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FOCUS ON TRANSCATHETER AORTIC VALVE REPLACEMENT AND CORONARY CANNULATION

ORIGINAL RESEARCH: CORONARY

Timing of Complete Multivessel Revascularization in Patients Presenting With Non-ST-Segment Elevation Acute Coronary Syndrome

Jacob J. Elscot, BSc,[a] Hala Kakar, MD,[a] Paola Scarparo, MD,[a] Wijnand K. den Dekker, MD, PhD,[a] Johan Bennett, MD, PhD,[b] Carl E. Schotborgh, MD,[c] René van der Schaaf, MD, PhD,[d] Manel Sabaté, MD, PhD,[e] Raúl Moreno, MD, PhD,[f] Koen Ameloot, MD, PhD,[g] Rutger J. van Bommel, MD, PhD,[h] Daniele Forlani, MD,[i] Bert Van Reet, MD,[j] Giovanni Esposito, MD, PhD,[k] Maurits T. Dirksen, MD, PhD,[l] Willem P.T. Ruifrok, MD, PhD,[m] Bert R.C. Everaert, MD, PhD,[n] Carlos Van Mieghem, MD, PhD,[o] Eduardo Pinar, MD, PhD,[p] Fernando Alfonso, MD, PhD,[q] Paul Cummins, RN,[a] Mattie Lenzen, PhD,[a] Salvatore Brugaletta, MD, PhD,[g] Joost Daemen, MD, PhD,[a] Eric Boersma, PhD,[a] Nicolas M. Van Mieghem, MD, PhD,[a] Roberto Diletti, MD, PhD,[a] the BIOVASC Investigators

ABSTRACT

BACKGROUND Complete revascularization of the culprit and all significant nonculprit lesions in patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) and multivessel disease (MVD) reduces major adverse cardiac events, but optimal timing of revascularization remains unclear.

OBJECTIVES This study aims to compare immediate complete revascularization (ICR) and staged complete revascularization (SCR) in patients presenting with NSTE-ACS and MVD.

METHODS This prespecified substudy of the BIOVASC (Percutaneous Complete Revascularization Strategies Using Sirolimus Eluting Biodegradable Polymer Coated Stents in Patients Presenting With Acute Coronary Syndrome and Multivessel Disease) trial included patients with NSTE-ACS and MVD. Risk differences of the primary composite outcome of all-cause mortality, myocardial infarction (MI), unplanned ischemia-driven revascularization (UIDR), or cerebrovascular events and its individual components were compared between ICR and SCR at 1 year.

RESULTS The BIOVASC trial enrolled 1,525 patients; 917 patients presented with NSTE-ACS, of whom 459 were allocated to ICR and 458 to SCR. Incidences of the primary composite outcome were similar in the 2 groups (7.9% vs 10.1%; risk difference 2.2%; 95% CI: −1.5 to 6.0; $P = 0.15$). ICR was associated with a significant reduction of MIs (2.0% vs 5.3%; risk difference 3.3%; 95% CI: 0.9 to 5.7; $P = 0.006$), which was maintained after exclusion of procedure-related MIs occurring during the index or staged procedure (2.0% vs 4.4%; risk difference 2.4%; 95% CI: 0.1 to 4.7; $P = 0.032$). UIDRs were also reduced in the ICR group (4.2% vs 7.8%; risk difference 3.5%; 95% CI: 0.4 to 6.6; $P = 0.018$).

CONCLUSIONS ICR is safe in patients with NSTE-ACS and MVD and was associated with a reduction in MIs and UIDRs at 1 year. (J Am Coll Cardiol Intv 2024;17:771–782) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ICR = immediate complete revascularization

MVD = multivessel disease

MI = myocardial infarction

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

SCR = staged complete revascularization

STEMI = ST-segment elevation myocardial infarction

Multivessel coronary artery disease is common in patients presenting with an acute coronary syndrome (ACS) without persistent ST-segment elevations. About 50% of the patients present with 1 or more significant nonculprit lesions, a condition associated with a higher risk of myocardial infarction (MI), repeat revascularization, and mortality.[1-5] An early invasive strategy is beneficial over a conservative approach in terms of better clinical outcomes, especially in high-risk patients.[6-10] Several retrospective studies suggested that complete revascularization of both culprit and nonculprit lesions is associated with lower cumulative mortality rates and risk of major adverse cardiac events.[3,11-13] Therefore, more recent European guidelines report that complete revascularization should be considered in patients with multivessel disease (MVD) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS), tailored to patients' characteristics, preferences, and comorbidities.[14] However, the ideal timing of nonculprit revascularization in an immediate or staged setting remains unclear. The European Society of Cardiology guidelines provide a Class IIb recommendation for complete revascularization during index percutaneous coronary intervention (PCI)[14] based on the SMILE (Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention) trial, the only randomized trial in patients with non-ST-segment myocardial infarction (NSTEMI) and MVD, which demonstrated a lower risk of major adverse cardiac events, driven by a lower repeat revascularization rate when immediate complete revascularization (ICR) was performed instead of staged complete revascularization (SCR).[15]

The recently published BIOVASC (Percutaneous Complete Revascularization Strategies Using Sirolimus Eluting Biodegradable Polymer Coated Stents in Patients Presenting With Acute Coronary Syndromes and Multivessel Disease) randomized trial showed that ICR is noninferior to SCR in terms of a composite of all-cause mortality, MI, any unplanned ischemia-driven revascularization, or cerebrovascular events in patients presenting with ACS at 1 year post-index procedure.[16]

Given this background, we now present the trial results in the subcohort of NSTE-ACS patients, which was prespecified in the protocol.

