Timing of Complete Revascularization Stratified by Index Presentation During On- and Off-Hours

Jacob J. Elscot, BSc[a], Hala Kakar, MD[a], Wijnand K. den Dekker, MD, PhD[a], Johan Bennett, MD, PhD[b], Manel Sabaté, MD, PhD[c], Giovanni Esposito, MD, PhD[d], Eric Boersma, PhD[a], Nicolas M. Van Mieghem, MD, PhD[a], and Roberto Diletti, MD, PhD[a,*], on behalf of the BIOVASC Investigators

Recent trials suggested immediate complete revascularization (ICR) as a safe alternative to staged complete revascularization (SCR), but the impact of the respective percutaneous coronary intervention strategies between on- versus off-hours is unclear. On-hours was defined as an index revascularization performed between 8:00 A.M. and 6:00 P.M., Monday to Friday, or else the procedure was defined as performed during off-hours. The primary end point consisted of a composite of all-cause mortality, myocardial infarction, unplanned ischemia-driven revascularization, and cerebrovascular events at 1-year follow-up. We used Cox regression models to relate randomized treatment with study end points. We evaluated multiplicative and additive interactions between on- versus off-hours and randomized treatment. The BIOVASC (Percutaneous Complete Revascularization Strategies Using Sirolimus Eluting Biodegradable Polymer Coated Stents in Patients Presenting With Acute Coronary Syndromes and Multivessel Disease) trial enrolled 1,097 and 428 patients during on- and off-hours, respectively. Patients randomized during off-hours were more likely to present with ST-segment elevation myocardial infarction (66.4% vs 29.5%, p <0.001). The composite primary outcome occurred in 8.4% and 10.1% of patients randomized to ICR and SCR, respectively, during on-hours (hazard ratio 0.80, 95% confidence interval 0.54 to 1.19). During off-hours, the primary composite outcome occurred in 5.4% and 7.7% in ICR and SCR (0.69, 95% confidence interval 0.32 to 1.46) with no evidence of a differential effect (interaction $p_{multiplicative} = 0.70$, $p_{additive} = 0.56$). No differential effect was found between treatment allocation and on- versus off-hours in any of the secondary outcomes. In conclusion, no differential treatment effect was found when comparing ICR versus SCR in patients presenting with acute coronary syndrome and multivessel disease during on- or off-hours. **(Am J Cardiol 2024;223:73−80)**

Keywords: acute coronary syndrome, multivessel disease, off-hours

Percutaneous coronary intervention (PCI) is the current guideline recommended therapy for patients presenting with acute coronary syndrome (ACS), and complete revascularization should be considered when multivessel disease (MVD) is present.[1] The recent BIOVASC and MULTISTARS-AMI trials demonstrated non-inferiority at 1-year follow-up of complete revascularization during index PCI compared with revascularization of non-culprit-related arteries in a staged setting, which indicates that immediate complete revascularization (ICR) is a safe alternative to staged complete revascularization (SCR).[2,3] In the BIOVASC trial, 28.1% of the patients underwent index PCI outside of office hours.[2] Previous studies have found no significant difference in the rate of complications and mortality between PCI during and outside of office hours. However, these studies mainly analyzed ST-segment elevation myocardial infarction (STEMI) patients with single-vessel coronary disease.[4−12] In addition to the complexity of a multivessel PCI, clinical outcomes and procedure-related complications could be influenced by operator fatigue and reduced availability of resources, especially in the setting of complete revascularization. Therefore, an operator might opt for reperfusion of the culprit lesion only, followed by delayed PCI of the non-culprit arteries, which could lead to fewer complications and early events.[13] Thus, this prespecified sub-analysis of the BIOVASC trial aimed to compare patients who underwent PCI during office hours with PCI outside office hours. In addition, ICR was compared with SCR, stratified by the timing of the index procedure during or outside office hours.

[a]Thorax Center, Department of Cardiology, Erasmus MC Cardiovascular Institute, Rotterdam, The Netherlands; [b]Department of Cardiovascular Medicine, University Hospital Leuven, Leuven, Belgium; [c]Interventional Cardiology Department, Cardiovascular Institute, Hospital Clinic, Barcelona, Spain; and [d]Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy. Manuscript received March 14, 2024; revised manuscript received and accepted May 11, 2024.

Funding: The BIOVASC trial was funded by the Erasmus University Medical Center, Rotterdam, the Netherlands and by Biotronik SE & Co. KG, Berlin, Germany

See page 79 for Declaration of Competing Interest.

*Corresponding author: Tel: 0031 10 703 52 60; fax 0031 10 703 52 54.

E-mail address: r.diletti@erasmusmc.nl (R. Diletti).

https://doi.org/10.1016/j.amjcard.2024.05.020

Methods

The BIOVASC trial enrolled 1,525 patients presenting with ACS and MVD eligible for PCI in 29 centers in the Netherlands, Belgium, Italy, and Spain to compare ICR with culprit-only revascularization followed by staged PCI within 6 weeks (SCR).[2] Details of the study's design have been previously published.[14] Eligible patients presented with ACS and MVD, defined as ≥1 significant non-culprit artery-related lesion in a vessel with ≥2.5 mm in diameter. A significant lesion was defined as at least 70% stenosis by visual estimation or positive coronary physiology testing. Utility of imaging and/or physiology was at the decision of the operator. Exclusion criteria included presence of an unclear culprit, previous coronary artery bypass grafting, presentation with cardiogenic shock, and a chronic total occlusion in a dominant vessel with ≥2.5 mm in diameter. The study was conducted according to the Declaration of Helsinki, and the Erasmus MC Medical Ethics Review Committee granted ethical approval.

