EuroIntervention
2024;20:e479-e486
published online e-edition April 2024
DOI: 10.4244/EIJ-D-23-00762

ORIGINAL RESEARCH

Immediate or staged complete revascularisation in patients presenting with acute coronary syndrome by number of diseased vessels: a substudy of the BIOVASC randomised trial

Hala Kakar[1], MD; Jacob J. Elscot[1], BSc; Paola Scarparo[1], MD; Wijnand K. Den Dekker[1], MD, PhD; Johan Bennett[2], MD, PhD; Manel Sabaté[3], MD, PhD; Giovanni Esposito[4], MD, PhD; Ignacio Amat-Santos[5], MD, PhD; Eric Boersma[1], MD, PhD; Nicolas M. Van Mieghem[1], MD, PhD; Roberto Diletti[1]*, MD, PhD

**Corresponding author: Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Dr. Molewaterplein 40, Room Rg-620k, 3015 GD, Rotterdam, the Netherlands. E-mail: r.diletti@erasmusmc.nl*

The authors' affiliations can be found at the end of this article.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00762

ABSTRACT

BACKGROUND: In patients presenting with acute coronary syndrome (ACS), the number of diseased vessels may affect the efficacy of a complete revascularisation strategy.

AIMS: The authors sought to evaluate the safety and efficacy of immediate complete revascularisation (ICR) and staged complete revascularisation (SCR) in patients presenting with ACS stratified by the number of diseased vessels.

METHODS: In this prespecified analysis of the BIOVASC trial, ICR was compared with SCR in patients with two-vessel disease (2VD) or three-vessel disease (3VD). The primary endpoint was a composite of all-cause mortality, myocardial infarction (MI), any unplanned ischaemia-driven revascularisation or cerebrovascular events at 1 year after the index procedure. Comparisons were performed using Cox regression.

RESULTS: A total of 1,525 patients were enrolled in the BIOVASC trial, of whom 1,177 presented with 2VD and 265 with 3VD. In the 2VD group, 613 patients were assigned to ICR and 564 to SCR. In the 3VD group, 117 patients were assigned to ICR and 148 to SCR. ICR and SCR led to similar results in both the 2VD (hazard ratio [HR] 0.76, 95% confidence interval [CI]: 0.50-1.13; p=0.18) and 3VD groups (HR 0.79, 95% CI: 0.39-1.59; p=0.51) ($p_{interaction}$=0.91) in terms of the primary endpoint. ICR was associated with a lower rate of MI in patients with 3VD (HR 0.21, 95% CI: 0.046-0.93; p=0.04) ($p_{interaction}$=0.30).

CONCLUSIONS: ICR might be an option in patients presenting with extensive 3VD and might be associated with a lower rate of myocardial infarction compared with SCR.

KEYWORDS: ACS/NSTE-ACS; multiple vessel disease; NSTEMI; STEMI

SUBMITTED ON 07/09/2023 - REVISION RECEIVED ON 1st 09/11/2023 / 2nd 20/12/2023 - ACCEPTED ON 20/12/2023

Multivessel coronary artery disease occurs in up to half of patients presenting with acute coronary syndromes (ACS)[1,2], and the number of diseased vessels might have a prognostic impact[2,3]. Complete revascularisation in patients with ACS and multivessel disease (MVD) improves clinical outcomes compared with a culprit-only treatment strategy[4-8], but the optimal timing for non-culprit lesion intervention remains unclear. The recent BIOVASC trial showed that immediate complete revascularisation (ICR) is safe and leads to a lower risk of myocardial infarction (MI) and ischaemia-driven revascularisation, as well as having ancillary advantages like an overall shorter hospital stay, when compared with staged complete revascularisation (SCR)[9]. However, ICR in the acute setting could be particularly challenging in patients with extensive three-vessel disease (3VD), burdened by long procedural time, and high contrast and radiation use. ICR might therefore be more appealing in patients with limited coronary disease, such as those with significant lesions in only two vessels, where there would be a high likelihood of procedural success without excessive use of radiation or contrast. Given this background and the lack of data on the adoption of ICR in ACS patients with 3VD, we evaluated the safety and efficacy of ICR and SCR in the BIOVASC trial, specifically stratifying for the number of diseased vessels.

Editorial, see page e461

Impact on daily practice

This prespecified analysis of the BIOVASC trial suggests that immediate complete revascularisation is safe in both patients with two-vessel disease and those with three-vessel disease. Therefore, immediate complete revascularisation is a feasible alternative to a staged approach for extensive and complex coronary disease and could represent a novel treatment paradigm.

Methods

STUDY DESIGN AND PARTICIPANTS

The BIOVASC trial was a randomised, open-label, multicentre, investigator-initiated, non-inferiority trial comparing ICR with SCR in patients presenting with ACS and MVD. Details of the trial design have been previously reported[10]. Briefly, 1,525 patients presenting with ACS and MVD were randomly assigned to either ICR or SCR in a 1:1 ratio. A significant non-culprit lesion was defined as having at least 70% stenosis in a vessel ≥2.5 mm in diameter by visual estimation or by positive physiology testing. Invasive coronary imaging or physiology assessment was per the operator's discretion. The exclusion criteria included the absence of a clear culprit lesion, previous coronary artery bypass grafting, cardiogenic shock, and the presence of a chronic total occlusion. This is a BIOVASC prespecified subanalysis comparing the clinical outcomes of ICR with SCR in patients with either two-vessel disease (2VD) or 3VD[10].

OUTCOMES

The definitions of all efficacy and safety outcomes have been previously published in detail[10]. The primary endpoint was a composite of all-cause mortality, MI, any unplanned ischaemia-driven revascularisation or cerebrovascular events at 1 year after the index procedure. Secondary endpoints included the individual components of the composite primary endpoint and a composite of cardiovascular death or MI.

