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ORIGINAL RESEARCH

# IVUS-Guided vs Angiography-Guided PCI in Patients With Diabetes With Acute Coronary Syndromes

## The IVUS-ACS Trial

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## ABSTRACT

**BACKGROUND** Intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) reduces the risk for clinical events in patients with acute coronary syndromes (ACS), compared with angiographic guidance. However, the benefits of IVUS guidance in high-risk patients with diabetes with ACS is uncertain.

**OBJECTIVES** The aim of this prespecified stratified subgroup analysis from the IVUS-ACS randomized trial was to determine the effectiveness of IVUS-guided PCI vs angiography-guided PCI in patients with diabetes with ACS.

**METHODS** From August 20, 2019, to October 27, 2022, 1,105 patients with diabetes with ACS were randomized, including 554 patients in the IVUS-guided group and 551 in the angiography-guided group. The primary endpoint was the rate of target vessel failure (TVF) at 1 year, defined as the composite of cardiac death, target vessel myocardial infarction, or clinically driven target vessel revascularization.

**RESULTS** At 1-year follow-up, TVF occurred in 20 patients in the IVUS guidance group and in 46 patients in the angiographic guidance group (Kaplan-Meier rates 3.6% vs 8.3%; HR: 0.46; 95% CI: 0.27-0.81; $P = 0.007$), driven by a reduction in clinically driven target vessel revascularization (0.9% vs 3.8%; $P = 0.003$). IVUS-guided PCI also reduced the risk for TVF without procedural myocardial infarction (2.0% vs 6.7%; HR: 0.29; 95% CI: 0.15-0.57; $P < 0.001$) and all-cause mortality (HR: 0.30; 95% CI: 0.10-0.93; $P = 0.037$). There were no significant differences in the rates of stent thrombosis or major bleeding between the groups.

**CONCLUSIONS** In the large-scale IVUS-ACS trial, IVUS-guided PCI improved 1-year clinical outcomes in high-risk patients with diabetes with ACS. (1-Month vs 12-Month DAPT for ACS Patients Who Underwent PCI Stratified by IVUS: IVUS-ACS and ULTIMATE-DAPT Trials; NCT03971500) (JACC Cardiovasc Interv. 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.


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**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndrome(s)

**DAPT** = dual antiplatelet therapy

**IVUS** = intravascular ultrasound

**MI** = myocardial infarction

**NSTEMI** = non-ST-segment elevation myocardial infarction

**PCI** = percutaneous coronary intervention

**SAPT** = single antiplatelet therapy

**STEMI** = ST-segment elevation myocardial infarction

**TLR** = target lesion revascularization

**TVF** = target vessel failure

**TVR** = target vessel revascularization

In 2021, 529 million people were living with diabetes worldwide, and the global age-standardized total diabetes prevalence was 6.1%.[1] Diabetes is estimated to contribute to 11.3% of deaths globally, with 4.2 million deaths in adults between 20 and 79 years of age attributable to diabetes.[2] Patients with diabetes mellitus represent 25% to 30% of subjects admitted with acute coronary syndromes (ACS), and their outcomes are poorer than those of patients without diabetes.[3,4] Patients with diabetes with unstable angina have a higher incidence of vulnerable plaques (plaque ulceration, intracoronary thrombus formation, calcification, and dissection),[5,6] smaller diameter coronary arteries in part because of lower levels of nitric oxide-mediated vasodilation,[7] and a greater prevalence of multivessel disease than patients without diabetes.[8] As a result, patients with diabetes have less favorable clinical outcomes after percutaneous coronary intervention (PCI), with higher incidences of restenosis, myocardial infarction (MI), and death.[8-12] Angiography has well-known limitations in accurately assessing lesion measurements and stent expansion that may be overcome by intravascular imaging. Intravascular imaging-guided PCI has been shown to reduce ischemic event rates compared with angiography-guided PCI.[13,14] However, these findings have not been confirmed in high-risk patients with diabetes presenting with ACS from a randomized clinical trial.[15-22]

In the IVUS-ACS (1-Month vs 12-Month DAPT for ACS Patients Who Underwent PCI Stratified by IVUS) trial (NCT03971500),[23] 3,505 patients with ACS were randomly assigned to either intravascular ultrasound (IVUS) guidance or angiographic guidance. Significant improvements in the 1-year primary endpoint of target vessel failure (TVF), nonprocedural MI, and repeat revascularization were demonstrated with IVUS guidance compared with angiographic guidance. Notably, randomization was stratified by the presence of diabetes. We thus conducted a prespecified analysis from IVUS-ACS to determine whether the benefits of IVUS guidance were present among patients with ACS with diabetes mellitus.

## METHODS

**STUDY DESIGN AND PARTICIPANTS.** IVUS-ACS was an investigator-sponsored, randomized, single-blind trial performed at 58 clinical sites in 4 countries (China, Italy, Pakistan, and the United Kingdom).[23] The steering committee designed the trial and is responsible for the study conduct and oversight, data analysis and interpretation, and publications. An expert global panel provided academic, medical, and operational input in each country. Patients were eligible for inclusion in the trial if they were 18 years or older, presented with ACS (ie, unstable angina, non-ST-segment elevation MI [NSTEMI] or ST-segment elevation MI [STEMI]) caused by a culprit lesion in an untreated coronary artery segment within 30 days prior to randomization, and had an indication PCI with a second-generation drug-eluting stent. Patients were excluded if they had a life expectancy of <1 year, were intolerant of antithrombotic therapy, had severe chronic kidney disease (defined as an estimated glomerular filtration rate <20 mL/min/1.73 $m^2$), or had histories of stroke within 3 months or any permanent neurologic deficit or any previous intracranial bleed or intracranial disease. The IVUS-ACS trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the ethics committees or Institutional Review Board at each site, and all participants provided written informed consent.