This substudy's aim was to determine possible interactions between treatment allocation and timing of index PCI. Timing of index PCI was stratified in on-hours and off-hours. On-hours was defined as an index PCI performed between 8:00 A.M. and 6:00 P.M. on Monday to Friday. Index PCI outside this interval was defined as off-hours. This analysis was prespecified in the BIOVASC trial's protocol, but parameters regarding the timing intervals defining on- or off-hours were classified post-hoc.

Primary end points include a composite of all-cause mortality, myocardial infarction, unplanned ischemia-driven revascularization, or cerebrovascular events, whichever occurred first. Secondary end points have previously been described in detail.[14] In short, revascularization had to be both classified as unplanned and ischemia driven to be counted as an end point. A revascularization was considered unplanned if a revascularization was performed before the staged due to a new ACS (with dynamic electrocardiogram changes and/or a new elevation of cardiac enzymes). After the staged procedure or in the ICR arm, any ischemia-driven revascularization was considered unplanned. Ischemia driven was considered if one of the following criteria was met: (1) the treated lesion had a stenosis >70% or positive physiology testing. (2) The treated lesion was identified as the culprit of a new ACS. The end point myocardial infarction consisted of a modification for the ACS setting, namely, for patients whose cardiac troponin values were already elevated or were recently elevated, new ischemic symptoms of at least 20 minutes and either new ST-segment elevation of at least 1 mm in 2 adjacent limb leads or 2 mm in 2 adjacent precordial leads had to be present. These electrocardiogram changes had to be distinct from the original myocardial infarction. Furthermore, due to a potential bias in the detection of procedure-related myocardial infarctions favoring ICR, outcomes including myocardial infarction have also been explored excluding type 4a related to the index or staged procedure. Complete revascularization was investigator reported and considered if all lesions with at least 70% stenosis or positive physiology testing were treated successfully. Successful treatment was defined as <20% residual stenosis and thrombolysis in myocardial infarction grade 3 coronary flow.

All patients randomized in the BIOVASC trial were included in the analysis as per an intention-to-treat principle. Continuous variables were presented as medians (first and third quartiles), and comparisons of on- versus off-hours and ICR versus SCR were made using the Mann-Whitney *U* test. Categorical data were presented as counts and percentages and tested by the chi-square or Fisher's exact test when appropriate. The cumulative incidence of study end points over time was estimated with the use of the Kaplan-Meier method. Censoring occurred at the first event or at the last follow-up date if end point-free. Differences in the incidence of study end points between patients randomized to ICR versus SCR were studied using Cox-proportional hazard (PH) regression. The regression models included treatment allocation, index PCI timing, and an index PCI timing × treatment allocation interaction to study effect modification by timing of index PCI. We tested multiplicative and additive interaction. The statistical significance of multiplicative interaction was tested on the null hypothesis that the beta of the interaction term equals 0. The statistical significance of the additive interaction was tested on the null hypothesis that the relative excess due to interaction equals 0 with the lowest joint category as reference. In addition, multivariable Cox models that included baseline characteristics that were associated with clinical outcomes ($p < 0.10$) were used (Supplementary Table 1 for more details). One variable per 10 events was taken into account to avoid overfitting of the model.

Results of Cox regression analyses were presented as hazard ratio (HR) with 95% confidence intervals (CIs). Regarding the PH assumption, assessment of the log-minus log survival plot demonstrated no suspicion of a violated PH assumption. A two-sided $p < 0.05$ was considered significant. p values were not adjusted for multiple testing. All analyses were performed using R Version 4.2.1 (R Core Team, Vienna, Austria. Packages used: data.table, dplyr, ggplot2, ggpubr, graphics, lubridate, stats, survival, survminer, tidycmprsk).

Results

The BIOVASC trial enrolled 1,097 patients during on-hours (557 to ICR and 540 to SCR) and 428 patients during off-hours (207 to ICR and 221 to SCR). In terms of baseline and procedural characteristics, patients randomized during off-hours were 63.6 (55.7 to 71.5) years old, and patients randomized during on-hours were 66.2 (58.6 to 72.5) years old ($p < 0.001$). Patients randomized during on-hours had more often renal insufficiency (5.8% vs 3.3%, $p = 0.041$), hypertension (55.8% vs 48.1%, $p = 0.0071$), and hypercholesterolemia (54.8% vs 43.1%, $p < 0.001$). The prevalence of STEMI was higher during off-hours (66.4% vs 29.5%, $p < 0.001$). In addition, the total use of contrast (230 vs 202 ml, $p = 0.0022$) and radiation (5,562 $cGycm^2$ vs 4,663 $cGycm^2$ $p = 0.0024$) was higher when the index PCI occurred during on-hours. No significant differences in terms of periprocedural complications were found between ICR and SCR during both on- and off-hours. Baseline and