Mortality was classified as cardiovascular or non-cardiovascular. Any undetermined death was considered cardiovascular. The Third Universal Definition was used to define[11] myocardial infarction, with a modification in which the ACS setting is taken into account, similarly to the COMPLETE trial[4]. An independent clinical events committee adjudicated all potential endpoints.

STATISTICAL ANALYSIS

Categorical data were presented as counts and percentage, and tested by chi-square tests or Fisher's exact tests if there was an expected cell value <5. Continuous data were presented as mean and standard deviation if a Gaussian distribution was present – the Shapiro-Wilk test was used to evaluate normality – and tested by unpaired t-tests. If a Gaussian distribution was not present, continuous data were presented as median and quartiles [25th percentile-75th percentile] and compared using Wilcoxon rank-sum tests.

For primary and secondary endpoints, a time-to-event analysis was performed applying the Kaplan-Meier method. Event-free patients were censored at the date on which they were last known to be alive. Differences in cumulative event-free survival between 2VD and 3VD were evaluated by the log-rank test. Cox proportional hazard regression models were applied to further study the relation between the extent of vessel disease and the study endpoints.

Multiplicative testing was used for the interaction of the number of diseased vessels on the treatment effect by using Cox proportional hazards models with an interaction term comprising the number of diseased vessels and the treatment allocation. The statistical significance of multiplicative interaction was tested on the null hypothesis that the exponentiated beta of the interaction term equals 1. We report hazard ratios (HR) which are presented with 95% confidence intervals (CI). Assessment of the log-minus-log plot led to no suspicion of a violated proportional hazards assumption for the primary or secondary endpoints. We added a sensitivity analysis using an intention-to-treat analysis of the primary and secondary endpoints, including the 83 patients

Abbreviations

2VD	two-vessel disease	**CI**	confidence interval	**MI**	myocardial infarction
3VD	three-vessel disease	**HR**	hazard ratio	**MVD**	multivessel disease
ACS	acute coronary syndrome	**ICR**	immediate complete revascularisation	**SCR**	staged complete revascularisation

with single-vessel disease. All analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing; packages used: data.table, dplyr, ggplot2, ggpubr, graphics, survival, lubridate, stats, survminer, tidycmprsk). For all tests, a two-sided p-value<0.05 was considered statistically significant.

Results

From 26 June 2018 to 21 October 2021, a total of 1,525 patients were enrolled in the BIOVASC trial. A total of 1,177 patients presented with 2VD and 265 with 3VD. In the 2VD group, 613 patients were assigned to ICR and 564 patients to SCR. In the 3VD group, 117 patients were assigned to ICR and 148 patients to SCR. Baseline and procedural characteristics for the overall population are reported in **Table 1** and **Table 2**, respectively. Patients randomised to SCR had a longer total hospital stay in both the 2VD and 3VD groups. Overall, there was higher total contrast use and radiation dose in the 3VD group compared with the 2VD group, but an ICR strategy was associated with a significant reduction of those parameters compared with an SCR strategy in both groups **(Table 2, Supplementary Figure 1, Supplementary Figure 2)**. Contrast use in patients assigned to ICR was not significantly different between the 2VD and 3VD groups (200 mL [interquartile rang {IQR}150-260 mL] vs 200 mL [IQR 163-280 mL]; p=0.17).

PRIMARY AND SECONDARY OUTCOMES

The cumulative incidence of the primary endpoint at 1-year follow-up in the 2VD group was 7.0% in ICR patients and 8.9% in the SCR patients. In the 3VD group, the primary endpoint occurred in 11.2% of patients treated with ICR and in 13.6% of the cases treated with SCR. The primary endpoint was not significantly different between the 2VD (HR 0.76, 95% CI: 0.50-1.13; p=0.18) and 3VD groups (HR 0.79, 95% CI: 0.39-1.59; p=0.51) ($p_{interaction}$=0.91) **(Table 3)**. No significant interactions were detected in terms of all-cause mortality, cardiovascular mortality, cerebrovascular events, stent thrombosis or unplanned ischaemia-driven revascularisation between ICR and SCR patients in the 2VD and 3VD groups.

Table 1. Baseline characteristics of patients undergoing immediate versus staged complete revascularisation in two- versus three-vessel disease.