**RANDOMIZATION.** Eligible participants were randomly assigned (1:1), using an interactive web-based response system, to undergo either IVUS-guided PCI or angiography-guided PCI. Randomization was stratified by diabetes status, sex, and site. Randomization assignment was not masked to the physicians and staff members in the cardiac catheterization laboratory. However, patients and all personnel interacting with the patient after catheterization (including researchers, treating physicians, and health outcomes assessors) were blinded to IVUS vs angiography randomization.

At 30 days, surviving patients free from major ischemic or bleeding events underwent a second double-blind randomization to receive either dual antiplatelet therapy (DAPT) with ticagrelor plus oral enteric aspirin or single antiplatelet therapy (SAPT) with ticagrelor plus a matching placebo for an additional 11 months (ULTIMATE-DAPT trial).[24]

**PROCEDURES.** PCI of the lesions responsible for the ACS (culprit lesions) was performed during the index procedure using standard techniques at the discretion of the operator. If necessary to treat additional nonculprit lesions, a staged PCI procedure was performed before discharge and followed the originally assigned IVUS vs angiographic guidance strategy.

In the angiography-guided group, stent diameter and length were selected by visual estimation with a

ratio of stent to vessel diameter of 1.1:1.0. Angiographic success was defined as TIMI (Thrombolysis In Myocardial Infarction) flow grade 3, residual stenosis < 20%, and the absence of type B or greater dissection. In the IVUS-guided group, the target criteria for non-left main lesions were minimal stent area > 5.0 $mm^2$ or >90% of the minimal luminal area at the distal reference segment, plaque burden <55% within 5 mm proximal or distal to the stent edge, and absence of a medial dissection >3 mm in length. For left main lesions, the target minimal stent area was >10 $mm^2$ for the left main segment, >7 $mm^2$ for the ostial or proximal left anterior descending artery, and >6 $mm^2$ for the ostial or proximal left circumflex artery (if stented); other criteria were the same as for non-left main lesions. All 3 criteria had to be present to declare optimal stent implantation.

**MEDICATIONS AND MEASUREMENTS.** Post-PCI, all patients received oral DAPT consisting of aspirin (100 mg/d) plus ticagrelor (90 mg twice daily). At 30 days after PCI, surviving patients without severe ischemic events or Bleeding Academic Research Consortium type 3 or 5 bleeding were treated with open-label ticagrelor (90 mg twice daily) and were randomized again to aspirin (100 mg/d) or a matching placebo for an additional 11 months (ie, between 1 and 12 months post-PCI).[24] Other medications were left to the discretion of the investigators.

**OUTCOMES AND ASSESSMENTS.** Follow-up visits were scheduled at 1 month, 12 months, and 2 years after discharge. Angiographic follow-up was done only for clinical indications. Angiograms and IVUS data were analyzed at independent core laboratories. At the present time, follow-up is complete in all patients through 12 months.

The primary endpoint was the 1-year rates of TVF, a composite of cardiac death, target vessel MI, or clinically driven target vessel revascularization (TVR). Cardiac death was defined as any death due to a proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed deaths, and deaths of unknown cause, as well as all procedure-related deaths. MIs were categorized as procedural vs nonprocedural; procedural MI was defined as MI occurring within 48 hours of the index procedure according to the Society for Cardiac Angiography and Interventions definition, and nonprocedural MI (beyond 48 hours after the index procedure) was defined according to the third universal definition of MI. Clinically driven revascularization included repeat PCI or coronary artery bypass graft surgery and was categorized according to its relationship to the target vessels and lesions treated during the index procedure. Secondary endpoints consisted of the individual components of the primary endpoint, TVF without procedural MI, clinically driven target lesion revascularization (TLR), Bleeding Academic Research Consortium–defined type 3 or 5 bleeding, and Academic Research Consortium–defined definite or probable stent thrombosis. Only adjusted events by independent clinical event committees were calculated in this analysis.

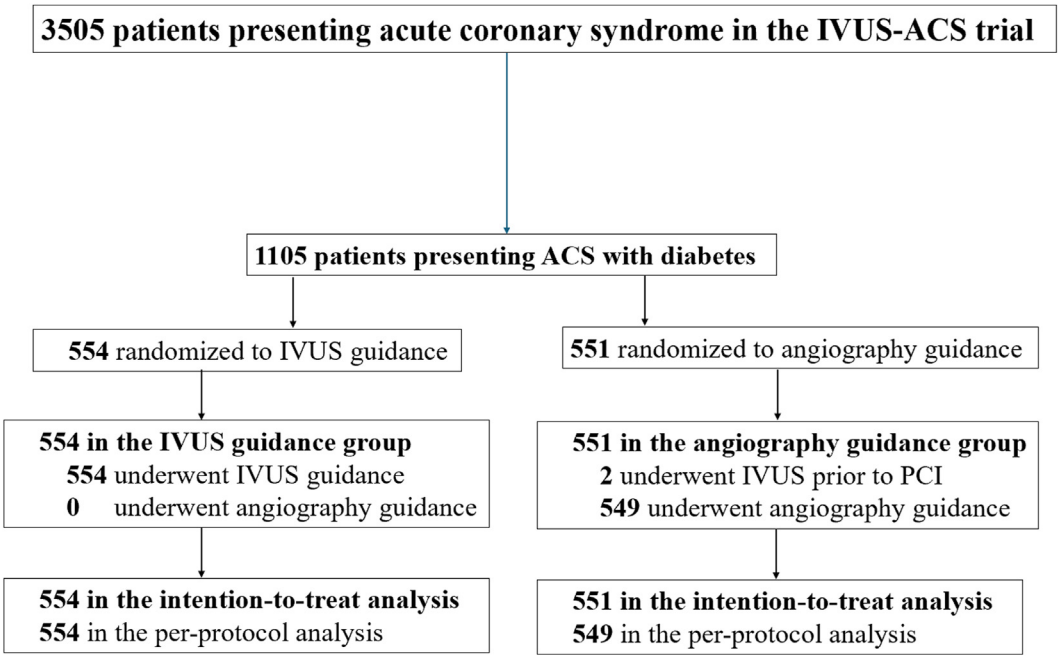
**STATISTICAL ANALYSIS.** This report presents the results from a prespecified substudy of randomized stratified patients with diabetes mellitus. Categorical variables are reported as numbers and percentages and were compared using the chi-square test or Fisher exact test. Continuous variables are reported as mean ± SD or median (Q1-Q3) if not normally distributed (using the Shapiro-Wilk test and Kolmogorov-Smirnov test) and were compared using Student's *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 HRs and corresponding 95% CIs. TVF with and without procedural MI was analyzed using the subdistribution method of Fine and Gray to account for the competing risk for noncardiac death. The treatment effects for the primary analyses were adjusted for the type of ACS (ie, unstable angina vs NSTEMI vs STEMI), randomized treatment with SAPT vs DAPT, dyslipidemia, target lesions in the left main coronary artery, those with moderate or severe calcification or containing thrombus, and geographic region (Chinese vs others). Adjustment for multiplicity was not done for secondary endpoints, which should therefore be considered hypothesis generating. Missing data were not imputed or otherwise replaced.