METHODS

PROTOCOL DESIGN AND RANDOMIZATION. The BIOVASC trial was a multicenter, investigator-initiated, open-label randomized controlled non-inferiority trial with participating sites in the Netherlands, Belgium, Italy, and Spain, comparing ICR with SCR in patients presenting with ACS and MVD. Details of the trial design and the main results have been previously reported.[16,17] In summary, 1,525 patients presenting with acute coronary syndrome including both ST-segment elevation myocardial infarction (STEMI) and NSTE-ACS and MVD, defined as at least 70% stenosis in a nonculprit vessel ≥2.5 mm in diameter by visual estimation or positive coronary physiology testing, were randomized in a 1:1 ratio to ICR or SCR within 6 weeks after index procedure. Utilization of the Orsiro Sirolimus-Eluting stent (Biotronik SE & Co KG) was mandatory, unless the required stent sizing was not available in the Orsiro platform. Invasive coronary imaging

From the [a]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; [b]Department of Cardiovascular Medicine, University Hospital Leuven, Leuven, Belgium; [c]Department of Cardiology, Haga Hospital, The Hague, the Netherlands; [d]Department of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; [e]Interventional Cardiology Department, Cardiovascular Institute, Hospital Clínic, Barcelona, Spain; [f]Interventional Cardiology Unit, Cardiology Department, La Paz University Hospital, Madrid, Spain; [g]Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos, Belgium; [h]Department of Cardiology, Tergooi MC, Hilversum, the Netherlands; [i]Department of Cardiology, Santo Spirito Hospital, Pescara, Italy; [j]Department of Cardiology, AZ Turnhout, Turnhout, Belgium; [k]Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; [l]Department of Cardiology, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands; [m]Department of Cardiology, Treant Zorggroep, Emmen, the Netherlands; [n]Department of Cardiology, AZ Monica Hospital, Antwerp, Belgium; [o]Department of Cardiology, AZ Groeninge, Kortrijk, Belgium; [p]Department of Cardiology, Interventional Cardiology Unit, Virgen de la Arrixaca Hospital, Murcia, Spain; and the [q]Department of Cardiology, Hospital Universitario de La Princesa Madrid, Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares, Madrid, Spain.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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or physiology assessment was performed at the operator's discretion. Exclusion criteria consisted of the absence of a clear culprit, previous coronary artery bypass grafting, cardiogenic shock, and the presence of a chronic total occlusion in a vessel ≥2.5 mm in diameter. The primary endpoint was a composite of all-cause mortality, nonfatal MI, any unplanned ischemia-driven revascularization, and cerebrovascular events at 1 year post-index procedure. The Erasmus MC Medical Ethics Review Committee granted ethical approval for the BIOVASC trial.

PRESPECIFIED ANALYSIS IN PATIENTS WITH NSTE-ACS. This BIOVASC substudy is a prespecified analysis designed to ascertain if there was a difference in clinical outcomes when comparing ICR with SCR in the NSTE-ACS population. NSTE-ACS was defined according to current guidelines.[14] In brief, a patient was considered presenting with NSTE-ACS if at least 2 of the following criteria were present: 1) history consistent with new or worsening ischemia, occurring at rest or with minimal activity; 2) coronary angiography with indication to PCI; 3) electrocardiographic changes compatible with ischemia but not diagnostic for STEMI (ie, ST-segment depression of 1 mm or greater in 2 contiguous leads, T-wave inversion more than 3 mm, or any dynamic ST-segment shifts). If cardiomyocyte necrosis was present or absent, a patient would be categorized as presenting with NSTEMI or unstable angina, respectively.

STUDY ENDPOINTS. Definitions of all efficacy and safety outcomes have been previously published in detail.[17] Deaths were classified as cardiovascular or noncardiovascular. If the cause of death was undetermined, it was considered cardiovascular. The definition of MI was in line with the Third Universal Definition,[18] including a modification taking into account the ACS setting similarly to the COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial.[19] Repeat revascularization had to be considered both unplanned and ischemia driven to be counted as an endpoint. Target vessel revascularization and target lesion revascularization refer to a revascularization in both the initial culprit and nonculprit vessels/lesions. If a staged revascularization occurred earlier than planned, adhered to the criteria of an unplanned and ischemia-driven revascularization and presented with dynamic electrocardiogram changes and/or a new rise in cardiac enzymes, this staged revascularization was considered as an anticipated target lesion revascularization. A clinical events committee, comprising 3 independent physicians with expertise in interventional cardiology or neurology, adjudicated all potential endpoints.

The primary outcome of the current analysis was a composite all-cause mortality, MI, unplanned ischemia-driven revascularization, and cerebrovascular events, similar to the main trial. Secondary outcomes include the individual components of the primary outcome composite and a composite of cardiovascular death and MI.

STATISTICAL ANALYSIS. All randomized patients presenting with NSTE-ACS were included in the analysis as per an intention-to-treat principle. Categorical data were presented as counts and percentages and tested by the chi-square test or Fisher exact test if there was an expected cell value <5. Continuous data were presented as mean ± SD if a Gaussian distribution was present and tested by the unpaired *t*-test. Alternatively, continuous data were presented as median (Q1-Q3) and compared using the Mann-Whitney *U* test. The distribution of continuous data was tested with the use of the Shapiro-Wilk test.

Cumulative time-to-event curves were calculated with the use of the Kaplan-Meier method. Patients were censored after the first event had occurred or, if event-free, at the date on which they were last known to be alive. Cox proportional hazards regression was conducted to further explore the relation between randomly allocated treatment and study endpoints. HRs were presented with 95% CIs and calculated with use of Cox regression analyses. Assessment of the log-minus log survival plot led to a suspicion of a violated proportional hazards assumption for the primary endpoint. Further testing of the Schoenfeld residuals concluded that the proportional hazards assumption was not met. Therefore, *P* values were computed with use of a log-rank or weighted log-rank test with Fleming-Harrington weight functions (rho = 1 and gamma = 0) in Cox regression analyses in which the proportional hazards assumption was violated. In addition, a piecewise Cox regression model was conducted as a sensitivity analysis to present HRs in the 0- to 30-day and 31- to 365-day intervals, which were also adjusted for history of previous PCI, age, and sex. A 2-sided *P* value <0.05 was considered statistically significant. All analyses were performed using R version 4.2.1 (packages used: data.table, dplyr, ggplot2, ggpubr, graphics, lubridate, nphRCT, stats, survival, survminer, tidycmprsk; R Foundation for Statistical Computing).