Characteristics	Two-vessel disease			Three-vessel disease		
	Immediate revascularisation (N=613)	Staged revascularisation (N=564)	*p*-value	Immediate revascularisation (N=117)	Staged revascularisation (N=148)	*p*-value
Age, years	66 (57.0-72.9)	65 (58.2-72.5)	0.98	58 (66-72)	59 (66-73)	0.50
Sex, male	482 (78.6)	434 (77.0)	0.49	89 (76.1)	117 (79.1)	0.56
BMI, kg/m²	27.3 (24.5-30.0)	27.3 (24.8-29.8)	0.93	25 (27-31)	25 (27-20)	0.51
Presentation			0.51			0.83
STEMI	246 (40.1)	221 (39.2)		53 (45.3)	68 (45.9)	
NSTEMI	318 (51.9)	287 (50.9)		58 (49.6)	70 (47.3)	
UA	49 (8.0)	56 (9.9)		6 (5.1)	10 (6.8)	
Medical history						
Previous PCI	73 (11.9)	92 (16.3)	0.029	6 (5.1)	23 (15.5)	0.007
History of MI	60/612 (9.8)	71/564 (12.6)	0.13	7 (6.0)	15 (10.1)	0.22
Peripheral artery disease	32/612 (5.2)	26/564 (4.6)	0.62	3 (2.6)	6 (4.1)	0.74
Valve disease	22/611 (3.6)	13/562 (2.3)	0.23	2 (1.7)	2 (1.4)	>0.99
Chronic obstructive pulmonary disease	40/612 (6.5)	34/564 (6.0)	0.72	9 (7.7)	11 (7.4)	0.94
Atrial fibrillation or flutter	27 (4.4)	17 (3.0)	0.21	5 (4.3)	3 (2.0)	0.29
Renal insufficiency	31 (5.1)	26 (4.6)	0.72	9 (7.7)	7 (4.7)	0.31
History of stroke	31/612 (5.1)	18/564 (3.2)	0.11	6 (5.1)	7 (4.7)	0.88
Hypertension	342 (55.8)	287 (52.7)	0.28	71 (60.7)	71 (48.0)	0.039
Diabetes	130 (21.2)	120 (21.3)	0.98	25 (21.4)	35 (23.6)	0.66
Hypercholesterolaemia	331/611 (54.2)	304/563 (54.0)	0.95	44 (37.6)	74 (50.0)	0.044
Family history of CVD	188/612 (30.7)	174//559 (31.1)	0.88	36 (31.0)	50 (34.2)	0.58
Smoking behaviour			0.82			0.52
Never	291/610 (47.7)	277/563 (49.2)		54 (46.2)	73 (50.0)	
Current	200/610 (32.8)	175/563 (31.1)		47 (40.2)	49 (33.6)	
Former	119/610 (19.5)	111/563 (19.7)		16 (13.7)	24 (16.4)	

Data are median (IQR), n (%), or n/N (%). BMI: body mass index; CVD: cardiovascular disease; IQR: interquartile range; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

Table 2. Procedural characteristics of immediate versus staged complete revascularisation in two- versus three-vessel disease.

Characteristics	Two-vessel disease			Three-vessel disease			
	Immediate revascularisation (N=613)	Staged revascularisation (N=564)	*p*-value	Immediate revascularisation (N=117)	Staged revascularisation (N=148)	*p*-value	$p_{interaction}$**
Systolic blood pressure, mmHg	125 (110-140)	125 (111-141)	0.57	126 (110-139)	120 (110-139)	0.33	
Diastolic blood pressure, mmHg	72 (63-81)	71 (62-80)	0.93	74 (66-82)	70 (62-79)	0.043	
Radial access	591/612	545/564	0.95	115 (98.3)	143 (96.6)	0.47	
Location of culprit lesion*			0.44			0.95	
Left main coronary artery	1/607 (0.2)	3/564 (0.5)		2/116 (1.7)	2/148 (1.4)		
Left anterior descending artery	240/607 (39.5)	206/564 (36.5)		34/116 (29.3)	47/148 (31.8)		
Circumflex artery	168/607 (27.7)	153/564 (27.1)		28/116 (24.1)	62/148 (41.9)		
Right coronary artery	198/607(32.6)	202/564 (35.8)		52/116 (44.8)	62/148 (41.9)		
Lesion complexity§			0.95			0.64	
Type A	133/1,193 (11.1)	112/1,081 (10.4)		40/343 (11.7)	41/411 (10.0)		
Type B1	358/1,193 (30.0)	327/1,081 (30.2)		76/343 (22.2)	80/411 (19.5)		
Type B2	285/1,193 (23.9)	259/1,081 (24.0)		61/343 (17.8)	77/411 (18.7)		
Type C	417/1,193 (35.0)	383/1,081 (35.4)		166/343 (48.4)	213/411 (51.8)		
Off-hours procedure‖	164 (26.8)	161 (28.5)	0.49	39 (33.3)	48 (32.4)	0.88	0.66
Complete revascularisation¶	596/613 (97.2)	543/563 (96.4)	0.44	111 (94.9)	135 (91.2)	0.25	0.60
FFR/iFR	77 (12.6)	115 (20.4)	<0.001	11 (9.4)	24 (16.2)	0.10	0.91
IVUS/OCT	35 (5.7)	75 (13.3)	<0.001	10 (8.6)	34 (23.0)	0.001	0.60
Total hospital stay, days	3 (2-5)	4 (3-6)	<0.001	3 (2-5)	5 (3-7)	<0.001	0.74
Time to staged procedure, days	NA	16 (4-28)	NA	NA	13 (3-23)	NA	NA
Total no. of stents used per patient	3 (2-3)	3 (2-4)	0.03	4 (3-6)	4 (4-5)	0.85	0.42
Total length of stents, mm	57 (44-77)	30 (22-44)	<0.001	100 (79-135)	104 (79-132)	0.74	0.63
Index procedure duration, minutes	62 (46-82)	47 (35-61)	<0.001	79 (61-95)	45 (35-64)	<0.001	<0.001
Total procedure duration, minutes	62 (46-82)	86 (63-115)	<0.001	79 (61-95)	116 (90-147)	<0.001	0.026
Index procedure contrast use, mL	200 (150-260)	140 (102-185)	<0.001	200 (163-280)	129 (100-180)	<0.001	0.09
Total procedure contrast use, mL	200 (150-260)	250 (196-320)	<0.001	200 (163-280)	300 (230-390)	<0.001	0.002
Index procedure total DAP, cGy·cm^2	4,640 (2,499-10,043)	2,819 (1,480-6,031)	<0.001	5,096 (2,998-10,369)	2,552 (1,486-4,895)	<0.001	0.08
Total procedure total DAP, cGy·cm^2	4,640 (2,499-10,043)	5,778 (3,328-12,681)	0.002	5,096 (2,998-10,369)	6,760 (4,026-14,067)	0.023	0.013
$P2Y_{12}$ inhibitor at discharge‡			0.54			0.65	0.23
Ticagrelor	423/612 (69.1)	400/563 (71.0)		83/115 (72.2)	100/148 (67.6)		
Prasugrel	82/612 (13.4)	78/563 (13.9)		19/115 (16.5)	26/148 (17.6)		
Clopidogrel	107/612 (17.5)	85/563 (15.1)		13/115 (11.3)	22/148 (14.9)		

