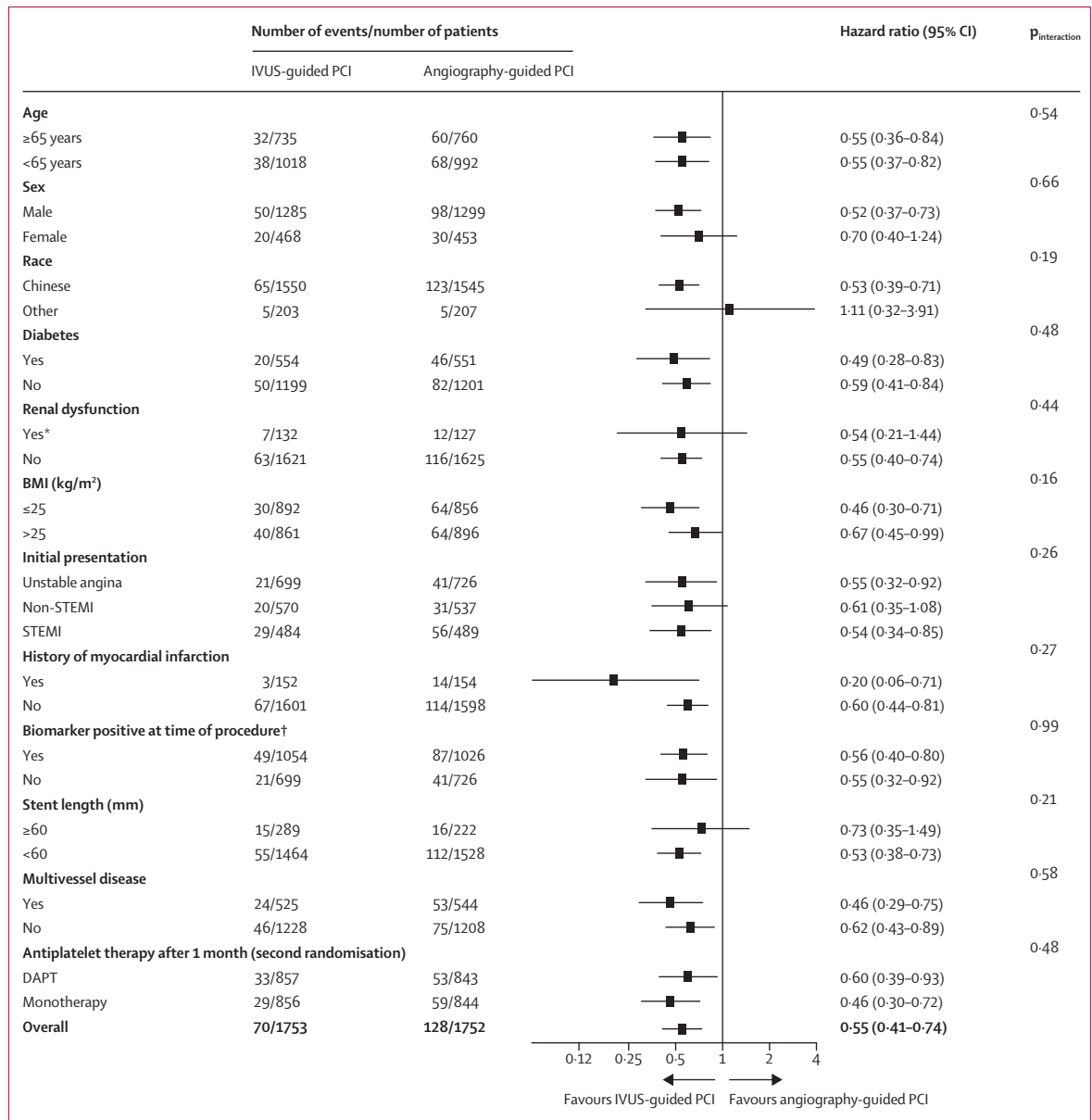


**Figure 2: Cumulative incidence of target vessel failure**

(A) The primary endpoint was target vessel failure, defined as the composite of death from cardiac causes, target vessel myocardial infarction, or clinically driven target vessel revascularisation in the intention-to-treat population through 1 year of follow-up. (B) The secondary endpoint of target vessel failure excluding procedural myocardial infarction. HR=hazard ratio. IVUS=intravascular ultrasound. PCI=percutaneous coronary intervention.

observed between the intravascular ultrasound and angiography guidance groups.