RESULTS

PATIENT CHARACTERISTICS. The BIOVASC trial enrolled 1,525 patients, of whom 917 (60.1%)

TABLE 1 Baseline Characteristics

	Immediate Complete Revascularization (n = 459)	Staged Complete Revascularization (n = 458)	*P* Value
Age, y	67.0 (58.1-74.3)	66.8 (59.3-73.9)	0.62
Male	350 (76.3)	355 (77.5)	0.65
BMI, kg/m^2	27.3 (24.5-30.4)	27.5 (25.0-30.0)	0.80
Presentation			0.25
NSTEMI	402 (87.6)	388 (84.7)	
UA	57 (12.4)	70 (15.3)	
Medical history			
Previous PCI	61 (13.3)	82 (17.9)	0.054
History of MI	53/458 (11.6)	65/458 (14.2)	0.24
Peripheral artery disease	27 (5.9)	23 (5.0)	0.57
COPD	38 (8.3)	34 (7.4)	0.63
Atrial fibrillation or flutter	23 (5.0)	17 (3.7)	0.34
Renal insufficiency	32 (7.0)	31 (6.8)	0.90
History of stroke	25 (5.5)	18 (3.9)	0.28
Hypertension	286 (62.3)	266 (58.1)	0.19
Diabetes	107 (23.3)	117 (25.5)	0.43
Hypercholesterolemia	261/457 (57.1)	270 (59.0)	0.57
Family history of CVD	150/458 (32.8)	151/451 (33.5)	0.82
Smoking behavior			0.57
Never	216/455 (47.5)	218/454 (48.0)	
Current	144/455 (31.6)	131/454 (28.9)	
Former	95/455 (20.9)	105/454 (23.1)	

Values are median (Q1-Q3), n (%), or n/N (%).

BMI = body mass index; COPD = chronic obstructive coronary disease; CVD = cardiovascular disease; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina.

presented with NSTEMI or unstable angina, with 459 and 458 patients randomized to ICR and SCR, respectively (Supplemental Figure S1). ICR and SCR showed similar baseline characteristics (**Table 1**). Investigator-reported complete revascularization was more prevalent in the patients randomized to ICR, despite intracoronary physiology and imaging being more frequently used in those randomized to SCR (**Table 2**). Additionally, ICR was associated with a lower total stent length, contrast use, radiation dose, and a shorter in-hospital stay. Information regarding missing continuous data are tabulated in Supplemental Table S1.

OUTCOMES. Follow-up was complete in 456 (99.3%) and 452 (98.6%) patients randomized to ICR and SCR respectively.

At 30 days post-index procedure, the primary composite outcome occurred in 1.8% (95% CI: 0.6%-3.3%) and 5.7% (95% CI: 3.8%-8.1%) of patients randomized to ICR and SCR, respectively (risk difference 4.0%; 95% CI: 1.5%-6.4%; $P = 0.001$) and the composite of cardiovascular death and MI occurred in 0.4% (95% CI: 0.1%-1.5%) of the ICR patients and in 3.3% (95% CI: 1.9%-5.2%) of the SCR patients (risk difference 2.9%; 95% CI: 1.1%-4.6%; $P = 0.001$) showing a statistically significant difference in favor of the patients randomized to ICR. The incidence of MI was 0.2% (95% CI: 0.0%-1.2%) and 3.1% (95% CI: 1.8%-5.0%) in ICR and SCR, respectively (risk difference 2.9%; 95% CI: 1.2%-4.5%; $P < 0.001$), and unplanned ischemia-driven revascularization occurred in 0.9% (95% CI: 0.3%-2.1%) of ICR and in 3.7% (95% CI: 2.3%-5.8%) of SCR patients (risk difference 2.9%; 95% CI: 0.9%-4.8%; $P = 0.004$) and was also lower in the patients randomized to ICR at 30-day follow-up. All type 1 MIs between the index and staged procedures in the BIOVASC trial occurred in patients that initially presented with NSTE-ACS. Thirteen patients presented earlier than planned for ischemia-driven revascularization of the nonculprit lesions. Additionally, there was a higher cumulative incidence of the composite of all-cause mortality, MI, stroke, or major bleeding (Bleeding Academic Research Consortium 3 or 5) in the SCR arm: 1.3% (95% CI: 0.5%-2.7%) vs 5.7% (95% CI: 3.8%-8.1%) in ICR and SCR, respectively (risk difference 4.4%; 95% CI: 2.0%-6.8%; $P < 0.001$). The primary and secondary outcomes at 30 days are tabulated in **Table 3**.

The cumulative incidence of the primary composite outcome at 1-year follow-up was 7.9% (95% CI: 5.7%-10.6%) and 10.1% (95% CI: 7.6%-13.1%) in the patients randomized to ICR and SCR, respectively (risk difference 2.2%; 95% CI: −1.5% to 6.0%; $P = 0.15$). In the 0- to 180-day interval, a divergence of the incidence curves was observed, followed by a convergence of the lines after 180 days (**Figure 1**). The incidence of cardiovascular death at 1 year was similar between the 2 trial arms, namely 1.1% (95% CI: 0.4%-2.4%) in patients randomized to ICR vs 0.9% (95% CI: 0.3%-2.1%) in patients randomized to SCR (risk difference −0.2%; 95% CI: −1.5% to 1.1%; $P = 0.75$). The composite of cardiovascular death and MI occurred in 3.1% (95% CI: 1.8%-5.0%) and 5.7% (95% CI: 3.9% to 8.1%) of the ICR and SCR patients, respectively, at 1 year (risk difference 2.7%; 95% CI: 0.0%-5.3%; $P = 0.041$). ICR was associated with a lower incidence of MI: 2.0% (95% CI: 1.0%-3.6%) vs 5.3% (95% CI: 3.5%-7.6%) in SCR (risk difference 3.3%; 95% CI: 0.9%-5.7%; $P = 0.006$). The incidence of unplanned ischemia-driven revascularization was also lower in ICR patients at 1 year: 4.2% (95% CI: 2.6%-6.4%) vs 7.8% (95% CI: 5.5%-10.5%) in SCR patients (risk difference 3.5%; 95% CI: 0.4%-6.6%; $P = 0.018$) (**Central Illustration**). The primary and secondary outcomes at 1 year are tabulated in **Table 4**.