Data are median (IQR), n (%), or n/N (%).*In seven patients, the culprit was reported as unclear. **$p_{interaction}$ denotes the interaction between two- and three-vessel disease. §The total number of vessels with significant lesions (with a vessel diameter ≥2.5 mm) was 3,179. However, the lesion complexity was not reported for 151 lesions (4.7%). ‖On-hours procedures were defined as those performed from Monday to Friday between 8 AM and 6 PM. A procedure outside this interval was considered off-hours. ¶A patient was considered completely revascularised if all the significant lesions with a vessel diameter ≥2.5 mm were treated and if they were assessed as having a final Thrombolysis in Myocardial Infarction grade 3. One patient withdrew consent before the staged procedure; therefore, completeness of revascularisation could not be ascertained. ‡Three patients died before discharge, so no medications were prescribed, and one patient was discharged with single antiplatelet therapy and anticoagulation (aspirin and warfarin). DAP: dose-area product; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; NA: not applicable; OCT: optical coherence tomography

The additional intention-to-treat analysis did not affect the results **(Supplementary Table 1)**.

ICR was associated with a lower rate of myocardial infarction in the 3VD group, at 1.8%, as opposed to 8.2% in patients undergoing SCR (HR 0.21, 95% CI: 0.046-0.93; p=0.04) and a trend towards significance in the 2VD group, at 2.0%, as opposed to 3.9% in patients undergoing SCR (HR 0.50, 95% CI: 0.25-1.00; p=0.050) **(Table 3, Central illustration)**. In total, the number of MIs in the ICR patients was similar between the 2VD (2%) and 3VD groups (1.8%), while in the SCR patients there were more MIs in the 3VD group (8.2%) compared with the 2VD group (3.9%).

Table 3. Primary and secondary outcomes in two- versus three-vessel disease.

Outcome		Immediate complete revascularisation (N=613)		Staged complete revascularisation (N=564)		Hazard ratio (95% CI)	*p*-value	$p_{interaction}$
		No. of events	Percentage†	No. of events	Percentage†			
Primary outcome								
All-cause mortality, any myocardial infarction, unplanned ischaemia-driven revascularisation or cerebrovascular event	2VD	42	7.0	50	8.9	0.76 (0.50-1.13)	0.18	0.91
	3VD	13	11.2	20	13.6	0.79 (0.39-1.59)	0.51	
Secondary outcomes								
Cardiovascular mortality or myocardial infarction	2VD	16	2.7	27	4.8	0.54 (0.29-1.00)	0.049	0.96
	3VD	5	4.3	12	8.2	0.52 (0.18-1.47)	0.22	
All-cause mortality	2VD	8	1.3	8	1.4	0.92 (0.35-2.45)	0.87	0.10
	3VD	5	4.3	1	0.7	6.43 (0.75-55.09)	0.089	
Cardiovascular mortality	2VD	5	0.8	6	1.1	0.77 (0.23-2.52)	0.66	0.13
	3VD	4	1.7	1	0.7	5.15 (0.58-46.11)	0.14	
Any myocardial infarction	2VD	12	2.0	22	3.9	0.50 (0.25-1.00)	0.0503	0.30
	3VD	2	1.8	12	8.2	0.21 (0.046-0.93)	0.040	
Unplanned ischaemia-driven revascularisation	2VD	22	3.7	33	5.9	0.60 (0.35-1.04)	0.067	0.95
	3VD	8	7.1	16	10.9	0.62 (0.27-1.46)	0.27	
Cerebrovascular event	2VD	9	1.5	9	1.6	0.92 (0.37-2.32)	0.86	0.94
	3VD	2	2.0	3	1.8	0.85 (0.14-5.10)	0.86	
Probable or definite stent thrombosis	2VD	5	0.8	5	0.9	0.92 (0.27-3.19)	0.90	0.56
	3VD	1	0.9	3	1.8	0.43 (0.04-4.10)	0.46	
Target vessel revascularisation	2VD	18	3.0	30	5.4	0.54 (0.30-0.97)	0.041	0.90
	3VD	7	6.0	15	10.2	0.58 (0.24-1.43)	0.24	
Target lesion revascularisation	2VD	14	2.3	27	4.9	0.47 (0.25-0.90)	0.022	0.82
	3VD	6	5.3	14	9.6	0.54 (0.21-1.40)	0.20	
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 or 5)	2VD	39	6.4	44	7.9	0.80 (0.52-1.23)	0.32	0.42
	3VD	7	6.0	16	10.9	0.53 (0.22-1.30)	0.17	
Major bleeding (BARC 3 or 5)	2VD	14	2.3	11	2.0	1.18 (0.54-2.60)	0.68	0.27
	3VD	1	0.9	4	2.7	0.32 (0.035-2.83)	0.30	
Excluding procedure-related infarction*								
All-cause mortality, any myocardial infarction, unplanned ischaemia-driven revascularisation or cerebrovascular event	2VD	41	6.8	47	8.4	0.79 (0.52-1.20)	0.26	0.76
	3VD	13	11.2	18	12.3	0.89 (0.44-1.82)	0.76	
Cardiovascular mortality or myocardial infarction	2VD	15	2.5	22	3.9	0.62 (0.32-1.20)	0.16	0.70
	3VD	5	4.3	8	5.5	0.80 (1.25-2.44)	0.69	
Any myocardial infarction	2VD	11	1.8	17	3.0	0.59 (0.27-1.26)	0.17	0.49
	3VD	2	1.8	8	5.5	0.32 (0.07-1.50)	0.15	
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 or 5)	2VD	38	6.3	40	7.1	0.86 (0.55-1.35)	0.52	0.62
	3VD	7	6.0	13	8.8	0.67 (0.27-1.68)	0.39	

†Cumulative incidence at 365 days according to the Kaplan-Meier method. *Only applicable for type 4a myocardial infarctions related to the index or staged procedure. 2VD: two-vessel disease; 3VD: three-vessel disease; BARC: Bleeding Academic Research Consortium; CI: confidence interval

The types of MI are reported in **Supplementary Table 2**. After excluding type 4a MIs, the incidence of MI was not significantly different between SCR and ICR patients **(Table 3)**.

