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

Jacob J. Elscot, BSc[1]; Hala Kakar, MD[1]; Paola Scarparo, MD[1]; Wijnand K. den Dekker, MD, PhD[1]; Johan Bennett, MD, PhD[2]; Carl E. Schotborgh MD[3]; Rene van der Schaaf, MD, PhD[4]; Manel Sabaté MD, PhD[5]; Raúl Moreno MD, PhD[6]; Koen Ameloot, MD, PhD[7]; Rutger J. van Bommel, MD, PhD[8]; Daniele Forlani MD[9]; Bert Van Reet, MD[10]; Giovanni Esposito, MD, PhD[11]; Maurits T. Dirksen, MD, PhD[12]; Willem P.T. Ruifrok MD, PhD[13]; Bert R. C. Everaert MD, PhD[14]; Carlos Van Mieghem, MD, PhD[15]; Eduardo Pinar, MD, PhD[16]; Fernando Alfonso, MD, PhD[17]; Paul Cummins, RN[1]; Mattie Lenzen, PhD[1]; Salvatore Brugaletta, MD, PhD[7]; Joost Daemen, MD, PhD[1]; Eric Boersma, PhD[1]; Nicolas M. Van Mieghem, MD, PhD[1]; Roberto Diletti, MD, PhD[1]; for the BIOVASC Investigators

[1] Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands
[2] Department of Cardiovascular Medicine, University Hospital Leuven, Leuven, Belgium
[3] Department of Cardiology, Haga Hospital, The Hague, The Netherlands
[4] Department of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[5] Interventional Cardiology Department, Cardiovascular Institute, Hospital Clinic, Barcelona, Spain
[6] Interventional Cardiology Unit, Cardiology Department, La Paz University Hospital, Paseo de la Castellana, Spain
[7] Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos, 3600 Genk, Belgium
[8] Department of Cardiology, Tergooi MC, Hilversum, The Netherlands
[9] Department of Cardiology, Santo Spirito Hospital, Pescara, Italy
[10] Department of Cardiology, AZ Turnhout , Turnhout , Belgium
[11] Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy
[12] Department of Cardiology, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands
[13] Department of Cardiology, Treant Zorggroep, Emmen, The Netherlands
[14] Department of Cardiology, AZ Monica Hospital, Antwerp, Belgium
[15] Department of Cardiology, AZ Groeninge, Kortrijk, Belgium
[16] Department of Cardiology, Interventional Cardiology Unit, Virgen de la Arrixaca Hospital, Murcia, Spain
[17] Department of Cardiology, Hospital Universitario de La Princesa Madrid, CIBER-CV, Madrid, Spain

Address for correspondence
Roberto Diletti, MD, PhD
Interventional Cardiology, Thoraxcenter, Erasmus MC
Dr. Molewaterplein 40,
3015 GD Rotterdam, The Netherlands
Visiting address: office Rg-632k
Telephone 0031 10 703 52 60
Fax 0031 10 703 52 54
E-mail: r.diletti@erasmusmc.nl

Word count (including references): 6133

Disclosures

RD has received institutional research grants from Biotronik, Medtronic, ACIST Medical Systems, and Boston Scientific. WKdD has received institutional research grants from Biotronik. NMVM 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. JB has received institutional grants from Biotronik, Abbott Vascular and Shockwave Medical. JD has received institutional grant/research support from Abbott Vascular, Boston Scientific, ACIST Medical, Medtronic, Microport, Pie Medical, and ReCor medical, and consultancy and speaker fees from Abbott Vascular, Abiomed, ACIST medical, Boston Scientific, Cardialysis BV, CardiacBooster, Kaminari Medical, ReCor Medical, PulseCath, Pie Medical, Sanofi, Siemens Health Care and Medtronic. All other authors declare no competing interests.

Abstract

Background

Multivessel coronary artery disease (MVD) is highly prevalent in patients presenting with non-ST-segment elevation myocardial infarction (NSTE-ACS) and is associated with worse clinical outcomes compared with single vessel disease patients. Complete revascularization of the culprit and all significant non-culprit lesions reduces the incidence of major adverse cardiac events, but the optimal timing of non-culprit artery revascularization remains unclear.