SENSITIVITY ANALYSES. An analysis excluding procedure-related MIs occurring during the index or

TABLE 2 Procedural Characteristics

	Immediate Complete Revascularization (n = 459)	Staged Complete Revascularization (n = 458)	*P* Value
Systolic blood pressure, mm Hg	127 (111-140)	126 (110-140)	0.67
Diastolic blood pressure, mm Hg	71 (63-80)	70 (62-80)	0.11
Radial access	448/458 (97.8)	440/458 (96.1)	0.12
Location of culprit lesion[a]			0.38
Left main coronary artery	2/452 (0.4)	5/457 (1.1)	
Left anterior descending artery	173/452 (38.3)	154/457 (33.7)	
Circumflex artery	140/452 (31.0)	147/457 (32.3)	
Right coronary artery	137/452 (30.3)	151/457 (33.0)	
Vessels with significant nonculprit lesions[b]			0.11
1	367/431 (85.2)	343/423 (81.1)	
≥2	64/431 (14.8)	80/423 (18.9)	
Lesion complexity (all lesions)[c]			0.27
Type A	116/921 (12.6)	112/908 (12.3)	
Type B1	305/921 (33.1)	266/908 (29.3)	
Type B2	217/921 (23.6)	220/908 (24.2)	
Type C	283/921 (30.7)	310/908 (34.1)	
Lesion complexity (nonculprit lesions per patient)			0.47
Type A	58/406 (14.3)	53/385 (13.8)	
Type B1	137/406 (33.7)	115/385 (29.9)	
Type B2	93/406 (22.9)	86/385 (22.3)	
Type C	118/406 (29.1)	131/385 (34.0)	
Complete revascularization[d]	448/459 (97.6)	435/457 (95.2)	0.0496
FFR/iFR[e]	77 (16.8)	122 (26.6)	<0.001
IVUS/OCT[e]	22 (4.8)	69 (15.1)	<0.001
Total hospital stay, d	3 (2-5)	4 (3-6)	<0.001
Staged procedure during index hospitalization		127 (27.7)	
Time to staged procedure, d	NA	15 (4-28)	
Stents used per patient			
Index procedure	3.0 (2.0-3.5)	1.0 (1.0-2.0)	<0.001
Index + staged procedures	3.0 (2.0-3.5)	3.0 (2.0-4.0)	0.059
Length of stents, mm			
Index procedure	57.5 (41.0-82.0)	30 (18.0-44.0)	<0.001
Index + staged procedures	57.5 (41.0-82.0)	66 (44.0-90.0)	0.025
Index procedure duration, min	68.0 (48.5-85.0)	50.0 (36.0-85.0)	<0.001
Index + staged procedure duration, min	68.0 (48.5-85.0)	91.0 (65.0-122.0)	<0.001
Index procedure contrast use, mL	206.5 (154.5-270.0)	144.5 (101.0-190.0)	<0.001
Index + staged procedure contrast use, mL	206.5 (154.5-270.0)	250.0 (196.0-330.0)	<0.001
Index procedure total area dose, cGy•cm^2	4,731 (2,476-12,495)	3,087 (1,561-6,622)	<0.001
Index + staged procedure total area dose, cGy•cm^2	4,731 (2,476-12,495)	6,271 (3,577-16,703)	0.001
$P2Y_{12}$ inhibitor at discharge[f]			0.38
Ticagrelor	334/458 (72.9)	328/456 (71.9)	
Prasugrel	32/458 (7.0)	43/456 (9.4)	
Clopidogrel	92/458 (20.1)	85/456 (18.6)	

Values are median (Q1-Q3), n/N (%), or n (%). [a]In 7 patients, the culprit was unclear and 1 patient was randomized but had no coronary artery disease. [b]In total, 63 patients had no significant multivessel disease when physiological assessment was performed after randomization. [c]The total number of vessels with significant lesions (with vessel diameter ≥2.5 mm) was 933. The lesion complexity was not reported for 104 lesions (5.4%). [d]A patient was considered completely revascularized if all significant lesions with vessel diameter ≥2.5 mm were treated and showed a final TIMI flow grade 3. One patient withdrew consent before the staged procedure; therefore, completeness of revascularization could not be ascertained. [e]These proportions reflect the use of physiology and imaging in the index and/or staged procedure. [f]1 patient died before discharge, so no medications were prescribed; 1 patient was discharged with single antiplatelet therapy and anticoagulation (aspirin and warfarin); and 1 patient did not have coronary artery disease and was not treated with antiplatelet therapy.

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; NA = not applicable; OCT = optical coherence tomography.

staged procedure was performed due to the possibility of a potential bias caused by the difficulty of diagnosing type 4a MIs during the index event. This analysis consistently showed a significant reduction of MIs in patients randomized to ICR, namely 2.0% (95% CI: 1.0%-3.6%) vs 4.4% (95% CI: 2.8%-6.6%) in patients randomized to SCR (risk difference 2.4%; 95% CI: 0.1%-4.7%; $P = 0.032$) (Figure 2). A total of 13

TABLE 3 Primary and Secondary Outcomes at 30 Days

	Immediate Complete Revascularization (n = 459)		Staged Complete Revascularization (n = 458)				
	Events	Percentage (95% CI)[c]	Events	Percentage (95% CI)[c]	HR (95% CI)	Risk Difference (95% CI)[a]	*P* Value[b]
Primary outcome							
All-cause mortality, any myocardial infarction, unplanned ischemia-driven revascularization or cerebrovascular event	8	1.8 (0.6-3.3)	26	5.7 (3.8-8.1)	0.30 (0.13-0.66)[d]	4.0 (1.5-6.4)	0.001
Secondary outcomes							
Cardiovascular mortality or myocardial infarction	2	0.4 (0.1-1.5)	15	3.3 (1.9-5.2)	0.13 (0.03-0.57)	2.9 (1.1-4.6)	0.001
All-cause mortality	2	0.4 (0.1-1.5)	2	0.4 (0.1-1.5)	1.00 (0.14-7.07)	0.0 (−0.9 to 0.9)	>0.99
Cardiovascular mortality	1	0.2 (0.0-1.2)	2	0.4 (0.1-1.5)	0.50 (0.05-5.49)	0.2 (−0.5 to 1.0)	0.56
Any myocardial infarction	1	0.2 (0.0-1.2)	14	3.1 (1.8-5.0)	0.07 (0.01-0.53)	2.9 (1.2-4.5)	<0.001
Unplanned ischemia-driven revascularization	4	0.9 (0.3-2.1)	17	3.7 (2.3-5.8)	0.23 (0.08-0.68)[d]	2.9 (0.9-4.8)	0.004
Cerebrovascular event	2	0.4 (0.1-1.5)	7	1.5 (0.7-3.0)	0.28 (0.06-1.36)	1.1 (−0.2 to 2.4)	0.09
Probable or definite stent thrombosis	2	0.4 (0.1-1.5)	3	0.7 (0.2-1.8)	0.66 (0.11-3.97)	0.2 (−0.7 to 1.2)	0.65
Target vessel revascularization	4	0.9 (0.3-2.1)	17	3.7 (2.3-5.8)	0.23 (0.08-0.68)[d]	2.9 (0.9-4.8)	0.004
Target lesion revascularization	4	0.9 (0.3-2.1)	15	3.3 (1.9-5.2)	0.26 (0.09-0.79)[d]	2.4 (0.6-4.3)	0.010
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 or 5)	6	1.3 (0.5-2.7)	26	5.7 (3.8-8.1)	0.22 (0.09-0.54)[d]	4.4 (2.0-6.8)	<0.001
Major bleeding (BARC 3 or 5)	1	0.2 (0.0-1.2)	5	1.1 (0.4-2.4)	0.20 (0.02-1.70)	0.9 (−0.2 to 1.9)	0.10