Discussion

The BIOVASC trial showed that ICR is non-inferior to SCR in patients with ACS and MVD in terms of the primary endpoint at 1-year follow-up. SCR was associated with more MIs and repeat revascularisation compared with ICR[9]. In the current subanalysis, we compared the impact of the timing of complete revascularisation between 2VD and 3VD. We did not identify significant interactions with respect to the effect of an immediate or staged strategy on the primary endpoint. ICR was associated with a lower risk of MI in patients with 3VD, and this was also a strong trend in patients with 2VD, resulting in a significant reduction in the composite of cardiovascular death and MI.

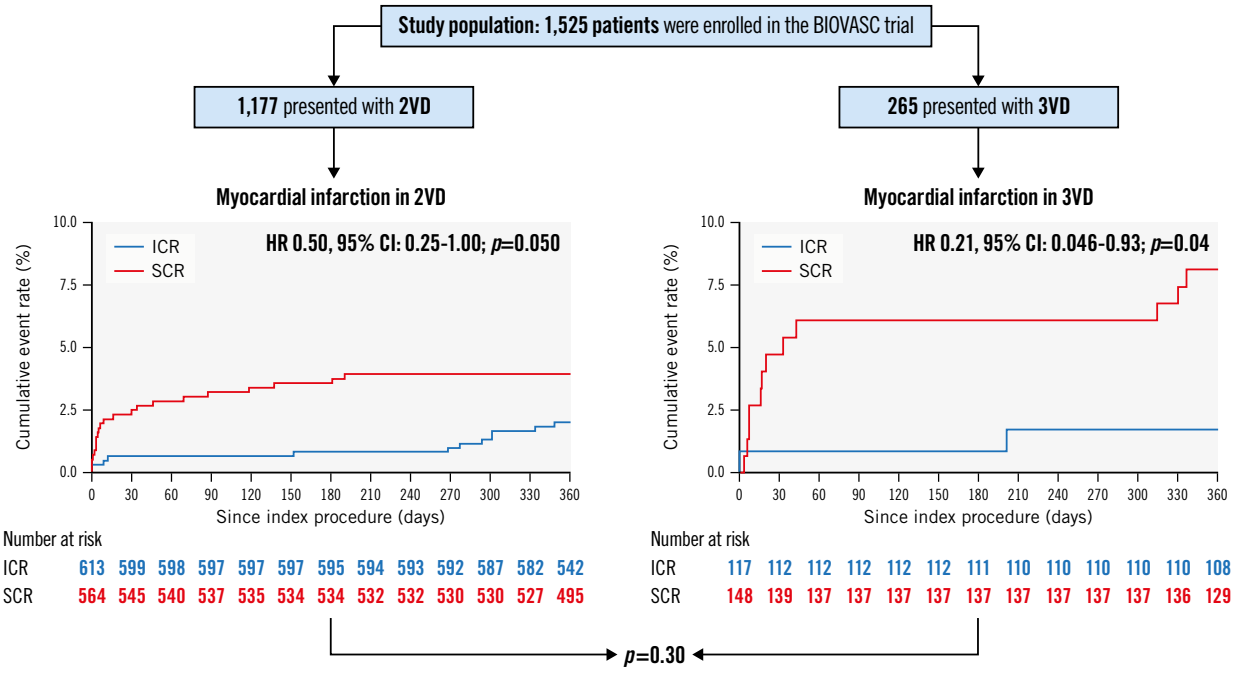
The reduction in MIs was evident in the 3VD population comparing ICR with SCR, despite the limited number of patients. In addition, a substantial difference in hazard ratio and absolute incidence in terms of any MI was evident when comparing 2VD and 3VD, indicating that patients with 3VD present with more MIs than patients with 2VD for those undergoing SCR, while the incidence among those undergoing ICR was similar. A statistical difference could not be established in the 2VD group, yet no significant interaction of 3VD/2VD was identified for the effect of ICR or SCR on MIs. However, it should be considered that an interaction test in a substudy of a clinical trial is likely to be underpowered[12,13].

Accurate culprit lesion identification in MVD might be challenging[14], especially in the case of complex and extensive 3VD, potentially leading to the treatment of a non-culprit lesion during the index procedure. This was also reiterated by the FIRE trial, which showed that more complex patients, such as elderly patients, benefit from a complete and timely revascularisation[15]. In addition, imaging studies in ST-elevation myocardial infarction (STEMI) patients revealed the presence of one or more non-culprit lesion with unstable characteristics in up to 50% of patients undergoing primary percutaneous coronary intervention[16], possibly translating into an early recurrent MI (re-MI) if those lesions remain untreated[17]. Specifically, in a staged procedure, residual vulnerable plaques might prompt ischaemic events in the time window between the index and the staged procedure[18].

The identification of procedure-related MI during the acute phase might be challenging; therefore, in our study we performed an exploratory analysis excluding all type 4a MIs occurring at the index or at the staged procedure. After excluding type 4a MIs, no significant difference was

EuroIntervention — Central Illustration

Clinical outcomes after immediate or staged complete revascularisation in patients presenting with two- or three-vessel disease.