Methods

This prespecified substudy of the randomized BIOVASC trial included patients who presented with NSTE-ACS and MVD, defined as ≥ 1 non-culprit related coronary artery with a diameter of ≥ 2.5 mm and ≥ 70% stenosis as per visual estimation or positive coronary physiology testing. Risk differences of the composite of all-cause mortality, myocardial infarction, unplanned ischemia driven revascularization or cerebrovascular events and its individual components were compared between the patients who were randomized to immediate and staged complete revascularization at 30 days and 1 year.

Results

The BIOVASC trial enrolled 1525 patients, 917 patients presented with NSTE-ACS, of whom 459 were allocated to the immediate complete and 458 to the staged complete revascularization group. The incidences of the primary composite outcome were similar in the two groups (7.9% vs. 10.1%, risk difference 2.2%, 95%CI -1.5 to 6.0, p = 0.24). Immediate complete revascularization was associated with a significant reduction in the incidence of myocardial infarction (2.0% vs. 5.3%, risk difference 3.3%, 95% confidence interval [CI] 0.9 to 5.7, p = 0.008), which was maintained after exclusion of procedure related myocardial infarctions occurring at the index or staged procedure (2.0% vs. 4.4%, risk difference 2.4%, 95%CI 0.1 to 4.7, p = 0.039). Unplanned ischemia driven revascularizations were also reduced in the immediate complete revascularization group (4.2% vs. 7.8%, risk difference 3.5%, 95%CI 0.4 to 6.6, p = 0.025).

Conclusions

Immediate complete revascularization is safe in patients with NSTE-ACS and MVD and was associated with a reduction in myocardial infarctions and unplanned ischemia driven revascularizations at 1 year.

Clinical Perspective

What Is New?

- This prespecified subanalysis of the BIOVASC trial shows that all spontaneous myocardial infarctions between the index and staged procedure occurred in the population of patients that initially presented with NSTE-ACS. At 30 days and 1 year patients randomized to immediate complete revascularization have fewer myocardial infarctions and unplanned ischemia driven revascularizations.

What Are the Clinical Implications?

- Immediate complete revascularization appears to be a safe strategy and can be a reasonable option for complete revascularization in patients presenting with NSTE-ACS and multivessel disease

- In patients presenting with NSTE-ACS and multivessel disease, misjudgment of the culprit lesion or presence of multiple vulnerable plaques could have a role in the reduction of early occurring myocardial infarctions when performing an immediate complete strategy.

List of Abbreviations

ACS	acute coronary syndrome
CI	confidence interval
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
PH	proportional hazards
SCR	staged complete revascularization
STEMI	ST-segment elevation myocardial infarction
UA	unstable angina

Introduction

Multivessel coronary artery disease (MVD) is common in patients presenting with an acute coronary syndrome (ACS) without persistent ST-elevations (NSTE-ACS). About 50% of the patients present with one or more significant non-culprit 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 non-culprit lesions is associated with lower cumulative mortality rates and risk of major adverse cardiac events[3,11-13]. Therefore, recent guidelines report that complete revascularization should be considered in patients with MVD and NSTE-ACS, tailored to patients' characteristics, preferences and comorbidities[14]. However, the ideal timing of non-culprit revascularization in an immediate or staged setting remains unclear. The ESC guidelines provide a class IIb recommendation for complete revascularization during index percutaneous coronary intervention (PCI) [14] based on one small randomized trial showing a lower risk of MACE, 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 randomized trial showed that ICR is non-inferior 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]

Against 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, 1525 patients presenting with acute coronary syndrome including both ST segment elevation myocardial infarction (STEMI) and NSTE-ACS and multivessel MVD, defined as at least 70% stenosis in a non-culprit 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. Invasive coronary imaging 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 myocardial infarction, any unplanned ischemia-driven revascularization, and cerebrovascular events at 1 year post index procedure.

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 two 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 ST-segment elevation myocardial infarction, (i.e. ST depression of 1 mm or greater in two contiguous leads, T-wave inversion more than 3 mm, or any dynamic ST shifts). If cardiomyocyte necrosis was present or absent, a patient would be categorized as presenting with non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA), respectively.

Study endpoints

Definitions of all efficacy and safety outcomes have been previously published in detail[17]. Deaths were classified as cardiovascular or non-cardiovascular. 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 trial[19]. Repeat revascularization had to be considered both unplanned and ischemia driven to be counted as an endpoint. A clinical events committee, comprising three 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 myocardial infarction.