All principal analyses were done in the intention-to-treat population, regardless of the actual guidance. As a sensitivity analysis, the primary endpoint was assessed in the per protocol population, defined as all patients in whom IVUS-guided and angiography-guided PCI was performed as assigned. All tests were 2 sided, and *P* values <0.05 were considered to indicate statistical significance. Statistical analyses were done using SAS version 9.4 (SAS Institute).

## RESULTS

**PATIENT POPULATION.** Between August 20, 2019, and October 27, 2022, 3,505 patients with ACS were

**FIGURE 1** Study Flowchart




A total of 1,105 patients with diabetes with acute coronary syndrome (ACS) were included in the stratified randomized diabetic substudy, including 554 patients in the intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) group and 541 in the angiography-guided PCI group. Two patients in the angiographic guidance group who underwent IVUS before PCI because of uncertain anatomy by angiography alone were excluded from the per protocol analysis.

included in the IVUS-ACS trial. Of them, 1,105 patients (31.5%) who had diabetes were included in the present prespecified subgroup analysis, including 554 randomized in the IVUS-guided group and 551 randomized in the angiography-guided group (**Figure 1**). Baseline characteristics are presented in **Table 1** and were well matched between the groups. Among the 1,105 patients with diabetes, the mean age was 62 ± 10 years, 349 (31.6%) were women, 293 (26.5%) were treated with insulin, and 676 (61.2%) presented with MI. Patients with diabetes had more comorbidities than patients without diabetes (Supplemental Table S1). Among 143 patients with STEMI in the IVUS-guided PCI group, 134 primary PCI procedures were guided by IVUS.

**LESIONS AND PROCEDURAL CHARACTERISTICS.** Patients with diabetes had more complex lesions than patients without diabetes (Supplemental Table S2). Angiographic characteristics in the IVUS-guided PCI and angiography-guided PCI groups are shown in **Table 2**. The target lesions in the IVUS guidance group were slightly more likely to be in the left main segment and to be heavily calcified, whereas target lesions in the angiographic guidance group were slightly more likely to contain thrombus. Among 534 patients in the IVUS-guided group who underwent pre-PCI grayscale and radiofrequency IVUS imaging, lipid-rich plaque was present in 530 (99.3%), and calcified plaque was present in 354 (66.3%) (Supplemental Table S3). As shown in **Table 2**, IVUS guidance led to the use of more stents per patient with a larger diameter and longer stent length used compared with angiographic guidance. Postdilation was also more frequently performed in the IVUS guidance group. The rate of procedural success was higher with IVUS-guided PCI compared with angiography-guided PCI (99.6% vs 98.4%; $P = 0.032$). Conversely, IVUS guidance increased the procedural duration by about 21 minutes and contrast use by about 17 mL (**Table 2**).

By quantitative coronary analysis (**Table 3**), baseline measures were similar between the groups. The post-PCI acute gain (postprocedural minus baseline minimal luminal diameter) was greater with IVUS guidance compared with angiographic guidance (1.74 ± 0.75 mm vs 1.65 ± 0.72 mm; $P = 0.045$),

although other post-PCI measures were not significantly different between the groups.

**CLINICAL OUTCOMES.** At 30 days post-PCI, 8 patients in the IVUS-guided PCI group and 22 patients in the angiography-guided PCI group did not undergo second randomization, for reasons detailed in Supplemental Table S4. At 1-year follow-up, TVF had occurred in 46 patients in the angiographic guidance group and in 20 patients in the IVUS guidance group (Kaplan-Meier rates 3.6% vs 8.3%; HR: 0.49; 95% CI: 0.27-0.81; $P = 0.007$) (**Table 4**, **Figure 2A**), driven by lower occurrence in clinically driven TVR with IVUS guidance (0.9% vs 3.8%; HR: 0.23; 95% CI: 0.09-0.61; $P = 0.003$). The results were similar in the per protocol population (Supplemental Figure S1). The incidence of TVF without procedural MI in the IVUS guidance group was also lower than that in the angiographic guidance group (2.0% vs 6.7%; HR: 0.29; 95% CI: 0.15-0.57; $P < 0.001$) (**Table 4**, **Figure 2B**). IVUS guidance also reduced the risk for clinically driven TLR (0.9% vs 2.7%; HR: 0.32; 95% CI: 0.12-0.89; $P = 0.029$) and all-cause mortality (0.7% vs 2.4%; HR: 0.30; 95% CI: 0.10-0.93; $P = 0.037$). The risks for stent thrombus and major bleeding were similar between the 2 groups. Landmark analysis showed that a significant reduction in the IVUS-guided PCI group happened after 30 days since PCI (Supplemental Figure S3).