Table 1
Baseline and procedural characteristics

Characteristic	On-hours			Off-hours			$P_{interaction}$*
	ICR (n = 557)	SCR (n = 540)	P Value	ICR (n = 207)	SCR (n = 221)	P Value	
Age, years	66.8 (57.7-73.9)	65.7 (59.3-73.2)	0.83	62.7 (56.0-70.9)	63.9 (55.3-72.2)	0.59	0.80
BMI	27.3 (24.7-30.2)	27.3 (24.8-29.7)	0.77	27.2 (24.5-29.8)	27.1 (24.6-30.1)	0.73	0.64
Previous PCI	67 (12.0%)	86 (15.9%)	0.063	16 (7.7%)	35 (15.8%)	0.010	0.18
Previous MI	53/556 (9.5%)	69/540 (12.8%)	0.088	16/207 (7.7%)	20/221 (9.1%)	0.62	0.69
Peripheral artery disease	31/557 (5.6%)	21/540 (3.9%)	0.19	4/206 (1.9%)	12/221 (5.4%)	0.058	0.027
Valve disease	18/555 (3.2%)	14/538 (2.6%)	0.53	7/207 (3.4%)	3/221 (1.4%)	0.17	0.37
COPD	46/557 (8.3%)	33/540 (6.1%)	0.17	8/206 (3.9%)	13/221 (5.9%)	0.34	0.14
Atrial fibrillation or flutter	25 (4.5%)	20 (3.7%)	0.51	8 (3.9%)	2 (0.9%)	0.043	0.13
Renal insufficiency	36 (6.5%)	28 (5.2%)	0.37	5 (2.4%)	9 (4.1%)	0.34	0.21
History of stroke	26/557 (4.7%)	19/540 (3.5%)	0.34	11/206 (5.3%)	8/221 (3.6%)	0.39	0.84
Hypertension	324 (58.2%)	288 (53.3%)	0.11	99 (47.8%)	107 (48.4%)	0.90	0.34
Diabetes	122 (21.9%)	120 (22.2%)	0.90	36 (17.4%)	43 (19.5%)	0.58	0.68
Hypercholesterolemia	297 (53.4%)	303 (56.2%)	0.35	88 (42.7%)	96 (43.4%)	0.88	0.72
Family history of CVD	169 (30.4%)	175 (32.8%)	0.40	68 (33.0%)	75 (34.1%)	0.81	0.80
Systolic blood pressure, mmHg	125 (110-140)	125 (110-140)	0.72	124 (109-140)	121 (110-140)	0.83	0.62
Diastolic blood pressure, mmHg	71 (63-80)	70 (62-80)	0.37	74 (65-84)	71 (62-79)	0.061	0.20
Radial access	537/556 (96.6%)	519/540 (96.1%)	0.68	202/207 (97.6%)	217/221 (98.2%)	0.66	0.57
STEMI at presentation	165 (29.6%)	159 (29.4%)	>0.99	140 (67.6%)	144 (65.2%)	0.66	0.68
LAD culprit vessel	209/550 (38.0%)	187/539 (34.7%)	0.26	76/207 (36.7%)	82/221 (37.1%)	0.93	0.50
Three vessel disease	78 (14.0%)	100 (18.5%)	0.043	39 (18.8%)	48 (21.7%)	0.46	0.60
Complete revascularization	540/557 (96.9%)	516/539 (95.7%)	0.28	200/207 (96.6%)	210/221 (95.0%)	0.41	0.93
FFR/iFR	93 (16.7%)	128 (23.7%)	0.0038	25 (12.1)	49 (22.2%)	0.0059	0.34
IVUS/OCT	37 (6.6%)	70 (13.0%)	<0.001	8 (3.9%)	41 (18.6%)	<0.001	0.028
Total hospital stay, days	3 (2-5)	4 (3-6)	<0.001	3 (2-5)	4 (3-6)	<0.001	0.50
Time to staged procedure, days		15 (4-28)			15 (3-28)		
No. of stents used per patient							
Index procedure	3 (2-4)	1 (1-2)	<0.001	3 (2-4)	1 (1-2)	<0.001	0.020
Index + staged procedure	3 (2-4)	3 (2-4)	0.024	3 (2-4)	3 (2-4)	0.36	0.39
Length of stents, mm							
Index procedure	60 (43-83)	30 (22-46)	<0.001	65 (48-89)	30 (22-48)	<0.001	0.070
Index + staged procedure	60 (43-83)	66 (46-91)	0.011	65 (48-89)	69 (45-98)	0.50	0.60
Procedure duration, minutes							
Index procedure	66 (47-85)	46 (34-61)	<0.001	60 (46-84)	44 (34-60)	<0.001	0.47
Index + staged procedure	66 (47-85)	90 (62-120)	<0.001	60 (46-84)	90 (68-118)	<0.001	0.33
Contrast use, mL							
Index procedure	210 (160-270)	145 (108-197)	<0.001	191 (144-230)	120 (100-160)	<0.001	0.55
Index + staged procedure	210 (160-270)	251 (200-330)	<0.001	191 (144-230)	250 (190-320)	<0.001	0.93
Total area dose, $cGycm^2$							
Index procedure	4905 (2564-11757)	3248 (2564-11757)	<0.001	4365 (2494-7800)	2354 (1568-4192)	<0.001	0.59
Index + staged procedure	4905 (2564-11757)	6348 (3512-16402)	<0.001	4365 (2494-7800)	5191 (3134-8840)	0.068	0.35
P2Y12 at discharge			0.78			0.94	0.69
Ticagrelor	393/556 (70.7%)	389/538 (72.3%)		139/205 (67.8%)	147/221 (66.5%)		
Prasugrel	61/556 (11.0%)	59/538 (11.0%)		44/205 (21.5%)	48/221 (21.7%)		
Clopidogrel	102/556 (18.3%)	90/538 (16.7%)		22/205 (10.7%)	26/221 (11.8%)		
Procedure-related complications	38 (6.8%)	32 (5.9%)	0.54	18 (8.7%)	13 (5.9%)	0.26	0.55

* $P_{interaction}$ indicates the p value considering the null-hypothesis that the *beta* of the multiplicative interaction term of timing of index PCI and treatment allocation equals 0.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; LAD = left anterior descending artery; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

procedural characteristics are tabulated in Table 1 and Supplementary Table 2.