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 and standard deviation if a Gaussian distribution was present and tested by the unpaired t-test. Alternatively, continuous data were presented as median and quartiles [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 hazard regression (PH) was conducted to further explore the relation between randomly allocated treatment and study endpoints. Hazard ratios (HR) were presented with 95% confidence intervals and calculated with use of Cox regression analyses. Assessment of the log-minus log survival plot led to a suspicion of a violated PH assumption for the primary endpoint. Further testing of the Schoenfeld residuals concluded that the PH assumption was not met. Therefore P values for all endpoints were computed on the difference in the cumulative incidence between the two groups for consistency. A two-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, stats, survival, survminer, tidycmprsk).

Results

Patient characteristics

The BIOVASC trial enrolled 1525 patients, of whom 917 (60.1%) presented with a NSTEMI or UA, with 459 and 458 patients randomized to ICR and and SCR, respectively. 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.

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 (1.8% vs. 5.7%, risk difference 4.0%, 95% confidence interval [CI] 1.5 to 6.4, p = 0.002) and the composite of cardiovascular death and MI (0.2% vs. 3.1%, risk difference 2.9%, 95%CI 1.1 to 4.6, p = 0.001) showed a statistically significant difference in favor of the patients randomized to ICR. The incidence of MI (0.2% vs. 3.1%, risk difference 2.9%, 95%CI 1.2 to 4.5, p < 0.001) and unplanned ischemia driven revascularization (0.9% vs. 3.7%, risk difference 2.9%, 95%CI 0.9 to 4.8, p = 0.004) was also lower in the patients randomized to ICR at 30-day follow-up. All spontaneous MIs between the index and staged procedure occurred in patients that initially presented with NSTE-ACS. Additionally, there was a higher incidence of the composite of all-cause mortality, MI, stroke or major bleeding (BARC 3 or 5) in the SCR arm (1.3% vs. 5.7%, risk difference 4.4%, 95%CI 2.0 to 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% and 10.1% in the patients randomized to ICR and SCR (risk difference 2.2%, 95% confidence interval [CI -1.5 to 6.0, p = 0.24). The incidence of cardiovascular death at 1 year was similar between the two trial arms (1.1% vs. 0.9%, 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% and 5.7% of the patients at 1 year, (risk difference 2.7%, 95%CI 0.0 to 5.3, p = 0.052). ICR was associated with a lower incidence of MI (2.0% vs. 5.3%, risk difference 3.3%, 95%CI 0.9 to 5.7, p = 0.008) and unplanned ischemia driven revascularization (4.2% vs. 7.8%, risk difference 3.5%, 95%CI 0.4 to 6.6, p = 0.025) at 1 year. The primary and secondary outcomes at 1 year are tabulated in Table 4.

An analysis excluding procedure related MIs occurring during the index or 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 the ICR group (2.0% vs. 4.4%, risk difference 2.4%, 95%CI 0.1 to 4.7, p = 0.039). A total of 13 non procedure related infarctions occurred between the index and staged

procedure, 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 related to the index or staged procedure, are tabulated in Table 5.

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 myocardial infarction associated with an ICR strategy persisted after exclusion of procedure-related events.

In the BIOVASC trial, 44% (N=15) of all first occurring non procedure related MIs in the SCR group, happened between the index and staged procedure. Ten of those MIs were type 1 MI and occurred only in patients that initially presented with a NSTE-ACS at randomization.

Plaque vulnerability of non-culprit 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 decrease in antioxidant enzymes[21], potentially impacting plaque vulnerability in non-culprit 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 non-culprit lesions, which is associated with a higher risk of future cardiac events[24].
The non-culprit 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 multivessel disease, culprit lesion assessment can be very challenging[25,26]. Despite the fact that unclear culprit lesion was an exclusion criteria in the BIOVASC trail, 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 procedure[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, re-hospitalization 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 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 timeframe. However, when comparing the results of the SMILE study 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 study 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 registry showed significantly lower myocardial infarctions 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 sub-population 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].

Limitations

This is a pre-specified post-hoc analysis of a randomized noninferiority trial. No formal power calculation was performed for this 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.

Conclusions

In patients presenting with NSTE-ACS and MVD, immediate complete revascularization was safe and associated with a lower cumulative incidence of myocardial infarctions and unplanned ischemia driven myocardial infarction at 1 year post index PCI compared with staged complete revascularization.