Hala Kakar *et al.* • *EuroIntervention* 2024;20:e479-e486 • DOI: 10.4244/EIJ-D-23-00762

Myocardial infarction rates and their p interactions in patients with 2VD and in patients with 3VD. 2VD: two-vessel disease; 3VD: three-vessel disease; CI: confidence interval; HR: hazard ratio; ICR: immediate complete revascularisation; SCR: staged complete revascularisation

found between ICR and SCR, and the interaction between 3VD/2VD remained similar. This could be because of the low number of events that remained after excluding the procedure-related MIs, therefore, reducing the ability to detect significant differences, yet showing a substantial difference in hazard ratio when comparing 2VD with 3VD.

The number of days in hospital, total contrast use and total radiation dose were higher in both the 3VD and 2VD groups when an SCR approach was adopted. In terms of interaction between treatment allocation and the number of diseased vessels, the ICR strategy in the 3VD population was associated with a greater reduction in hospital stay, total contrast use and total radiation dose compared with the 2VD group. The safety of an increased use of contrast during the index procedure compared with an increased overall use of contrast in the staged procedure remains to be established. One of the main determinants of contrast use and radiation exposure is the number of diseased vessels[19,20], implying that patients with 3VD receive more contrast and radiation than patients with 2VD, which is in line with our findings. Hence, the advantage of ICR is a subsequent decrease in contrast use and radiation.

Finally, the staged procedure is often performed days to weeks after the index procedure, resulting in a potential increase in healthcare costs[21,22].

Limitations

Identification of the culprit lesions was more challenging to assess by angiography, as there was limited use of imaging, which might have led to an incorrect determination of the culprit lesion. Furthermore, this trial was supposedly not powered to compare 2VD with 3VD; despite this, a numerically significant increase in the risk of MI in the 3VD group was found. Given the sample size, it is not possible to draw conclusions regarding the potential interaction of STEMI versus non ST-elevation acute coronary syndrome in 2VD and 3VD. Due to randomisation, the allocation of ICR and SCR was uneven in the 2VD and 3VD group, which might have had an effect on the results.

Conclusions

ICR is safe in patients presenting with ACS and MVD and might also be an option in patients with extensive 3VD. It could represent a novel treatment paradigm, associated with potential clinical and ancillary advantages.

Authors' affiliations

1. Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; 2. Department of Cardiovascular Medicine, University Hospital Leuven, Leuven, Belgium; 3. Interventional Cardiology Department, Hospital Clinic, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; 4. Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; 5. Cardiology Department, Hospital Clínico de Valladolid, Valladolid, Spain

Conflict of interest statement

R. Diletti has received institutional research grants from Biotronik, Medtronic, ACIST Medical Systems, and Boston Scientific. N. Van Mieghem has received institutional research grants from Biotronik, Abbott, Medtronic, Edwards Lifesciences, PulseCath, Abiomed, and Daiichi Sankyo; speaker fees from Abiomed and Amgen; and a travel grant from JenaValve. W. Den Dekker has received institutional research grants from Biotronik. J. Bennett has received institutional grants from Biotronik, Abbott, and Shockwave Medical. The other authors have no conflicts of interest to declare.

References

1. Park DW, Clare RM, Schulte PJ, Pieper KS, Shaw LK, Califf RM, Ohman EM, Van de Werf F, Hirji S, Harrington RA, Armstrong PW, Granger CB, Jeong MH, Patel MR. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. *JAMA*. 2014;312:2019-27.

2. Hassanin A, Brener SJ, Lansky AJ, Xu K, Stone GW. Prognostic impact of multivessel versus culprit vessel only percutaneous intervention for patients with multivessel coronary artery disease presenting with acute coronary syndrome. *EuroIntervention*. 2015;11:293-300.

3. Fuster V, Gotto AM, Libby P, Loscalzo J, McGill HC. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 1. Pathogenesis of coronary disease: the biologic role of risk factors. *J Am Coll Cardiol*. 1996;27:964-76.

4. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, López-Sendón J, Faxon DP, Mauri L, Rao SV, Feldman L, Steg PG, Avezum Á, Sheth T, Pinilla-Echeverri N, Moreno R, Campo G, Wrigley B, Kedev S, Sutton A, Oliver R, Rodés-Cabau J, Stanković G, Welsh R, Lavi S, Cantor WJ, Wang J, Nakamya J, Bangdiwala SI, Cairns JA; COMPLETE Trial Steering Committee and Investigators. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019;381:1411-21.

5. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115-23.

6. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol*. 2015;65:963-72.

7. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L; DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet*. 2015;386:665-71.

8. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med*. 2017;376:1234-44.

9. Diletti R, den Dekker WK, Bennett J, Schotborgh CE, van der Schaaf R, Sabaté M, Moreno R, Ameloot K, van Bommel R, Forlani D, van Reet B, Esposito G, Dirksen MT, Ruifrok WPT, Everaert BRC, Van Mieghem C, Elscot JJ, Cummins P, Lenzen M, Brugaletta S, Boersma E, Van Mieghem NM; BIOVASC Investigators. Immediate versus staged complete revascularisation in patients presenting with acute coronary syndrome and multivessel coronary disease (BIOVASC): a prospective, open-label, non-inferiority, randomised trial. *Lancet*. 2023;401:1172-82.

10. den Dekker WK, Van Mieghem NM, Bennett J, Sabate M, Esposito G, van Bommel RJ, Daemen J, Vrolix M, Cummins PA, Lenzen MJ, Boersma E, Zijlstra F, Diletti R; BioVasc Trial Investigators. Percutaneous complete revascularization strategies using sirolimus-eluting biodegradable

polymer-coated stents in patients presenting with acute coronary syndrome and multivessel disease: Rationale and design of the BIOVASC trial. *Am Heart J*. 2020;227:111-7.