Among 554 patients in the IVUS guidance group, IVUS-defined optimal PCI was achieved in 429 (77.4%). The 1-year TVF rate was 2.3% in the optimal PCI group and 8.0% in the suboptimal PCI subgroup (HR: 0.23; 95% CI: 0.09-0.56; $P = 0.001$) (Supplemental Figure S2). The reasons for IVUS-defined suboptimal PCI are shown in Supplemental Figure S4. The 1-year TVF rate was nonsignificantly different between patients with unstable angina and with acute MI (Supplemental Table S5) and between patients with NSTEMI (5 of 194 [2.6%]) and those with STEMI (7 of 143 [4.9%]) ($P = 0.373$).

Among the 293 insulin-treated patients with diabetes, the 1-year rate of TVF was 3.4% with IVUS guidance and 13.8% with angiographic guidance (HR: 0.23; 95% CI: 0.09-0.62). In contrast, among the 812 non-insulin-treated patients with diabetes, the 1-year rate of TVF was 3.7% with IVUS guidance and 6.4% with angiographic guidance (HR: 0.57; 95% CI: 0.30-1.08) ($P_{\text{interaction}} = 0.086$). Finally, among the 1,075 patients with diabetes with ACS who were stable at 30 days and were randomized to SAPT (n = 540) vs DAPT (n = 535) between 1 and 12 months (**Table 2**), the 1-year rate of TVF was 2.8% with IVUS guidance and 8.9% with angiographic guidance (HR: 0.31; 95% CI: 0.14-0.69) in the SAPT group and 3.8% with IVUS guidance and 5.5% with angiographic guidance (HR: 0.68; 95% CI: 0.31-1.52) in the DAPT group ($P_{\text{interaction}} = 0.179$).

**TABLE 1 Baseline Characteristics and Medications in the IVUS-Guided and Angiography-Guided PCI Groups With Diabetes Mellitus**

| | Overall (N = 1,105) | IVUS-Guided PCI (n = 554) | Angiography-Guided PCI (n = 551) |
|---|---|---|---|
| Age, y | 62 ± 10 | 63 ± 10 | 62 ± 10 |
| Male | 756 (68.4) | 372 (67.1) | 384 (69.7) |
| Diabetes treated with insulin | 293 (26.5) | 148 (26.7) | 145 (26.3) |
| Initial presentation | | | |
| Unstable angina | 429 (38.8) | 217 (39.2) | 212 (38.5) |
| NSTEMI | 362 (32.8) | 194 (35.0) | 168 (30.5) |
| STEMI | 314 (28.4) | 143 (25.8) | 171 (31.0) |
| Medical history | | | |
| Hypertension | 794 (71.9) | 391 (70.6) | 403 (73.1) |
| Dyslipidemia | 824 (74.6) | 395 (71.3) | 429 (77.9) |
| Fast glucose at admission, mg/mL | 152.7 ± 65.6 | 152.9 ± 67.4 | 152.5 ± 63.7 |
| Current smoking | 276 (25.0) | 141 (25.5) | 135 (24.5) |
| Chronic kidney disease | 103 (9.3) | 54 (9.7) | 49 (8.9) |
| Previous PCI | 131 (11.9) | 64 (11.6) | 67 (12.2) |
| Previous CABG | 2 (0.2) | 0 (0.0) | 2 (0.4) |
| Previous myocardial infarction | 121 (11.0) | 63 (11.4) | 58 (10.5) |
| Previous stroke | 127 (11.5) | 54 (9.7) | 73 (13.2) |
| Peripheral arterial disease | 61 (5.5) | 29 (5.2) | 32 (5.8) |
| Heart failure | 77 (7.0) | 42 (7.6) | 35 (6.4) |
| Left ventricular ejection fraction, % | 58 ± 9 | 58 ± 9 | 58 ± 10 |
| Medications at discharge | | | |
| Aspirin | 1,105 (100.0) | 554 (100.0) | 551 (100.0) |
| Ticagrelor | 1,105 (100.0) | 554 (100.0) | 551 (100.0) |
| Beta-blocker | 578 (52.3) | 302 (54.5) | 276 (50.1) |
| ACEI or ARB | 572 (51.8) | 282 (50.9) | 290 (52.6) |
| Calcium-channel antagonist | 357 (32.3) | 181 (32.7) | 176 (31.9) |
| Statin | 922 (83.4) | 458 (82.7) | 464 (84.2) |

Values are mean ± SD or n (%). Diabetes mellitus is defined as glycated hemoglobin ≥6.5% (the test should be performed in a laboratory using a method that is National Glycohemoglobin Standard Program certified and standardized to the DCCT [Diabetes Control and Complications Trial] assay), fasting blood glucose ≥126 mg/dL (7.0 mmol/L) (fasting is defined as no caloric intake for at least 8 hours), or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (the test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; IVUS = intravascular ultrasound; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

## DISCUSSION

As shown in the **Central Illustration**, the major findings of the present prespecified subgroup analysis in the stratified high-risk diabetic subgroup from the IVUS-ACS trial are as follows: 1) among patients with diabetes with ACS, IVUS-guided PCI resulted in the use of larger, longer and more stents that were more aggressively postdilated, with higher rates of procedural success compared with angiography-guided PCI; 2) As a result, the 1-year rate of TVF was reduced in patients with diabetes with ACS