[a]Based on the Kaplan-Meier estimates. A difference in favor of immediate complete revascularization is presented as a positive value. [b]The *P* value resulted from a log-rank test or weighted log-rank test with Fleming-Harrington weight functions rho = 1 and gamma = 0, if appropriate. [c]Cumulative incidence at 365 days according to the Kaplan-Meier method. [d]The Cox proportional hazards assumption was not met.

BARC = Bleeding Academic Research Consortium.

nonprocedure-related infarctions occurred between the index and staged procedures, of which 10 were type 1, 1 was type 2, and 2 were type 4b MIs. The primary and secondary outcomes at 1 year, excluding type 4a MIs occurring during the index or staged procedure, are tabulated in **Table 5**.

A piecewise Cox regression with adjustment for history of previous PCI, age, and sex was performed as additional sensitivity analyses. In the 0- to 30-day interval, ICR was associated with a significant reduction in risk of the primary outcome (adjusted HR: 0.29; 95% CI: 0.13-0.65; $P = 0.003$), whereas no difference in risk was observed between the allocated treatments in the 31- to 365-day interval (adjusted HR: 1.30; 95% CI: 0.73-2.31; $P = 0.37$). The risk of MI was significantly reduced in patients randomized to ICR in the 0- to 30-day interval (adjusted HR: 0.07; 95% CI: 0.02-0.52; $P = 0.010$), similar to the risk of unplanned ischemia-driven revascularization (adjusted HR: 0.23; 95% CI: 0.08-0.68; $P = 0.008$). Both MI (adjusted HR: 0.77; 95% CI: 0.30-1.94; $P = 0.57$) and unplanned ischemia-driven revascularization (adjusted HR: 0.80; 95% CI: 0.40-1.58; $P = 0.52$) did not significantly differ between ICR and SCR in the 31- to 365-day interval. The results of the piecewise Cox regression in the 0- to 30-day and 31- to 365-day intervals, unadjusted and adjusted, are tabulated in Supplemental Tables S2.1 and S2.2, respectively. Furthermore, competing risk analyses corroborated our findings and are tabulated in Supplemental Table S3.