11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020-35.

12. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. A survey of three medical journals. *N Engl J Med*. 1987;317:426-32.

13. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA*. 1991;266:93-8.

14. Balbi MM, Scarparo P, Tovar MN, Masdjedi K, Daemen J, Den Dekker W, Ligthart J, Witberg K, Cummins P, Wilschut J, Zijlstra F, Van Mieghem NM, Diletti R. Culprit Lesion Detection in Patients Presenting With Non-ST Elevation Acute Coronary Syndrome and Multivessel Disease. *Cardiovasc Revasc Med*. 2022;35:110-8.

15. Biscaglia S, Guiducci V, Escaned J, Moreno R, Lanzilotti V, Santarelli A, Cerrato E, Sacchetta G, Jurado-Roman A, Menozzi A, Amat Santos I, Díez Gil JL, Ruozzi M, Barbierato M, Fileti L, Picchi A, Lodolini V, Biondi-Zoccai G, Maietti E, Pavasini R, Cimaglia P, Tumscitz C, Erriquez A, Penzo C, Colaiori I, Pignatelli G, Casella G, Iannopollo G, Menozzi M, Varbella F, Caretta G, Dudek D, Barbato E, Tebaldi M, Campo G; FIRE Trial Investigators. Complete or Culprit-Only PCI in Older Patients with Myocardial Infarction. *N Engl J Med*. 2023;389:889-98.

16. Pinilla-Echeverri N, Mehta SR, Wang J, Lavi S, Schampaert E, Cantor WJ, Bainey KR, Welsh RC, Kassam S, Mehran R, Storey RF, Nguyen H, Meeks B, Wood DA, Cairns JA, Sheth T. Nonculprit Lesion Plaque Morphology in Patients With ST-Segment-Elevation Myocardial Infarction: Results From the COMPLETE Trial Optical Coherence Tomography Substudys. *Circ Cardiovasc Interv*. 2020;13:e008768.

17. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226-35.

18. Yin Y, Fang C, Jiang S, Wang J, Wang Y, Guo J, Lei F, Sun S, Pei X, Jia R, Tang C, Li L, Wang Y, Yu H, Dai J, Yu B. Culprit and Non-Culprit Plaque Characteristics With vs. Without a Healed Phenotype in Patients With Acute Myocardial Infarction Caused by Plaque Erosion - A 3-Vessel OCT Study. *Circ J*. 2022;86:846-54.

19. Fetterly KA, Lennon RJ, Bell MR, Holmes DR Jr, Rihal CS. Clinical determinants of radiation dose in percutaneous coronary interventional procedures: influence of patient size, procedure complexity, and performing physician. *JACC Cardiovasc Interv*. 2011;4:336-43.

20. Manicardi M, Nocetti L, Brigidi A, Cadioli C, Sgreccia D, Valenti AC, Vitolo M, Arrotti S, Monopoli DE, Sgura F, Rossi R, Guidi G, Boriani G. Anthropometric parameters and radiation doses during percutaneous coronary procedures. *Phys Med*. 2022;100:164-75.

21. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. 2020;141:e139-596.

22. Cerrud-Rodriguez RC, Rashid SMI, Wiley KA, Gonzalez M, Kosmacheva VA, Castillero-Norato I, Rivera C, Villablanca P, Wiley J. Complete Revascularization of Stable STEMI Patients Offers a Significant Benefit if Done During the Index PCI, but Not if It's Done as a Staged Procedure. *Int J Gen Med*. 2021;14:2239-48.

Supplementary data

Supplementary Table 1. Intention-to-treat analysis – primary and secondary outcomes in two- versus three-vessel disease.

Supplementary Table 2. Types of myocardial infarction.

Supplementary Figure 1. Box plot of total contrast use in ICR versus SCR.

Supplementary Figure 2. Box plot of total radiation dose in ICR versus SCR.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00762

Supplementary data

Supplementary Table 1. Intention-to-treat analysis – primary and secondary outcomes in two- versus three-vessel disease.