**TABLE 2 Lesions, Procedural Characteristics, and Antiplatelet Agent Assignment in the IVUS-Guided and Angiography-Guided PCI Groups With Diabetes**

| | Overall (N = 1,105) | IVUS-Guided PCI (n = 554) | Angiography-Guided PCI (n = 551) | *P* Value |
|---|---|---|---|---|
| Lesion characteristics | | | | |
| Single-vessel disease | 723 (65.4) | 365 (65.9) | 358 (65.0) | 0.750 |
| Multivessel disease | 382 (34.6) | 189 (34.1) | 193 (35.0) | 0.750 |
| Two-vessel disease | 287 (26.0) | 143 (25.8) | 144 (26.1) | 0.903 |
| Three-vessel disease | 95 (8.6) | 46 (8.3) | 49 (8.9) | 0.727 |
| Total number of lesions treated | 1.3 ± 0.6 | 1.3 ± 0.6 | 1.4 ± 0.6 | 0.581 |
| Culprit lesion[a] location | | | | 0.169 |
| Unprotected left main coronary artery | 53 (4.8) | 34 (6.1) | 19 (3.4) | 0.036 |
| Left anterior descending coronary artery | 590 (53.4) | 291 (52.5) | 299 (54.3) | 0.563 |
| Left circumflex coronary artery | 157 (14.2) | 74 (13.4) | 83 (15.1) | 0.417 |
| Right coronary artery | 305 (27.6) | 155 (28.0) | 150 (27.2) | 0.779 |
| Culprit lesion type[b] | | | | |
| True bifurcation[c] | 167 (15.1) | 85 (15.3) | 82 (14.9) | 0.831 |
| Long or diffuse[d] | 855 (77.4) | 441 (79.6) | 414 (75.1) | 0.076 |
| Moderate or greater calcification[e] | 93 (8.4) | 56 (10.1) | 37 (6.7) | 0.042 |
| Thrombus containing[f] | 94 (8.5) | 38 (6.9) | 56 (10.2) | 0.049 |
| Procedural data | | | | |
| Transradial access | 1,044 (94.5) | 522 (94.2) | 522 (94.7) | 0.709 |
| Aspiration thrombectomy used | 18 (1.6) | 7 (1.3) | 11 (2.0) | 0.336 |
| Rotational atherectomy used | 7 (0.6) | 4 (0.7) | 3 (0.5) | 1.000 |
| Number of stents implanted | 1.5 ± 0.7 | 1.6 ± 0.7 | 1.4 ± 0.7 | <0.001 |
| Maximum stent diameter, mm | 3.2 ± 0.5 | 3.3 ± 0.5 | 3.1 ± 0.4 | <0.001 |
| Total stent length, mm | 40 ± 20 | 43 ± 21 | 37 ± 19 | <0.001 |
| Postdilation performed | 1,049 (94.9) | 537 (96.9) | 512 (92.9) | 0.002 |
| Maximum balloon pressure, atm | 17 ± 3 | 17 ± 3 | 17 ± 3 | 0.107 |
| Contrast media, mL | 164 ± 56 | 172 ± 58 | 155 ± 52 | <0.001 |
| Procedural time, min | 50 ± 38 | 60 ± 44 | 39 ± 26 | <0.001 |
| Procedural success[g] | 1,094 (99.0) | 552 (99.6) | 542 (98.4) | 0.033 |
| Contrast-induced nephropathy | 79 (7.1) | 34 (6.1) | 45 (8.2) | 0.201 |
| Antiplatelet agent assignment between 1 and 12 mo | | | | |
| Did not undergo second randomization | 30 (2.7) | 8 (1.4) | 22 (4.0) | 0.009 |
| Underwent second randomization | 1,075 (97.3) | 546 (98.6) | 529 (96.0) | 0.009 |
| Assigned to aspirin plus ticagrelor | 535 (48.4) | 264 (48.4) | 271 (51.2) | 0.346 |
| Assigned to ticagrelor alone | 540 (48.9) | 282 (51.6) | 258 (48.8) | 0.346 |

Values are mean ± SD or n (%). [a]The lesion most likely responsible for the acute coronary syndrome as determined by the operator. [b]In patients with ST-segment elevation myocardial infarction, culprit lesions were assessed after lesions were crossed with a wire. [c]Defined as Medina 0,1,1 or 1,1,1 bifurcation lesion with a side branch ≥2.5 mm in diameter by visual estimation. [d]Defined as lesion length at least 30 mm by visual estimation. [e]Defined as the angiographic presence of calcium on both sides of the vessel at the lesion site. [f]Defined as an intraluminal filling defect seen in multiple projections. [g]Defined as TIMI (Thrombolysis In Myocardial Infarction) flow grade 3, residual stenosis <20%, and absence of type B or greater dissection, with no intraprocedural complications.

Abbreviations as in Table 1.

undergoing PCI with IVUS guidance compared with angiographic guidance, driven by a marked reduction in clinically driven TVR; 3) in addition, the 1-year rate of all-cause mortality was lower with IVUS guidance compared with angiographic guidance; 4) TVF rates after IVUS guidance were particularly low in patients in whom optimal IVUS results were achieved; 5) the results favoring IVUS guidance compared with angiographic guidance were consistent in insulin-treated and non-insulin-treated patients with diabetes; and 6) the results favoring IVUS guidance were also consistent in patients randomized to SAPT vs DAPT between 1 and 12 months after PCI.