Follow-up at 1 year was complete for 425/428 (99.3%) patients randomized during off-hours and for 1,081/1,097 (98.5%) patients randomized during on-hours. At 1 year, the primary composite outcome occurred in 9.3% and 6.6% of the patients in the on-hours and off-hours group, respectively (adjusted HR 1.36, 95% CI 0.89 to 2.07, p = 0.16). The cumulative incidence of myocardial infarction was 2.6% and 3.4% in the off-hours and on-hours groups, respectively (adjusted HR 1.33, 95% CI 0.68 to 2.62, p = 0.41). The Kaplan-Meier curves of the primary composite outcome and myocardial infarction for the off-hours and on-hours groups are shown in Figure 1. Mortality occurred in 1.9% and 0.5% of the patients treated during on- and off-hours, respectively (adjusted HR 4.08, 95% CI 0.96 to 17.38, p = 0.058). There were no significant differences in terms of the secondary outcomes between on- and off-

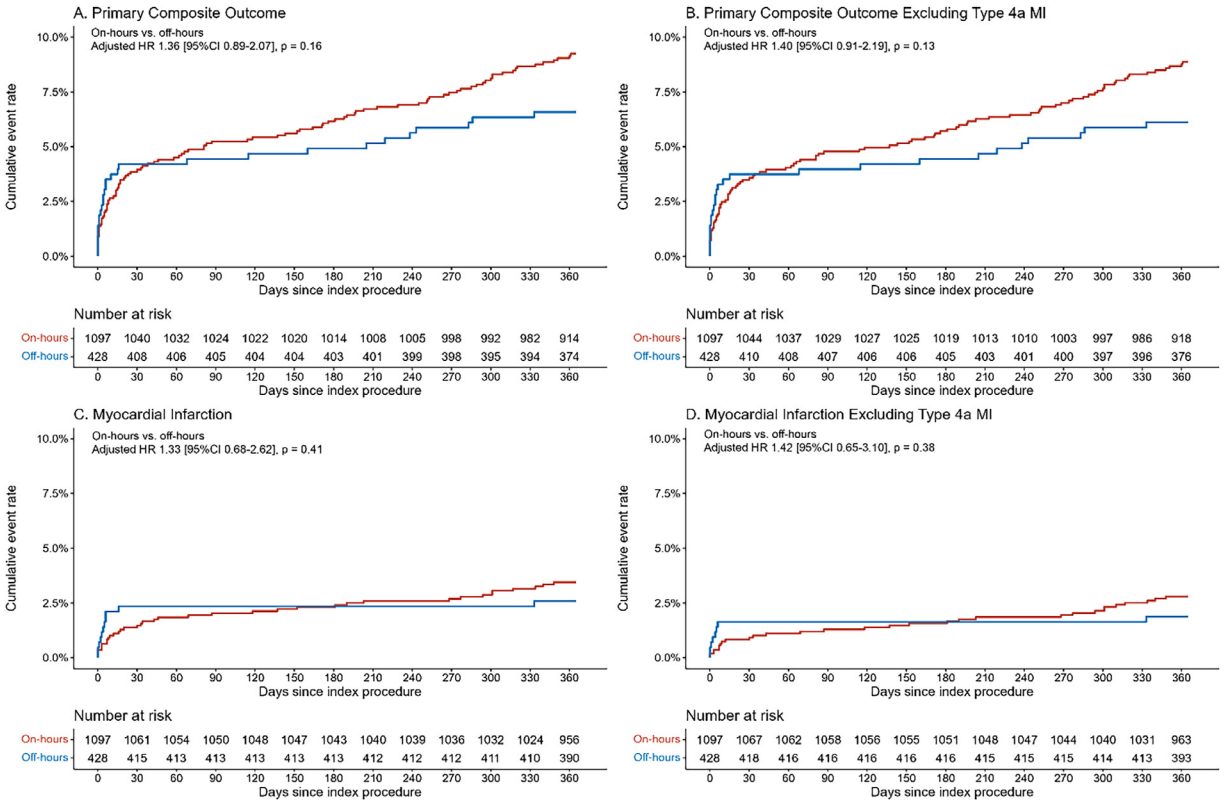

Figure 1. Primary composite outcome in on- versus off-hours. On-hours was defined as an index PCI performed between 8:00 A.M. and 6:00 P.M. on Monday to Friday. Index PCI outside this interval was defined as off-hours.

hours. Comparisons of the primary and secondary outcomes comparing on- and off-hours are tabulated in Table 2.