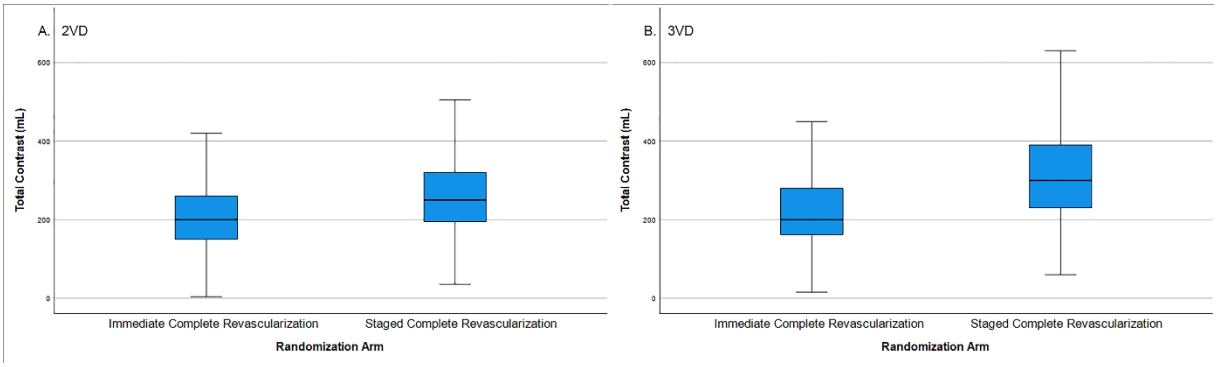
Outcome		Immediate Complete Revascularisation (N=764)		Staged Complete Revascularisation (N=761)		Hazard Ratio (95% CI)	P value	$P_{Interaction}$
		No. events	Percentage †	No. events	Percentage †			
Primary outcome								
All-cause mortality, any myocardial infarction, unplanned ischemia driven revascularisation or cerebrovascular event	2VD	44	6.9	51	8.4	0.80 (0.53, 1.20)	0.28	0.98
	3VD	13	11.2	20	13.6	0.79 (0.39, 1.59)	0.51	
Secondary outcomes								
Cardiovascular mortality or myocardial infarction	2VD	17	2.7	27	4.4	0.59 (0.32, 1.08)	0.087	0.84
	3VD	5	4.3	12	8.2	0.52 (0.18, 1.47)	0.22	
All-cause mortality	2VD	9	1.3	8	1.4	1.06 (0.41, 2.76)	0.90	0.13
	3VD	5	4.3	1	0.7	6.43 (0.75, 55.09)	0.089	
Cardiovascular mortality	2VD	6	0.8	6	1.0	0.94 (0.31, 2.94)	0.93	0.18
	3VD	4	1.7	1	0.7	5.15 (0.58, 46.11)	0.14	
Any myocardial infarction	2VD	12	1.9	22	3.6	0.51 (0.25, 1,03)	0.061	0.29
	3VD	2	1.8	12	8.2	0.21 (0.046, 0.93)	0.040	
Unplanned ischemia driven revascularisation	2VD	23	3.7	34	6.3	0.63 (0.37, 1.07)	0.089	0.98
	3VD	8	7.1	16	10.9	0.62 (0.27, 1.46)	0.27	
Cerebrovascular event	2VD	9	1.5	9	1.6	0.95 (0.38, 2.39)	0.90	0.92
	3VD	2	2.0	3	1.8	0.85 (0.14, 5.10)	0.86	
Probable or definite stent thrombosis	2VD	5	0.8	5	0.8	0.95 (0.27, 3.28)	0.90	0.54
	3VD	1	0.9	3	2.1	0.43 (0.04, 4.10)	0.46	
Target vessel revascularisation	2VD	19	3.0	31	5.7	0.57 (0.32, 1.01)	0.056	0.97
	3VD	7	6.2	15	10.2	0.58 (0.24, 1.43)	0.24	
Target lesion revascularisation	2VD	15	2.4	28	5.0	0.50 (0.27, 0.94)	0.031	0.90
	3VD	6	5.3	14	9.6	0.54 (0.21, 1.40)	0.20	
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 or 5)	2VD	42	6.6	45	7.4	0.87 (0.57, 1.32)	0.52	0.33
	3VD	7	6.0	16	10.9	0.53 (0.22, 1.30)	0.17	
Major bleeding (BARC 3 or 5)	2VD	16	2.5	12	2.0	1.27 (0.60, 2.69)	0.53	0.24
	3VD	1	0.9	4	2.7	0.32 (0.035, 2.83)	0.30	

BARC=bleeding academic research consortium. † Cumulative incidence at 365 days according to the Kaplan-Meier method. *Only applicable for type 4a myocardial infarctions related to the index or staged procedure.

Supplementary Table 2. Types of myocardial infarction.

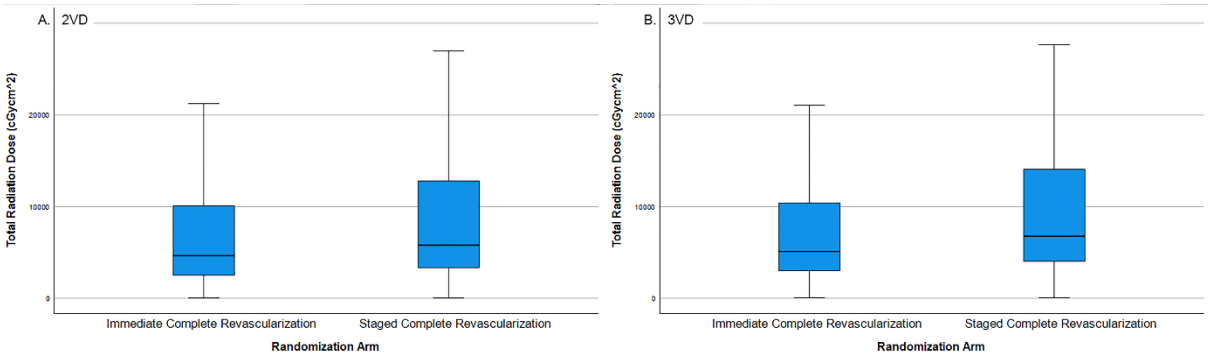
		2VD	*3VD*	*Total*
Type of MI	Type 1	18	7	25
	Type 2	2	0	2
	Type 3	1	0	1
	Type 4a	7	5	12
	Type 4b	6	2	8
Total		34	14	48

Abbreviations 2VD = two vessel disease, 3VD = three vessel disease, MI = myocardial infarction



Supplementary Figure 1. Box plot of total contrast use in ICR versus SCR.

2VD = two vessel disease, 3VD = three vessel disease, ICR = immediate complete revascularization, SCR = staged complete revascularization
A: Boxplots of total contrast use in immediate versus staged complete revascularization in patients with 2VD
B: Boxplots of total contrast use in immediate versus staged complete revascularization in patients with 3VD



Supplementary Figure 2. Box plot of total radiation dose in ICR versus SCR.

2VD = two vessel disease, 3VD = three vessel disease, , ICR = immediate complete revascularization, SCR = staged complete revascularization
A: Boxplots of total radiation dose in immediate versus staged complete revascularization in patients with 2VD
B: Boxplots of total radiation dose in immediate versus staged complete revascularization in patients with 3VD