The results of this trial are consistent with those of previous studies done mostly in patients with a chronic coronary syndrome.<sup>5</sup> Improved outcomes of intravascular ultrasound-guided percutaneous coronary intervention compared with angiography guidance have been attributed to the implantation of larger and longer stents at higher pressures (which results in achievement of a greater minimum stent area); more precise identification of the



**Figure 3: Subgroup analysis for the primary endpoint at 1 year**

The hazard ratio for the primary endpoint of target vessel failure at 1 year was consistent across 12 prespecified subgroups, including acute coronary syndrome type and the second randomisation. Antiplatelet therapy between 1 month and 12 months represents the outcomes in event-free patients at 1-month after percutaneous coronary intervention who were randomised again to DAPT (ticagrelor plus aspirin) or ticagrelor plus placebo. DAPT=dual antiplatelet therapy. IVUS=intravascular ultrasound. PCI=percutaneous coronary intervention. STEMI=ST segment elevation myocardial infarction. \*Defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup>. †Defined as either troponin or CK-NB >1 time increase.

landing zone (which minimises undertreatment of the reference segment disease); and better detection and treatment of edge dissections.<sup>2,3,22,23</sup> However, the outcomes of intravascular ultrasound-guided percutaneous coronary intervention have not previously been studied in a dedicated randomised trial of patients with an acute coronary syndrome, which is currently the most common indication for percutaneous coronary intervention.<sup>17,18</sup> Ulceration with thrombosis of a lipid-rich

plaque is present in most patients with an acute coronary syndrome; stenting such lesions entails greater procedural risks and might evoke different vascular responses compared with percutaneous coronary intervention of more chronic fibrocalcific lesions.<sup>6</sup> Some, but not all previous non-randomised studies have reported improved outcomes from intravascular ultrasound-guided percutaneous coronary intervention compared with angiography guidance in patients with an acute coronary



syndrome.<sup>10–13</sup> Previous large randomised trials of intravascular ultrasound guidance have either included few patients with an acute coronary syndrome<sup>2–4</sup> or excluded patients with recent myocardial infarction.<sup>2</sup> Only three small trials have randomly assigned patients exclusively with an acute coronary syndrome to an intravascular imaging-guided percutaneous coronary intervention strategy, but these studies used optical coherence tomography for imaging guidance rather than intravascular ultrasound, and, with only 526 total patients, their findings were inconclusive.<sup>14–16</sup> This large-scale trial shows that, in the era of contemporary drug-eluting stents, intravascular ultrasound guidance improves clinical outcomes from percutaneous coronary intervention in patients with an acute coronary syndrome compared with angiography guidance alone.

All types of acute coronary syndromes were included in this study, with consistent reductions in target vessel failure with intravascular ultrasound-guided percutaneous coronary intervention observed in recent NSTEMI, STEMI, and unstable angina. As in previous studies, intravascular ultrasound guidance informed stent selection and technique and resulted in the use of longer stents with larger diameters and more frequent post-dilatation compared with angiography guidance. Although intravascular ultrasound was not done for the angiography guidance group, these procedural differences probably resulted in greater luminal dimensions and more optimal lesion coverage free from edge dissections, the principal correlates of improved long-term percutaneous coronary intervention outcomes.<sup>2–4,22–25</sup> Intravascular ultrasound-defined optimal stent implantation according to the ULTIMATE trial criteria for non-left main lesions<sup>3</sup> and the EXCEL trial criteria for left main lesions<sup>19</sup> was achieved in 79·9% of patients. 1-year target vessel failure rates were low in patients with optimal intravascular ultrasound-defined stent implantation, whereas those with suboptimal intravascular ultrasound results had outcomes similar to those in the angiography-guided percutaneous coronary intervention group. The relationships between the intravascular ultrasound-defined lesion morphologies and outcomes after percutaneous coronary intervention will be discussed in a subsequent report.

Our study has some limitations. First, random assignment to intravascular ultrasound-guided and angiography-guided percutaneous coronary intervention could not be masked to the operators; as such, performance bias cannot be excluded. However, we believe that masking of patients and caregivers outside of the catheterisation laboratory, and the clinical events committee, minimised the risk of placebo and Hawthorne effects and ascertainment bias. Second, 1425 (40·7%) of 3505 patients were classified as having unstable angina, but because high-sensitivity troponin tests were not routinely used at many of the sites during the enrolment period, many of these patients might have had NSTEMI