In patients with index PCI during on-hours, ICR and SCR were associated with an incidence of 8.4% and 10.1%, respectively, in terms of the primary composite outcome (HR 0.80, 95% CI 0.54 to 1.19, p = 0.27). In the off-hours group, the primary composite outcome occurred in 5.4% and 7.7% of the patients randomized to ICR and SCR, respectively (HR 0.69, 95% CI 0.32 to 1.46, p = 0.33). No significant multiplicative or additive interactions between

Table 2
Clinical outcomes between on- and off-hours

Outcome	On-hours N=1097 No. events (%)	Off-hours N=428 No. events (%)	Univariable hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)*	P value
All-cause mortality, myocardial infarction, unplanned ischemia driven revascularisation or cerebrovascular event	100 (9.3%)	28 (6.6%)	1.41 (0.92, 2.14)	0.11	1.36 (0.89, 2.07)	0.16
All-cause mortality, myocardial infarction excluding type 4a during index or staged procedure, unplanned ischemia driven revascularization or cerebrovascular event	96 (8.9%)	26 (6.1%)	1.45 (0.94, 2.24)	0.090	1.40 (0.91, 2.17)	0.13
All-cause mortality	21 (1.9%)	2 (0.5%)	4.12 (0.97, 17.58)	0.056	4.08 (0.96, 17.38)	0.058
Cardiovascular mortality	15 (1.4%)	2 (0.5%)	2.94 (0.67, 12.87)	0.15	2.92 (0.67, 12.76)	0.16
Any myocardial infarction	37 (3.4%)	11 (2.6%)	1.32 (0.67, 2.59)	0.42	1.33 (0.68, 2.62)	0.41
Any myocardial infarction excluding type 4a during index or staged PCI	30 (2.8%)	8 (1.9%)	1.48 (0.68, 3.21)	0.33	1.42 (0.65, 3.10)	0.38
Unplanned ischemia driven revascularisation	61 (5.7%)	20 (4.7%)	1.20 (0.72, 1.99)	0.48	1.22 (0.74, 2.03)	0.44
Cerebrovascular event	19 (1.8%)	4 (0.9%)	1.87 (0.64, 5.49)	0.26	1.87 (0.64, 5.51)	0.25
Probable or definite stent thrombosis	10 (0.9%)	4 (0.9%)	0.98 (0.31, 3.12)	0.97	0.98 (0.31, 3.14)	0.98
Target vessel revascularisation	55 (5.1%)	17 (4.0%)	1.27 (0.74, 2.19)	0.39	1.28 (0.74, 2.22)	0.37
Target lesion revascularisation	48 (4.5%)	15 (3.5%)	1.26 (0.70, 2.25)	0.44	1.26 (0.70, 2.26)	0.44
Major bleeding (BARC 3 or 5)	25 (2.3%)	8 (1.9%)	1.23 (0.55, 2.73)	0.61	1.16 (0.52, 2.58)	0.71

* Adjusted for randomization arm. Additional covariates potentially included in the model (taking into account 10 events per covariate): age, BMI, previous PCI, previous MI, peripheral artery disease, valve disease, chronic obstructive pulmonary disease, atrial fibrillation or flutter, renal insufficiency, previous stroke, hypertension, diabetes mellitus, hypercholesterolemia, family history of cardiovascular disease, STEMI at presentation, LAD culprit and three vessel disease.