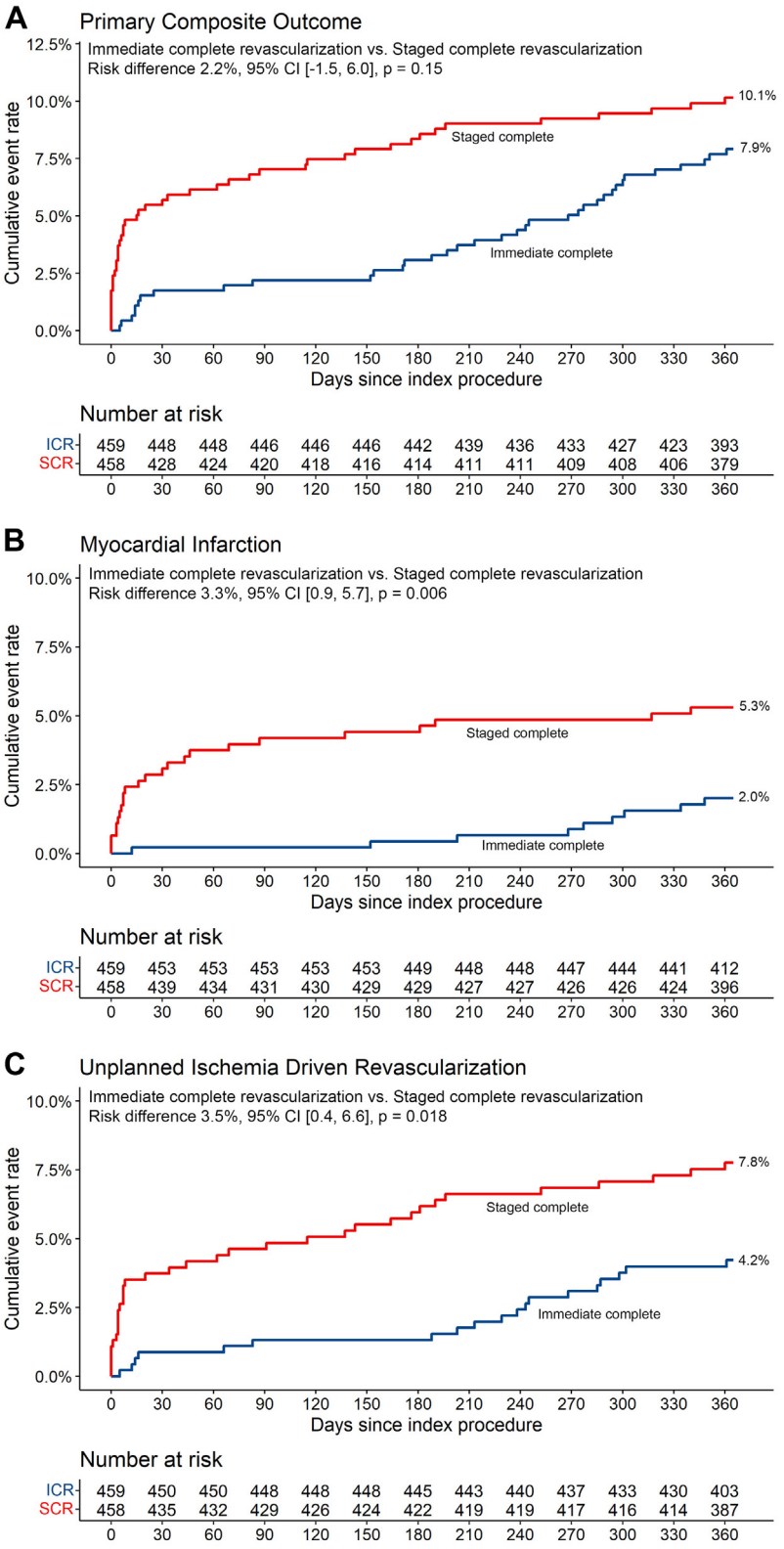
DISCUSSION

The current further analysis of the BIOVASC trial, which was prespecified in the trial protocol, suggests a reduction in the incidence of MIs and unplanned ischemia-driven revascularizations at 1 year post-index PCI when performing ICR in the NSTE-ACS population. The reduction in MI associated with an ICR strategy persisted after exclusion of procedure-related events.

In the BIOVASC trial, 44.1% (n = 15) of all first occurring MIs in the SCR group were non-procedure-related and happened between the index and staged procedures. Ten of those MIs were type 1 MI and occurred only in patients that initially presented with a NSTE-ACS at randomization.

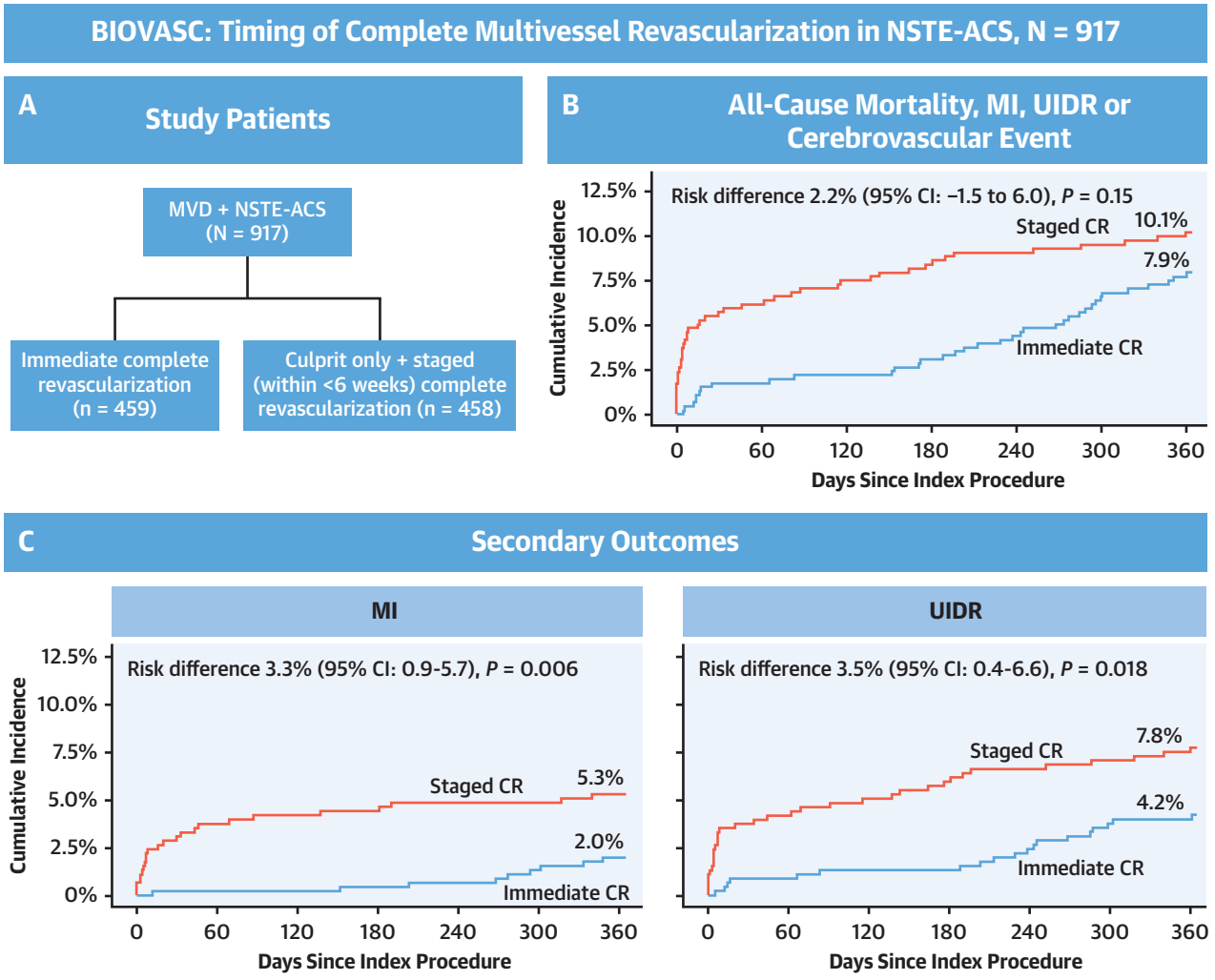
The results of the 0- to 30-day and 31- to 365-day piecewise Cox regressions suggest that the

FIGURE 1 Outcomes



The primary outcome is a composite of (A) all-cause mortality, (B) myocardial infarction, (C) unplanned ischemia-driven revascularization, and cerebrovascular events. A difference in favor of immediate complete revascularization (ICR) is presented as a positive value. SCR = staged complete revascularization.