The presence of both ACS and diabetes signifies a complex interplay of inflammatory and metabolic processes that can exacerbate the risk for adverse cardiovascular events. Managing these risks is crucial in the treatment and prevention of ACS in patients with diabetes.[5,6] In the PROSPECT (Providing Regional Observations to Study Predictors of Events in Coronary Tree) study,[25] untreated lesions in patients with ACS with diabetes and metabolic syndrome were longer and had greater plaque burden and smaller luminal areas, with greater necrotic core and calcium content than in patients without diabetes, findings that were associated with higher rates of major adverse events during 3-year follow-up following successful PCI. Moreover, in the present study about 70% of patients with diabetes with ACS had long or diffuse lesions, and about 66% of patients had IVUS evidence of lesion calcification, both strong predictors of adverse events post-PCI.[7,8] Thus,

**TABLE 3 Quantitative Coronary Analysis in the IVUS-Guided and Angiography-Guided PCI Groups With Diabetes**

| | IVUS-Guided PCI (n = 554) | Angiography-Guided PCI (n = 551) | Difference (95% CI) | *P* Value |
|---|---|---|---|---|
| Baseline | | | | |
| Reference vessel diameter, mm | 2.92 ± 0.61 | 2.94 ± 0.57 | −0.02 (−0.097 to 0.06) | 0.690 |
| Minimal luminal diameter, mm | 0.95 ± 0.57 | 0.97 ± 0.58 | −0.02 (−0.09 to 0.05) | 0.538 |
| Diameter stenosis, % | 61.2 ± 12.2 | 60.5 ± 12.4 | 0.8 (−0.9 to 2.4) | 0.358 |
| Lesion length, mm | 31.3 ± 15.8 | 30.8 ± 15.9 | 0.5 (−1.6 to 2.6) | 0.647 |
| Postprocedure | | | | |
| Reference vessel diameter, mm | 3.13 ± 0.62 | 3.09 ± 0.58 | 0.05 (−0.03 to 0.12) | 0.208 |
| Minimal luminal diameter, mm | 2.68 ± 0.62 | 2.62 ± 0.57 | 0.07 (−0.01 to 0.14) | 0.073 |
| Acute gain, mm | 1.74 ± 0.75 | 1.65 ± 0.72 | 0.09 (0.00 to 0.18) | 0.045 |
| Diameter stenosis, % | 14.1 ± 10.1 | 14.9 ± 9.7 | −0.9 (−2.1 to 0.3) | 0.147 |

Values are mean ± SD.
Abbreviations as in Table 1.

diabetes is a critical factor in determining the clinical outcomes of patients with ACS undergoing PCI, given the high prevalence of vulnerable lesions, diffuse disease and negative vessel remodeling, and increased neointimal hyperplasia after PCI.[5,7,26,27]

The nonrandomized design and limited number of patients with diabetes in previous ACS studies has resulted in uncertainty as to the utility of IVUS guidance in high-risk patients with diabetes with ACS.[15,16,22] A study from the Korea acute MI registry,[18] which included 3,339 patients with diabetes with acute MI (683 in the IVUS group and 2,656 in the control group), showed a significantly lower 1-year major adverse cardiovascular event rate in the IVUS group compared with the control group (10.1% vs 15.1%; $P = 0.001$). Subgroup analysis from the JAPAN-ACS study in 251 patients with diabetes with ACS showed a composite major adverse cardiovascular event rate of 22.1% at 8- to 12-month follow-up.[21] The IVUS-ACS trial was the first large-scale dedicated study of IVUS guidance in patients with ACS. The stratification of randomization by diabetes in this study ensured a balance of measured and unmeasured confounders in baseline covariates in the large diabetic population. The 1-year rate of TVF rate was reduced by 54% in patients with diabetes with ACS in the IVUS guidance group compared with the angiographic guidance group. TVF was also reduced at 1 year after excluding procedural MIs. The improved outcomes with IVUS guidance in high-risk patients with diabetes with ACS are likely attributed to the use of larger and longer stents with more frequent post-dilatation, resulting in a larger minimal stent area and more complete lesion coverage, the principal determinant of freedom from long-term adverse events.[13,14,23] Although IVUS was not performed in the angiography group to verify these findings, the greater angiographic acute gain with IVUS guidance (despite the insensitivity of angiography) is indicative of superior stent expansion. Consistent with this hypothesis and the results from previous studies,[15,22] a lower TVF rate was observed at 1-year follow-up in patients who achieved IVUS-defined optimal PCI criteria compared with those with suboptimal PCI results. Furthermore, although less revascularization

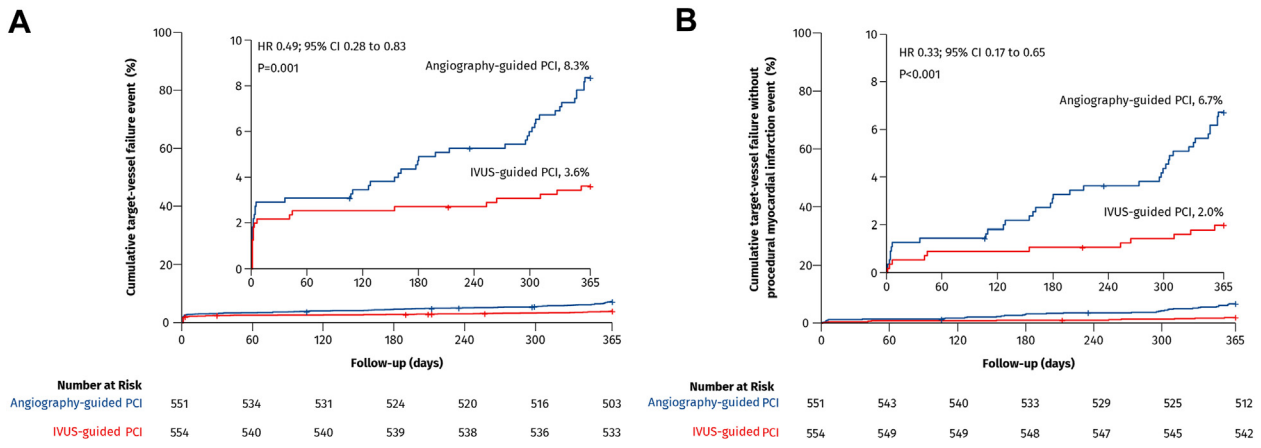
**TABLE 4 Primary and Secondary Endpoints in the IVUS-Guided and Angiography-Guided Groups With Diabetes**