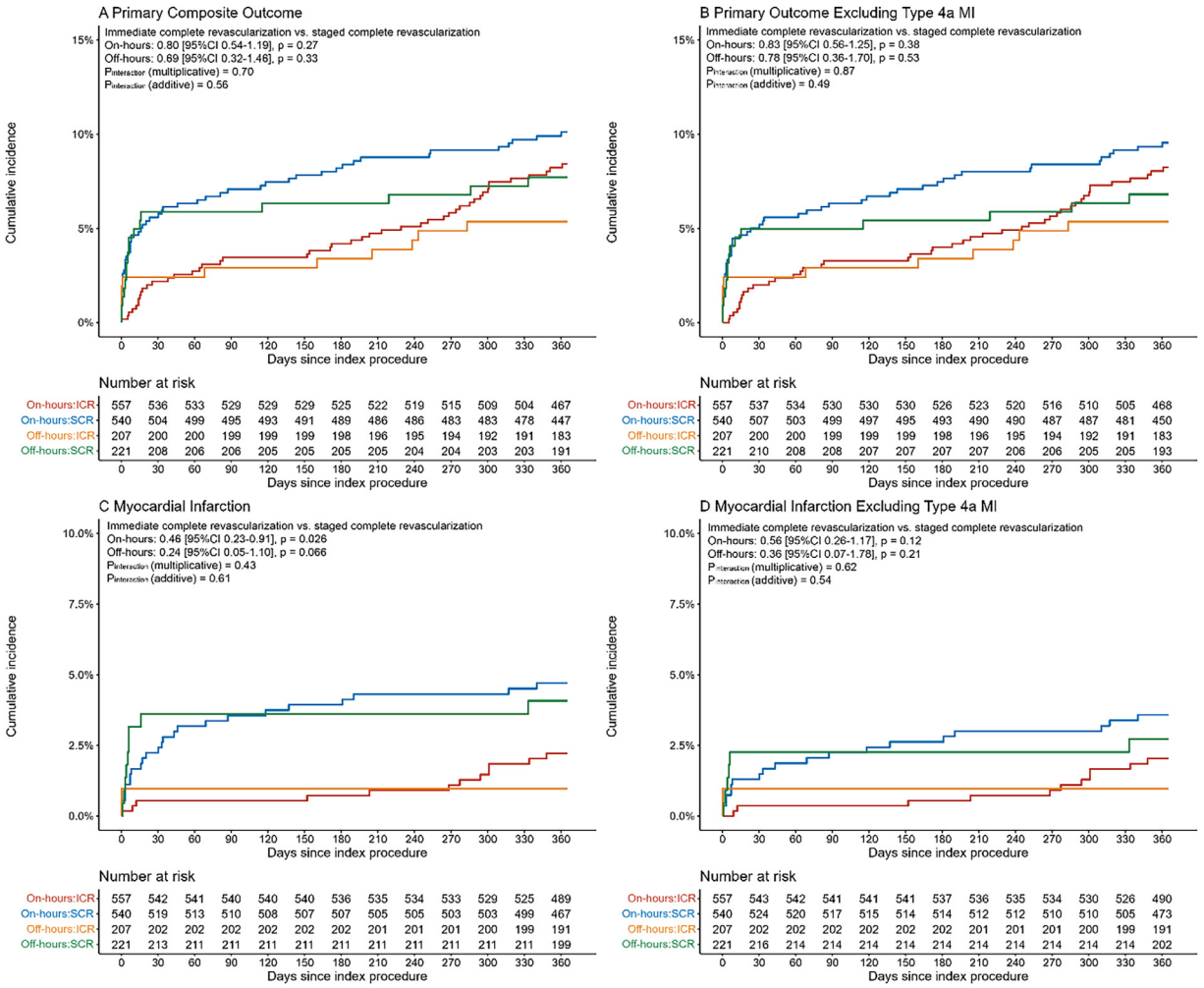

Figure 2. Primary composite outcome and myocardial infarction in ICR and SCR, stratified by on- and off-hours. The primary composite is a composite of all-cause mortality, myocardial infarction, unplanned ischemia-driven revascularization, and cerebrovascular events.

the timing of index PCI and treatment allocation were found in the primary and secondary outcomes. The incidence curves of the primary composite outcome and myocardial infarction for the off-hours and on-hours groups, stratified by treatment allocation to ICR or SCR, are shown in Figure 2. Comparisons of the primary and secondary outcomes comparing ICR and SCR between off- and on-hours are tabulated in Table 3.

Discussion

This prespecified study of the BIOVASC trial did not establish a significant difference in clinical end point between index PCI during on- versus off-hours. In addition, no significant interaction was found between timing of index PCI and treatment allocation in terms of the primary and secondary outcomes. Overall, the risk comparisons between ICR and SCR were comparable in the on- and off-hours populations.

In terms of procedural characteristics, patients treated during on-hours received more total contrast and radiation. These data contradict a previous study comparing on- versus off-hours, which report more contrast and radiation when patients were treated during off-hours.[15] However, this study did not focus primarily on MVD, and only patients with STEMI were analyzed, which could explain the different results compared with our study. Namely, a higher prevalence of non-ST-segment elevation (NSTE)-ACS was observed in our study during on-hours, and NSTE-ACS is known to involve a higher use of contrast and radiation compared with STEMI.[16]

After adjustment for potential confounders, our study did not find a significant difference in the primary and secondary outcomes when comparing on- with off-hours. Previous observations in literature are conflicting, with most studies supporting our finding suggesting no difference in clinical outcomes when comparing on- with off-hours.[4–12] However, some studies reported a higher incidence of mortality during off-hours, especially in high-risk patients.[17,18] Rashid et al[6] reported a higher door-to-balloon time in patients presenting during off-hours, which was also found to be an independent predictor for mortality in this study. A study by Rodríguez-Arias et al[19] aimed to also observe potential delays attributed to off-hours presentation of STEMI and found a significantly higher delay between time from symptom onset to first medical contact, which was

Table 3
Clinical outcomes in ICR versus SCR, stratified by timing of presentation

Outcome	Immediate Complete Revascularisation On-hours, N = 557 Off-hours, N = 207 No. events (%)	Staged Complete Revascularisation On-hours, N = 540 Off-hours, N = 221 No. events (%)	Hazard ratio (95% CI)	P for multiplicative interaction*	P for additive interaction†
All-cause mortality, myocardial infarction, unplanned ischemia driven revascularization or cerebrovascular event				0.70	0.56
On-hours	46 (8.4%)	54 (10.1%)	0.80 (0.54, 1.19)		
Off-hours	11 (5.4%)	17 (7.7%)	0.69 (0.32, 1.46)		
All-cause mortality, myocardial infarction excluding type 4a during index or staged procedure, unplanned ischemia driven revascularization or cerebrovascular event				0.87	0.49
On-hours	45 (8.2%)	51 (9.6%)	0.83 (0.56, 1.25)		
Off-hours	11 (5.4%)	15 (6.8%)	0.78 (0.36, 1.70)		
All-cause mortality				0.97	0.50
On-hours	12 (2.2%)	9 (1.7%)	1.29 (0.55, 3.07)		
Off-hours	2 (1.0%)	0 (0.0%)	NA		
Cardiovascular mortality				0.97	0.50
On-hours	8 (1.5%)	7 (1.3%)	1.11 (0.40, 3.06)		
Off-hours	2 (1.0%)	0 (0.0%)	NA		
Any myocardial infarction				0.43	0.61
On-hours	12 (2.2%)	25 (4.7%)	0.46 (0.23, 0.91)		
Off-hours	2 (1.0%)	9 (4.1%)	0.24 (0.05, 1.10)		
Any myocardial infarction excluding type 4a during index or staged PCI				0.62	0.54
On-hours	11 (2.0%)	19 (3.6%)	0.56 (0.26, 1.17)		
Off-hours	2 (1.0%)	6 (2.7%)	0.36 (0.07, 1.78)		
Unplanned ischemia driven revascularization				0.70	0.27
On-hours	23 (4.3%)	38 (7.2%)	0.58 (0.34, 0.97)		
Off-hours	8 (3.9%)	12 (5.4%)	0.71 (0.29, 1.74)		
Cerebrovascular event				0.84	0.59
On-hours	9 (1.7%)	10 (1.9%)	0.87 (0.35, 2.14)		
Off-hours	2 (1.0%)	2 (0.9%)	1.07 (0.15, 7.62)		
Probable or definite stent thrombosis				0.67	0.65
On-hours	4 (0.7%)	6 (1.1%)	0.65 (0.18, 2.29)		
Off-hours	2 (1.0%)	2 (0.9%)	1.08 (0.15, 7.65)		
Target vessel revascularization				0.92	0.34
On-hours	20 (3.7%)	35 (6.6%)	0.54 (0.31, 0.94)		
Off-hours	6 (2.9%)	11 (5.0%)	0.58 (0.21, 1.57)		
Target lesion revascularization				0.42	0.83
On-hours	15 (2.8%)	33 (6.2%)	0.43 (0.24, 0.80)		
Off-hours	6 (2.9%)	9 (4.1%)	0.71 (0.25, 2.00)		
Major bleeding (BARC 3 or 5)				0.40	0.74
On-hours	12 (2.2%)	13 (2.5%)	0.90 (0.41, 1.97)		
Off-hours	5 (2.5%)	3 (1.4%)	1.81 (0.43, 7.57)		