CENTRAL ILLUSTRATION **Timing Modalities of Nonculprit Revascularization in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome and Multivessel Disease**



- In patients with multivessel disease and NSTE-ACS, the primary composite endpoint of all-cause mortality, MI, UIDR, or cerebrovascular event at 1 year did not significantly differ between patients randomized to immediate and staged complete revascularization
- Immediate complete revascularization was associated with lower risk of MI and lower risk of UIDR at 1 year compared with staged complete revascularization

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BIOVASC = Percutaneous Complete Revascularization Strategies Using Sirolimus Eluting Biodegradable Polymer Coated Stents in Patients Presenting With Acute Coronary Syndromes and Multivessel Disease; CR = complete revascularization; MI = myocardial infarction; MVD = multivessel disease; NSTE-ACS = non–ST-segment elevation myocardial infarction; UIDR = unplanned ischemia-driven revascularization.

reduction in MIs is driven by those events that occur early. Plaque vulnerability of nonculprit lesions might have a role in the occurrence of early spontaneous infarctions in patients with ACS. Several factors could induce plaque instability in the acute phase, such as an enhanced general inflammatory status, oxidative stress, which is an imbalance between the generation of reactive oxygen species and its clearance through the intrinsic antioxidant defense system.[20] Acute MI has been associated with a

TABLE 4 Primary and Secondary Outcomes at 1 Year

	Immediate Complete Revascularization (n = 459)		Staged Complete Revascularization (n = 458)				
	Events	Percentage (95% CI)[c]	Events	Percentage (95% CI)[c]	HR (95% CI)	Risk Difference (95% CI)[a]	*P* Value[b]
Primary outcome							
All-cause mortality, any myocardial infarction, unplanned ischemia-driven revascularization or cerebrovascular event	36	7.9 (5.7-10.6)	46	10.1 (7.6-13.1)	0.75 (0.48-1.16)[d]	2.2 (−1.5 to 6.0)	0.15
Secondary outcomes							
Cardiovascular mortality or myocardial infarction	14	3.1 (1.8-5.0)	26	5.7 (3.9-8.1)	0.52 (0.27-1.00)[d]	2.7 (0.0-5.3)	0.041
All-cause mortality	7	1.5 (0.6-3.0)	5	1.1 (0.4-2.4)	1.39 (0.44-4.38)	−0.4 (−1.9 to 1.1)	0.57
Cardiovascular mortality	5	1.1 (0.4-2.4)	4	0.9 (0.3-2.1)	1.24 (0.33-4.62)	−0.2 (−1.5 to 1.1)	0.75
Myocardial infarction	9	2.0 (1.0-3.6)	24	5.3 (3.5-7.6)	0.36 (0.17-0.78)[d]	3.3 (0.9-5.7)	0.006
Unplanned ischemia-driven revascularization	19	4.2 (2.6-6.4)	35	7.8 (5.5-10.5)	0.52 (0.30-0.91)[d]	3.5 (0.4-6.6)	0.018
Cerebrovascular event	7	1.6 (0.7-3.1)	8	1.8 (0.8-3.3)	0.86 (0.31-2.38)[d]	0.2 (−1.5 to 1.9)	0.77
Probable or definite stent thrombosis	2	0.4 (0.1-1.5)	5	1.1 (0.5-2.4)	0.40 (0.08-2.05)	0.7 (−0.5 to 1.8)	0.25
Target vessel revascularization	16	3.6 (2.1-5.6)	33	7.3 (5.2-10.0)	0.47 (0.26-0.85)[d]	3.8 (0.8-6.7)	0.009
Target lesion revascularization	13	2.9 (1.6-4.7)	30	6.7 (4.6-9.2)	0.42 (0.22-0.80)[d]	3.8 (1.0-6.6)	0.006
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 or 5)	30	6.6 (4.6-9.1)	40	8.8 (6.4-11.6)	0.72 (0.45-1.15)[d]	2.2 (−1.2 to 5.7)	0.14
Major bleeding (BARC 3 or 5)	8	1.8 (0.8-3.3)	9	2.0 (1.0-3.6)	0.88 (0.34-2.28)	0.2 (−1.5 to 2.0)	0.79

[a]Based on the Kaplan-Meier estimates. A difference in favor of immediate complete revascularization is presented as a positive value. [b]The *P* value resulted from a log-rank test or weighted log-rank test with Fleming-Harrington weight functions rho = 1 and gamma = 0, if appropriate. [c]Cumulative incidence at 365 days according to the Kaplan-Meier method. [d]The Cox proportional hazards assumption was not met.

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decrease in antioxidant enzymes,[21] potentially impacting plaque vulnerability in nonculprit lesions. Several studies in ACS and MVD patients[22,23] showed the presence of thin-cap fibroatheroma in up to 40% of the analyzed obstructive nonculprit lesions, which is associated with a higher risk of future cardiac events.[24]

The nonculprit lesion vulnerability remains yet to be fully evaluated in NSTE-ACS, but a role of diffuse inflammation and plaque instability cannot be excluded in the pathogenesis of the early ischemic events in our population.

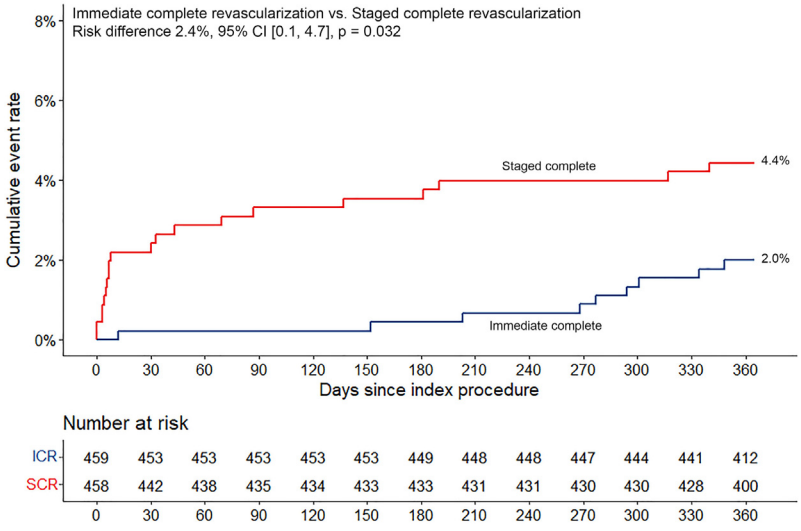
Another distinct mechanism that could also explain early ischemic events is the incorrect culprit lesion identification during the index procedure. At variance with STEMI patients in whom the culprit lesion is angiographically evident in the vast majority of the cases, in NSTE-ACS and MVD, culprit lesion assessment can be very challenging.[25,26] Despite the fact that unclear culprit lesion was an exclusion criteria in the BIOVASC trial, misjudgment of the culprit lesion could have occurred, leading to some acute plaques being left untreated possibly triggering a second early event between the index and staged procedures.[27]

This difference in culprit lesion identification between STEMI and NSTE-ACS patients might also explain the dissimilar progression of the time-to-event curves in this study compared with the COMPLETE trial,[19] in which in the culprit-only revascularization group events accrued over time in the long-term follow-up.