rather than unstable angina. However, the effects of this potential misclassification should be negligible, given that the reduction in target vessel failure was consistent in patients with unstable angina, NSTEMI, and STEMI. Third, clinically driven target vessel revascularisation was strictly defined in the present study and required either objective evidence of ischaemia or a severe angiographic stenosis. This precise definition might have increased the specificity but decreased the sensitivity of detection of clinically driven target vessel revascularisation events. Fourth, the lower rate of stent thrombosis with intravascular ultrasound guidance compared with angiography guidance did not reach statistical significance; however, stent thrombosis is a low frequency event, and a recent comprehensive network meta-analysis has shown conclusively that both intravascular ultrasound and optical coherence tomography guidance reduce stent thrombosis across the spectrum of coronary artery disease presentations.<sup>5,26</sup> Fifth, intravascular ultrasound guidance was associated with a small increase in the amount of contrast administered (median 13·1 mL) compared with angiography guidance, associated with iterative procedures to optimise stent implantation and which, along with imaging performance and review, extended the duration of the percutaneous coronary intervention procedure by a median of 19·6 min. Despite the benefits of intravascular ultrasound guidance, the associated need for a greater amount of contrast should be considered in the choice of imaging technique for patients with severe chronic kidney disease. Sixth, intravascular ultrasound was the sole imaging method studied in the present trial because it was widely used by the participating centres, but whether optical coherence tomography-guided percutaneous coronary intervention might have resulted in the same or greater benefits as seen with intravascular ultrasound guidance is unknown. Seventh, the diagnosis of procedural myocardial infarction was based on clinical suspicion of an event. This method might have added some imprecision to the event rates, but as this bias applied equally to both arms and all health-care assessors were masked after the patient left the catheterisation laboratory, it should not have affected the relative outcomes of intravascular ultrasound versus angiography guidance. Eighth, the COVID-19 pandemic reduced the originally planned diversity of recruiting sites, resulting in only 410 (11·7%) of 3505 patients being enrolled outside of China, and a larger trial outside of China is warranted to confirm the present findings. Ninth, the rate of target vessel failure rate in the angiography guidance group (7·3%) was lower than anticipated (10·0%), which reflects some imprecision in the estimates due to the paucity of available predicate randomised trial data. Nevertheless, the treatment effect size was substantial, allowing the null hypothesis to be rejected with a high degree of confidence. Tenth, although data on the number of days from the initial presentation with acute coronary syndrome to percutaneous coronary intervention were

not collected, most patients in both groups were recruited directly from the emergency room, minimising the effect of this limitation on the results. Finally, participation in the present study required annual volumes of more than 1000 percutaneous coronary intervention procedures per centre (except for the UK site) and more than 200 percutaneous coronary intervention procedures per operator; whether these results would be replicated at sites with a lesser volume of percutaneous coronary intervention is uncertain. Two additional ongoing trials (NCT04775914 and NCT05007535) might provide additional insight into this issue.

In summary, IVUS-ACS is the first large randomised controlled trial to test the outcomes of intravascular ultrasound-guided versus angiography-guided implantation of contemporary drug-eluting stents in a large population with acute coronary syndromes, and has shown that percutaneous coronary intervention performed with intravascular ultrasound guidance results in a lower 1-year risk of target vessel failure compared with angiography guidance alone.

#### Contributors

GWS and S-LC designed the study, analysed the data, prepared outlines of and revised the manuscript. XL, ZG, and MA enrolled patients into the study and wrote the draft of the manuscript. JK provided crucial input into the conduct of the trial and drafting of the manuscript. PX, XC, HSK, XG, TS, JC, BUAG, NG, IS, J-JZ, and AR enrolled patients into the study and revised the manuscript. YW and FC were the primary biostatisticians. This investigator-sponsored study was led by S-LC at the Nanjing First Hospital in China. All authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and had final responsibility for the decision to submit for publication. XL and S-LC accessed and verified the data. GSM reviewed all intravascular ultrasound measurements.

#### Declaration of interests

GWS reports speaker fees from Medtronic, Pulnovo, Infraredx, Abiomed, Abbott, Amgen, and Boehringer Ingelheim; has served as a consultant to 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 Oxitepe; has equity or options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave paid directly to institution; and his daughter is an employee at IQVIA. S-LC reports speaker fees from Microport, Pulnovo, Boston International Scientific, Medtronic, Sanofi, and BioMed; and grants from the National Scientific Foundation of China. GSM received honorarium from Boston Scientific. All other authors declare no competing interests.

#### Data sharing

Patient-level data collected for this study will not be made publicly available. However, the investigators will consider collaboration and data sharing for specific projects; requests should be addressed to author Shao-Liang Chen.

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