* $P_{interaction}$ indicates the p value considering the null-hypothesis that the *beta* of the multiplicative interaction-term of index revascularization timing (on- or off-hours) and treatment allocation equals 0.

† $P_{interaction}$ indicates the p value considering the null-hypothesis that the relative excess due to interaction equals 0 with the lowest joint category as reference.

compensated by a significantly lower door-to-balloon time. Therefore, this study found no significant difference in total ischemic time between on- and off-hours. These contradicting observations could be attributed to the difference in study end points. Namely, Rashid et al[6] defined door-to-balloon time as the time of first hospital encounter to the time of the first balloon inflation or device usage, whereas Rodríguez-Arias et al[19] defined door-to-balloon time as the time from first medical contact to reperfusion therapy, including fibrinolysis.

Operator fatigue and understaffing could be more common during off-hours and could therefore impact clinical outcomes, favoring a less complex culprit-only procedure.[13] Still, in our study, we did not find a significant interaction between on- versus off-hours and ICR versus SCR. This could be ascribed to the population size of the study, which was powered to establish non-inferiority between ICR and SCR and could therefore be considered limited for tests of interaction.[20] However, when comparing the results of the risk comparisons between ICR and SCR, a similar treatment effect was found in almost all end points. Specifically, the results favored an ICR strategy in terms of myocardial infarction and unplanned ischemia-driven revascularization during on-hours, but this was not statistically significant in

the off-hours population. Yet, the negative interaction tests and similar risk comparisons of ICR versus SCR between the on- and off-hours populations might suggest that the treatment effect of performing ICR was irrespective of the timing of the index procedure, but adequately powered studies are required to fully investigate the treatment effect of ICR versus SCR stratified by the timing of revascularization.

Our study has limitations that should be acknowledged. First, this is a post-hoc analysis of a randomized non-inferiority trial and therefore not sufficiently powered for interaction tests between the on- and off-hours populations. Second, presentation with NSTE-ACS was less prevalent during off-hours, which is expected since STEMI requires emergent primary PCI whereas NSTE-ACS does not. Nevertheless, this could limit the interpretation of the results in the context of ACS in general, considering that the population differs between on- and off-hours. Third, there may have been meaningful selection bias to enroll patients in the BIOVASC trial, more so during off-hours. Fourth, MVD was not diagnosed using intravascular physiology testing in the majority of cases. It must be acknowledged that use of angiography-only has significant limitation in the diagnosis of MVD. Fifth, one type of stent was primarily used in this population (Orsiro stent platform; Biotronik SE & Co. KG, Berlin, Germany), which could have an impact on the generalizability of the results. At last, use of invasive imaging differed between ICR and SCR during both on- and off-hours, which could have impacted clinical outcomes. The results of this study should be considered exploratory and hypothesis generating.

In conclusion, no differential treatment effect was found when comparing ICR versus SCR in patients presenting with ACS and MVD during on- or off-hours.

Declaration of competing interest

Dr. Diletti has received institutional research grants from Biotronik, Medtronic, ACIST Medical Systems, and Boston Scientific. Dr. den Dekker has received institutional research grants from Biotronik. Dr. 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. Dr. Bennett has received institutional grants from Biotronik, Abbott Vascular, and Shockwave Medical. Dr. Sabaté has received consultancy fees from Abbott Vascular and iVascular. The remaining authors have no competing interests to declare.

CRediT authorship contribution statement

Jacob J. Elscot: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hala Kakar:** Writing – review & editing. **Wijnand K. den Dekker:** Writing – review & editing, Funding acquisition, Conceptualization. **Johan Bennett:** Writing – review & editing, Conceptualization. **Manel Sabaté:** Writing – review & editing, Conceptualization. **Giovanni Esposito:** Writing – review & editing, Conceptualization. **Eric Boersma:** Writing – review & editing, Validation, Methodology. **Nicolas M. Van Mieghem:** Writing – review & editing, Funding acquisition, Conceptualization. **Roberto Diletti:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.05.020.