| | IVUS-Guided PCI (n = 554) | Angiography-Guided PCI (n = 551) | Adjusted HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Primary endpoint | | | | |
| TVF | 20 (3.6) | 46 (8.3) | 0.46 (0.27-0.81) | 0.007[a,b] |
| Secondary endpoints | | | | |
| TVF without PMI | 11 (2.0) | 37 (6.7) | 0.29 (0.15-0.57) | <0.001[b] |
| Cardiac death | 3 (0.5) | 10 (1.8) | 0.30 (0.09-1.07) | 0.065 |
| TVMI | 13 (2.3) | 18 (3.3) | 0.71 (0.35-1.45) | 0.355 |
| PMI | 9 (1.6) | 10 (1.8) | 0.89 (0.36-2.19) | 0.807 |
| Non-PMI | 4 (0.7) | 8 (1.5) | 0.49 (0.15-1.63) | 0.246 |
| Clinically driven TVR | 5 (0.9) | 21 (3.8) | 0.23 (0.09-0.61) | 0.003 |
| Clinically driven TLR | 5 (0.9) | 15 (2.7) | 0.32 (0.12-0.89) | 0.029 |
| Safety endpoints | | | | |
| Definite or probable ST | 3 (0.5) | 4 (0.7) | 0.74 (0.17-3.31) | 0.697 |
| All-cause death | 4 (0.7) | 13 (2.4) | 0.30 (0.10-0.93) | 0.037 |
| Major bleeding[c] | 7 (1.3) | 11 (2.0) | 0.63 (0.24-1.61) | 0.333 |

Values are n (%). Event rates are numbers of events generated using Kaplan-Meier analysis, and overall *P* values are from the log-rank test for overall IVUS guidance vs angiographic guidance. [a]TVF with and without PMI was analyzed with the subdistribution method of Fine and Gray to account for the competing risk of noncardiac death. [b]The treatment effects for the primary analyses were adjusted for type of acute coronary syndrome (ie, unstable angina vs non-ST-segment elevation myocardial infarction vs ST-segment elevation myocardial infarction), second-stage randomization (treatment with single vs dual antiplatelet therapy after 30 days), geographic region, dyslipidemia, left main coronary artery disease, moderate or severe calcification, and thrombus-containing lesion. [c]Defined as Bleeding Academic Research Consortium type 3 or 5.

PMI = procedural myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVF = target vessel failure; TVMI = target vessel myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Table 1.

**FIGURE 2 Principal Clinical Outcomes**




(A) Rates of target vessel failure (TVF) in the IVUS-guided PCI group and the angiography-guided PCI group. (B) Rates of TVF excluding procedural myocardial infarction in the IVUS-guided PCI group and the angiography-guided PCI group. Abbreviations as in Figure 1.

was needed by IVUS guidance in the present analysis and 2 previous trials,[15,22] 2 recent trials[16,28] did not show a reduction of risk for revascularization by IVUS guidance. The reasons might include the following: 1) only patients with ACS were included in the IVUS-ACS trial[23] and this analysis thereafter, but it was only 50.8% in the RENOVATE COMPLEX-PCI (Intravascular Imaging- Versus Angiography-Guided Percutaneous Coronary Intervention For Complex Coronary Artery Disease) trial[15] and 57.1% in the ILUMIEN IV trial[29]; 2) the present analysis analyzed only the treatment difference among patients with ACS and diabetes; and 3) IVUS guidance was used in the IVUS-ACS trial[23] and this subgroup analysis, but both IVUS and optical coherence tomography were used in the RENOVATE COMPLEX-PCI trial[15] and only optical coherence tomography in the ILUMIEN IV trial.[29] The difference in treatment effect (particularly in revascularization) between IVUS guidance and optical coherence tomographic guidance remains nonsignificant, but further clinical trial is warranted to test IVUS over optical coherence tomographic guidance in patients with ACS and diabetes.[30,31]

The principal benefit of IVUS guidance in patients with diabetes with ACS in our study was a reduction in clinically driven TVR (and TLR). MI and stent thrombosis occurred infrequently, and the differences favoring IVUS guidance did not reach statistical significance. However, although the reduction in cardiac death with IVUS-guided PCI compared with angiography-guided PCI also was not significant, all-cause death was significantly reduced in patients with diabetes with ACS with IVUS guidance compared with angiographic guidance. Although the trial was not powered for a reduction in mortality and thus this outcome remains hypothesis generating, all-cause mortality is less prone to adjudication error than any other single endpoint.

**STUDY LIMITATIONS.** First, the IVUS-ACS trial was not powered for the diabetic subgroup. Nonetheless, the results were markedly improved with IVUS guidance in this cohort, allowing its benefits compared with angiographic guidance to emerge. Nonetheless, the study was underpowered to elicit differences in low-frequency secondary endpoints such as target vessel MI and stent thrombosis and to examine outcomes in more specific subgroups such as patients treated with insulin or those randomized again to SAPT vs DAPT.