The SMILE trial showed a significant reduction of the composite of mortality, MI, rehospitalization for unstable angina, target vessel revascularization, and stroke at 1 year when performing ICR instead of SCR in patients presenting with NSTE-ACS and MVD.[15] This effect was driven by a lower risk of target vessel revascularization in the ICR group. In contrast to our study, the time-to-event curves did not diverge early in the follow-up period, but rather only after 100 days. This discrepancy might be caused by the different study designs. In our study the median time to the staged procedure was 15 days, which is a longer interval than the mean 4.8 days in the SMILE trial, potentially leading to more events in the 30-day time frame. However, when comparing the results of the SMILE trial with ours, the difference in total event rates must also be taken into account. Our study showed a total event rate of 8.9% for the primary composite endpoint, as opposed to 18.4% in the SMILE trial driven by a remarkably high rate of target vessel revascularization (15.4% at 1-year follow-up).[28]

Similarly, to our study, an analysis from the CREDO-Kyoto (Coronary Revascularization Demonstration Outcome Study in Kyoto Percutaneous

FIGURE 2 MI Excluding Procedure-Related MIs



Type 4a myocardial infarctions (MIs) occurring during the index and staged procedures were excluded from the analysis. A difference in favor of ICR is presented as a positive value. Abbreviations as in Figure 1.

Coronary Intervention/Coronary Artery Bypass Graft) registry showed significantly lower MIs and revascularizations occurring in the ICR group at 30 days post-index PCI.[29] At 5 years, the study showed no difference in the composite primary outcome or any of its individual components, but both the incidence curves and 30-day results suggest a similar temporal progression of events compared with our study.

Our data support the adoption of an ICR approach in NSTE-ACS and MVD. In this subpopulation of the BIOVASC trial, the clinical benefit of ICR was evident in terms of MIs and unplanned ischemia-driven revascularizations regardless of procedure-related events. In addition, similarly to the BIOVASC trial, in the present subanalysis the ICR approach was associated with a reduction in total hospital stay, suggesting possible health economic implications in NSTE-ACS patients.[30]

STUDY LIMITATIONS. This is a prespecified post hoc analysis of a randomized noninferiority trial. No formal power calculation was performed for this

TABLE 5 Clinical Outcomes Excluding Index and Staged Procedure-Related Myocardial Infarctions

	Immediate Complete Revascularization (n = 459)		Staged Complete Revascularization (n = 458)				
	Events	Percentage[c]	Events	Percentage[c]	HR (95% CI)	Risk Difference (95% CI)[a]	*P* Value[b]
All-cause mortality, myocardial infarction, unplanned ischemia-driven revascularization or cerebrovascular event	36	7.9 (5.7-10.6)	43	9.5 (7.0-12.4)	0.80 (0.52-1.25)[d]	1.6 (−2.1 to 5.2)	0.28
Cardiovascular mortality or myocardial infarction	14	3.1 (1.8-5.0)	22	4.9 (3.1-7.1)	0.62 (0.32-1.21)[d]	1.8 (−0.8 to 4.3)	0.15
Myocardial infarction	9	2.0 (1.0-3.6)	20	4.4 (2.8-6.6)	0.44 (0.20-0.96)[d]	2.4 (0.1-4.7)	0.032
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 and 5)	30	6.6 (4.6-9.1)	37	8.2 (5.9-10.9)	0.78 (0.48-1.26)	1.6 (−1.8 to 5.0)	0.31

[a]Based on the Kaplan-Meier estimates. A difference in favor of immediate complete revascularization is presented as a positive value. [b]The *P* value resulted from a log-rank test or weighted log-rank test with Fleming-Harrington weight functions rho = 1 and gamma = 0, if appropriate. [c]Cumulative incidence at 365 days according to the Kaplan-Meier method. [d]The Cox proportional hazards assumption was not met.

BARC = Bleeding Academic Research Consortium.

analysis. The use of intracoronary imaging was low, reflecting the current European clinical practice. A higher adoption of imaging might have had an impact on culprit lesion identification providing further insights on the mechanism of early ischemic events. A bias may be present in terms of procedure-related MIs in favor of ICR because a rise in cardiac enzymes can be concealed during the index procedure due to the initial MI.

CONCLUSIONS

In patients presenting with NSTE-ACS and MVD, ICR was safe compared with SCR. A lower cumulative incidence of MIs and unplanned ischemia-driven MI at 1 year post-index PCI was observed when performing ICR.

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ADDRESS FOR CORRESPONDENCE: Dr Roberto Diletti, Department of Cardiology, Thoraxcenter, Erasmus MC, Dr. Molewaterplein 40, Office Rg-632k, 3015 GD Rotterdam, the Netherlands. E-mail: r.diletti@erasmusmc.nl.

PERSPECTIVES

WHAT IS KNOWN? In patients presenting with NSTEMI, an early invasive strategy is beneficial over a conservative approach in terms of better clinical outcomes, especially in high-risk patients. In the context of MVD, several retrospective studies suggested that complete revascularization of both culprit and nonculprit lesions is associated with lower cumulative mortality rates and risk of major adverse cardiac events. However, the timing of complete revascularization remains unclear, specifically in an immediate or staged setting.

WHAT IS NEW? This prespecified subanalysis of the BIOVASC trial shows that all Type 1 MIs between the index and staged procedures occurred in the population of patients that initially presented with NSTE-ACS. At 30 days and 1 year, patients randomized to ICR had fewer non-procedure-related MIs and unplanned ischemia-driven revascularizations.

WHAT IS NEXT? A higher adoption of imaging might have had an impact on culprit lesion identification providing further insights on the mechanism of early ischemic events.

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KEY WORDS acute coronary syndrome, multivessel disease, percutaneous coronary intervention, revascularization strategy

APPENDIX For supplemental tables and a figure, please see the online version of this paper.