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan G-A, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B, ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;44:3720–3826.
2. 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;401:1172–1182.
3. Stähli BE, Varbella F, Linke A, Schwarz B, Felix SB, Seiffert M, Kesterke R, Nordbeck P, Witzenbichler B, Lang IM, Kessler M, Valina C, Dibra A, Rohla M, Moccetti M, Vercellino M, Gaede L, Bott-Flügel L, Jakob P, Stehli J, Candreva A, Templin C, Schindler M, Wischnewsky M, Zanda G, Quadri G, Mangner N, Toma A, Magnani G, Clemmensen P, Lüscher TF, Münzel T, Schulze PC, Laugwitz K-L, Rottbauer W, Huber K, Neumann F-J, Schneider S, Weidinger F, Achenbach S, Richardt G, Kastrati A, Ford I, Maier W, Ruschitzka F, MULTISTARS AMI Investigators. Timing of complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2023;389:1368–1379.
4. Lattuca B, Kerneis M, Saib A, Nguyen Lee S, Payot L, Barthélemy O, Le Feuvre C, Helft G, Choussat R, Collet J-P, Montalescot G, Silvain J, ACTION Study Group. On- versus off-hours presentation and mortality of ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019;12:2260–2268.
5. Noman A, Ahmed JM, Spyridopoulos I, Bagnall A, Egred M. Mortality outcome of out-of-hours primary percutaneous coronary intervention in the current era. *Eur Heart J* 2012;33:3046–3053.
6. Rashid MK, Wells G, So DY, Chong AY, Dick A, Froeschl M, Glover C, Hibbert B, Labinaz M, Russo J, Bernick J, Le May M. Off-hours presentation, door-to-balloon time, and clinical outcomes in patients referred for primary percutaneous coronary intervention. *J Invasive Cardiol* 2023;35:E185–E193.
7. Ma WJ, Gao SD, Huang SZ, Lin XZ, Yang YJ, Yu MY. Quality Control & Improvement Center of Cardiovascular Intervention of Beijing. Off-hours admission does not impact outcomes in patients undergoing primary percutaneous coronary intervention and with a first medical contact-to-device time within 90 min. *Chin Med J (Engl)* 2021;134:1795–1802.
8. Geraiely B, Nematipour E, Amirzadegan A, Nozari Y, Aghajani H, Jalali A, Haji Zeinali AM, Mortazavi SH. One-month clinical outcomes of ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention at a high-volume cardiac tertiary center: routine hours versus off-hours. *Crit Pathw Cardiol* 2020;19:33–36.
9. Dharma S, Dakota I, Sukmawan R, Andriantoro H, Siswanto BB, Rao SV. Two-year mortality of primary angioplasty for acute myocardial infarction during regular working hours versus off-hours. *Cardiovasc Revasc Med* 2018;19:826–830.
10. Cubeddu RJ, Palacios IF, Blankenship JC, Horvath SA, Xu K, Kovacic JC, Dangas GD, Witzenbichler B, Guagliumi G, Kornowski R, Dudek

D, Stone GW, Mehran R. Outcome of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention during on- versus off-hours (a harmonizing outcomes with revascularization and stents in acute myocardial infarction [HORIZONS-AMI] trial substudy). *Am J Cardiol* 2013;111:946–954.
11. Sag CM, Zeymer U, Ouarrak T, Schneider S, Montalescot G, Huber K, Fuernau G, Freund A, Feistritzer H-J, Desch S, Thiele H, Maier LS. Effects of ON-hours versus OFF-hours admission on outcome in patients with myocardial infarction and cardiogenic shock: results from the CULPRIT-SHOCK trial. *Circ Cardiovasc Interv* 2020;13:e009562.
12. de Boer SP, Oemrawsingh RM, Lenzen MJ, van Mieghem NM, Schultz C, Akkerhuis KM, van Leeuwen MA, Zijlstra F, van Domburg RT, Serruys PW, Boersma E. Primary PCI during off-hours is not related to increased mortality. *Eur Heart J Acute Cardiovasc Care* 2012;1:33–39.
13. Needleman J, Buerhaus P, Pankratz VS, Leibson CL, Stevens SR, Harris M. Nurse staffing and inpatient hospital mortality. *N Engl J Med* 2011;364:1037–1045.
14. 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;227:111–117.
15. Tokarek T, Dziewierz A, Plens K, Rakowski T, Jaroszyńska A, Bartuś S, Siudak Z. Percutaneous coronary intervention during on- and off-hours in patients with ST-segment elevation myocardial infarction. *Hellenic J Cardiol* 2021;62:212–218.
16. Stocker TJ, Abdel-Wahab M, Möllmann H, Deseive S, Massberg S, Hausleiter J. Trends and predictors of radiation exposure in percutaneous coronary intervention: the PROTECTION VIII study. *EuroIntervention* 2022;18:e324–e332.
17. Geng J, Ye X, Liu C, Xie J, Chen J, Xu B, Wang B. Outcomes of off- and on-hours admission in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: a retrospective observational cohort study. *Medicine* 2016;95:e4093.
18. Sorita A, Ahmed A, Starr SR, Thompson KM, Reed DA, Prokop L, Shah ND, Murad MH, Ting HH. Off-hour presentation and outcomes in patients with acute myocardial infarction: systematic review and meta-analysis. *BMJ* 2014;348:f7393.
19. Rodríguez-Arias JJ, Ortega-Paz L, Brugaletta S, Freixa X, Masotti M, Regueiro A, Ariza A, Carrillo X, Lidon R-M, Garcia J, Cardenas M, Rojas SG, Muñoz JF, Zielonka M, Tizon-Marcos H, Sabaté M. Comparison of clinical outcomes in STEMI patients treated with primary PCI according to day-time of medical attention and its relationship with circadian pattern. *Int J Cardiol* 2020;305:35–41.
20. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;266:93–98.