Second, all patients in the present study had confirmed diabetes; the results may not be directly applicable to patients with ACS with prediabetes or metabolic syndrome. Third, the analysis by type of diabetes treatment (insulin vs noninsulin) was underpowered and showed an interaction bordering on significance. However, our results showed a similar rate of 1-year TVF between insulin- and non-insulin-treated patients with diabetes, indicating that all patients with diabetes benefit from IVUS guidance.

Finally, the majority of patients in the IVUS-ACS trial were enrolled in China, and the investigators were highly experienced with IVUS guidance during PCI; additional studies are required to confirm these

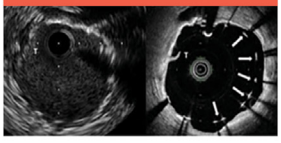
**CENTRAL ILLUSTRATION** **Subgroup Analysis of IVUS-ACS Trial**

## Subgroup Analysis of IVUS-ACS Trial: IVUS-Guided PCI Versus Angiography-Guided PCI in Diabetic Patients With ACS, N = 1,105

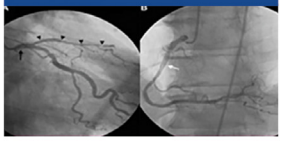
### Patient Flow

Diabetic patients with ACS (N = 1,105)

IVUS-guided PCI



Angiography-guided PCI

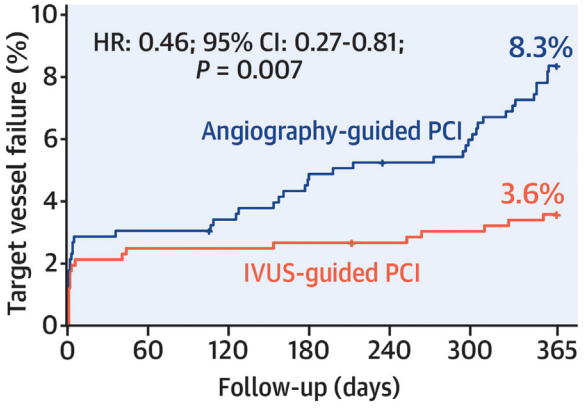


Open-labeled DAPT for 1 month

Randomization to DAPT or SAPT at 30 days

1,105 patients in the ITT analysis

### Target Vessel Failure Over 1 Year




### Other 1-Year Clinical Outcomes

| | IVUS-guided PCI (n = 554) | Angiography-guided PCI (n = 551) | *P* value |
|---|---|---|---|
| TVF without PMI | 2.0% | 6.7% | <0.001 |
| TVR | 0.9% | 3.8% | 0.003 |
| Cardiac death | 0.5% | 1.8% | 0.065 |
| TVMI | 2.3% | 3.3% | 0.355 |

- IVUS-guided PCI leads to a lower rate of TVF at 1 year
- IVUS-guided PCI also reduced the risk of TVF without procedural myocardial infarction and all-cause mortality

**Gao X, et al. JACC Cardiovasc Interv. 2024;■(■):■–■.**

In the prespecified diabetic substudy of the IVUS-ACS (1-Month vs 12-Month DAPT for ACS Patients Who Underwent PCI Stratified by IVUS: IVUS-ACS and ULTIMATE-DAPT Trials) trial, 1,105 patients with diabetes presenting with acute coronary syndrome (ACS) were randomized to intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) vs angiography-guided PCI. Patients who were free from major ischemic or bleeding events at 30 days and who were compliant with dual antiplatelet therapy (DAPT) with aspirin plus ticagrelor were randomized again to DAPT (open-label ticagrelor plus aspirin) vs single antiplatelet therapy (SAPT) (open-label ticagrelor plus a matching aspirin placebo). The primary endpoint was target vessel failure (TVF) at 1-year follow-up. As seen in the lower right graph, outcomes were especially improved if predefined criteria for optimal IVUS stent implantation were achieved. ITT = intention-to-treat; PMI = periprocedural myocardial infarction; TV-MI = target vessel myocardial infarction; TVR = target vessel revascularization.

results in other geographies and with less experienced operators.

## CONCLUSIONS

In the IVUS-ACS trial, among high-risk patients with diabetes presenting with an ACS, IVUS-guided PCI substantially reduced the rate of TVF at 1 year compared with angiography-guided PCI. IVUS guidance also reduced the 1-year rates of clinically driven TVR and TLR and all-cause mortality, with nonsignificantly different rates of target vessel MI and stent thrombosis. The benefits of IVUS guidance were consistent in patients with diabetes treated with or without insulin and in those treated with SAPT vs DAPT between 1 and 12 months after PCI and were especially marked if optimal IVUS criteria for stent implantation were achieved.

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## PERSPECTIVES

**WHAT IS KNOWN?** IVUS-guided implantation of drug-eluting stents reduces the risks for early and late adverse clinical events in patients with ACS compared with angiographic guidance.

**WHAT IS NEW?** In this prespecified analysis from the IVUS-ACS trial in the stratified randomized diabetic subgroup, IVUS-guided PCI resulted in a lower 1-year rate of TVF, mainly by a significant reduction in unplanned repeat revascularization, compared with angiography-guided PCI.

**WHAT IS NEXT?** Patients with diabetes presenting with ACS benefited from IVUS-guided PCI, especially if predefined optimal IVUS criteria for stent implantation were met. The benefits of IVUS guidance were consistent in patients with diabetes treated with or without insulin and with SAPT vs DAPT between 1 and 12 months after PCI.

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**KEY WORDS** acute coronary syndrome(s), angiography, diabetes, intravascular ultrasound, target vessel failure

**APPENDIX** For supplemental tables and figures, please see the online version of this paper.