References

1. Thiele H, Rach J, Klein N, Pfeiffer D, Hartmann A, Hambrecht R, Sick P, Eitel I, Desch S, Schuler G, et al. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). *European Heart Journal*. 2011;33:2035-2043. doi: 10.1093/eurheartj/ehr418
2. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *The Lancet*. 1999;354:708-715. doi: https://doi.org/10.1016/S0140-6736(99)07349-3
3. Rathod KS, Koganti S, Jain AK, Astroulakis Z, Lim P, Rakhit R, Kalra SS, Dalby MC, O'Mahony C, Malik IS, et al. Complete Versus Culprit-Only Lesion Intervention in Patients With Acute Coronary Syndromes. *Journal of the American College of Cardiology*. 2018;72:1989-1999. doi: https://doi.org/10.1016/j.jacc.2018.07.089
4. Corpus RA, House JA, Marso SP, Grantham JA, Huber KC, Laster SB, Johnson WL, Daniels WC, Barth CW, Giorgi LV, et al. Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction. *American Heart Journal*. 2004;148:493-500. doi: https://doi.org/10.1016/j.ahj.2004.03.051
5. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple Complex Coronary Plaques in Patients with Acute Myocardial Infarction. *New England Journal of Medicine*. 2000;343:915-922. doi: 10.1056/nejm200009283431303
6. Fox KAA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JGP, Lagerqvist B, Wallentin L. Long-Term Outcome of a Routine Versus Selective Invasive Strategy in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome: A Meta-Analysis of Individual Patient Data. *Journal of the American College of Cardiology*. 2010;55:2435-2445. doi: https://doi.org/10.1016/j.jacc.2010.03.007
7. Jobs A, Mehta SR, Montalescot G, Vicaut E, van't Hof AWJ, Badings EA, Neumann F-J, Kastrati A, Sciahbasi A, Reuter P-G, et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *The Lancet*. 2017;390:737-746. doi: https://doi.org/10.1016/S0140-6736(17)31490-3
8. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann F-J, Robertson DH, DeLucca PT, DiBattiste PM, et al. Comparison of Early Invasive and Conservative Strategies in Patients with Unstable Coronary Syndromes Treated with the Glycoprotein IIb/IIIa Inhibitor Tirofiban. *New England Journal of Medicine*. 2001;344:1879-1887. doi: 10.1056/nejm200106213442501
9. Poole-Wilson PA, Pocock SJ, Fox KAA, Henderson RA, Wheatley DJ, Chamberlain DA, Shaw TRD, Clayton TC. Interventional versus conservative treatment in acute non-ST elevation coronary syndrome:

time course of patient management and disease events over one year in the RITA 3 trial. *Heart*. 2006;92:1473-1479. doi: 10.1136/hrt.2005.060541

10. Wallentin L, Lindhagen L, Ärnström E, Husted S, Janzon M, Johnsen SP, Kontny F, Kempf T, Levin L-Å, Lindahl B, et al. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. *The Lancet*. 2016;388:1903-1911. doi: https://doi.org/10.1016/S0140-6736(16)31276-4
11. Kim MC, Hyun JY, Ahn Y, Bae S, Hyun DY, Cho KH, Sim DS, Hong YJ, Kim JH, Jeong MH, et al. Optimal Revascularization Strategy in Non-ST-Segment-Elevation Myocardial Infarction With Multivessel Coronary Artery Disease: Culprit-Only Versus One-Stage Versus Multistage Revascularization. *J Am Heart Assoc*. 2020;9:e016575.
12. Ibrahim H, Sharma PK, Cohen DJ, Fonarow GC, Kaltenbach LA, Effron MB, Zettler ME, Peterson ED, Wang TY. Multivessel Versus Culprit Vessel-Only Percutaneous Coronary Intervention Among Patients With Acute Myocardial Infarction: Insights From the TRANSLATE-ACS Observational Study. *J Am Heart Assoc*. 2017;6.
13. Zapata GO, Lasave LI, Kozak F, Damonte A, Meiriño A, Rossi M, Carbó S, Pollice A, Paolasso E, Picabea E. Culprit-only or multivessel percutaneous coronary stenting in patients with non-ST-segment elevation acute coronary syndromes: one-year follow-up. *J Interv Cardiol*. 2009;22:329-335.
14. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2020;42:1289-1367. doi: 10.1093/eurheartj/ehaa575
15. Sardella G, Lucisano L, Garbo R, Pennacchi M, Cavallo E, Stio RE, Calcagno S, Ugo F, Boccuzzi G, Fedele F, et al. Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients: The SMILE Trial. *J Am Coll Cardiol*. 2016;67:264-272.
16. Diletti R, den Dekker WK, Bennett J, Schotborgh CE, van der Schaaf R, Sabaté M, Moreno R, Ameloot K, van Bommel R, Forlani D, et al. 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. *The Lancet*. doi: 10.1016/s0140-6736(23)00351-3
17. den Dekker WK, Van Mieghem NM, Bennett J, Sabate M, Esposito G, van Bommel RJ, Daemen J, Vrolix M, Cummins PA, Lenzen MJ, et al. 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.
18. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESCAAHAWHFTFftUDoMI, Katus HA, Lindahl B, Morrow DA, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020-2035.

19. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, López-Sendón J, Faxon DP, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019;381:1411-1421.

20. Vichova T, Motovska Z. Oxidative stress: Predictive marker for coronary artery disease. *Exp Clin Cardiol*. 2013;18:e88-91.

21. Rodrigo R, Libuy M, Feliú F, Hasson D. Oxidative Stress-Related Biomarkers in Essential Hypertension and Ischemia-Reperfusion Myocardial Damage. *Disease Markers*. 2013;35:974358. doi: 10.1155/2013/974358

22. Natalia P-E, Shamir RM, Jia W, Shahar L, Erick S, Warren JC, Kevin RB, Robert CW, Saleem K, Roxana M, et al. Nonculprit Lesion Plaque Morphology in Patients With ST-Segment–Elevation Myocardial Infarction. *Circulation: Cardiovascular Interventions*. 2020;13:e008768. doi: doi:10.1161/CIRCINTERVENTIONS.119.008768

23. Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, Ijsselmuiden AJJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT–FFR trial. *European Heart Journal*. 2021;42:4671-4679. doi: 10.1093/eurheartj/ehab433

24. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, et al. A Prospective Natural-History Study of Coronary Atherosclerosis. *New England Journal of Medicine*. 2011;364:226-235. doi: 10.1056/NEJMoa1002358

25. Balbi MM, Scarparo P, Tovar MN, Masdjedi K, Daemen J, Den Dekker W, Ligthart J, Witberg K, Cummins P, Wilschut J, et al. Culprit Lesion Detection in Patients Presenting With Non-ST Elevation Acute Coronary Syndrome and Multivessel Disease. *Cardiovascular Revascularization Medicine*. 2022;35:110-118. doi: https://doi.org/10.1016/j.carrev.2021.03.019

26. John FH, Annamalai S, Harrison JK, Igor K, Michael HS, Alexandr I, Carine H, Lowie Van A, James W, Jeffrey W, et al. Identifying the Infarct-Related Artery in Patients With Non–ST-Segment–Elevation Myocardial Infarction. *Circulation: Cardiovascular Interventions*. 2019;12:e007305. doi: doi:10.1161/CIRCINTERVENTIONS.118.007305

27. Di Gioia G, Toth G, Rusinaru D, Pellicano M, Wijns W, De Bruyne B, Barbato E. Acute coronary syndromes in patients with multivessel disease: the key role of optical coherence tomography. *Journal of Cardiovascular Medicine*. 2016;17.

28. Henriques JP, Claessen BE. A SMILE and a Frown: One-Stage or Multistage PCI in NSTEMI Patients With Multivessel Disease. *J Am Coll Cardiol*. 2016;67:273-274.

29. Toyota T, Morimoto T, Shiomi H, Yamaji K, Ando K, Ono K, Shizuta S, Saito N, Kato T, Kaji S, et al. Single-session versus staged procedures for elective multivessel percutaneous coronary intervention. *Heart*. 2018;104:936-944.

30. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. 2020;141:e139-e596.

Tables and Figures

Table 1. Baseline Characteristics.

Characteristics	Immediate Complete Revascularization (N=459)	Staged Complete Revascularization (N=458)	P Value
Age, years	67.0 (58.1–74.3)	66.8 (59.3–73.9)	0.62
Male sex	350 (76.3%)	355 (77.5%)	0.65
BMI	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%)	

Data are presented as median (Q1, Q3), n (%), or n/N (%).. BMI indicates body-mass index; COPD, chronic obstructive coronary disease; CVD, cardiovascular disease; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina

Table 2. Procedural Characteristics

Characteristics	Immediate Complete Revascularization (N=459)	Staged Complete Revascularization (N=458)	P Value
Systolic blood pressure, mmHg	127 (111–140)	126 (110–140)	0.67
Diastolic blood pressure, mmHg	71 (63–80)	70 (62–80)	0.11
Radial access	448/458 (97.8%)	440/458 (96.1%)	0.12
Location of culprit lesion*			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%)	
No. of vessels with significant non-culprit lesions†			0.11
1	367/431 (85.2%)	343/423 (81.1%)	
≥2	64/431 (14.8%)	80/423 (18.9%)	
Lesion complexity§			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%)	
Complete revascularization¶	448/459 (97.6%)	435/457 (95.2%)	0.0496
FFR/iFR	77 (16.8%)	122 (26.6%)	<0.001
IVUS/OCT	22 (4.8%)	69 (15.1%)	<0.001
Total hospital stay, days	3 (2–5)	4 (3–6)	<0.001
Time to staged procedure, days	NA	15 (4–28)	
No. of stents used per patient			
Index procedure	3 (2–3.5)	1 (1–2)	<0.001
Index + staged procedure	3 (2–3.5)	3 (2–4)	0.059
Length of stents, mm			
Index procedure	57.5 (41–82)	30 (18–44)	<0.001
Index + staged procedure	57.5 (41–82)	66 (44–90)	0.025
Index procedure duration, minutes	68 (48.5–85)	50 (36–85)	<0.001
Index + staged procedure duration, minutes	68 (48.5–85)	91 (65–122)	<0.001
Index procedure contrast use, mL	206.5 (154.5–270)	144.5 (101–190)	<0.001
Index + staged procedure contrast use, mL	206.5 (154.5–270)	250 (196–330)	<0.001
Index procedure total area dose, $cGycm^2$	4731 (2476–12495)	3087 (1561–6622)	<0.001
Index + staged procedure total area dose, $cGycm^2$	4731 (2476–12495)	6271 (3577–16703)	0.001
P2Y12 inhibitor at discharge‡			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%)	

Data are median (Q1,Q3), n (%), or n/N (%). NA=not applicable. *In seven patients the culprit was unclear and one patient was randomized but had no coronary artery disease. †In total, 63 patients had no significant multivessel disease when physiological assessment was performed after randomization. §The total number of vessels with significant lesions (with vessel diameter ≥ 2.5 mm) was 1933. The lesion complexity was not reported for 104 lesions (5.4%). ¶A patient was considered completely revascularized if all significant lesions with vessel diameter ≥ 2.5 mm were treated and showed a final Thrombolysis in Myocardial Infarction grade 3. One patient withdrew consent before the staged procedure, therefore completeness of revascularization could not be ascertained. ‡One

patient died before discharge so no medications were prescribed; one patient was discharged with single antiplatelet therapy and anticoagulation (aspirin and warfarin); and one patient did not have coronary artery disease and was not treated with antiplatelet therapy.

Table 3. Primary and Secondary Outcomes at 30 Days.

Outcome	Immediate Complete Revascularization (N=459)		Staged Complete Revascularization (N=458)		Hazard Ratio (95% CI)	Risk difference (95% CI) ‡	P Value
	No. events	Percentage †	No. events	Percentage †			
Primary outcome							
All-cause mortality, any myocardial infarction, unplanned ischemia driven revascularization or cerebrovascular event	8	1.8%	26	5.7%	0.30 (0.13, 0.66)*	4.0% (1.5, 6.4)	0.002
Secondary outcomes							
Cardiovascular mortality or myocardial infarction	2	0.4%	15	3.3%	0.13 (0.03, 0.57)	2.9% (1.1, 4.6)	0.001
All-cause mortality	2	0.4%	2	0.4%	1.00 (0.14, 7.07)	0.0% (-0.9, 0.9)	>0.99
Cardiovascular mortality	1	0.2%	2	0.4%	0.50 (0.05, 5.49)	0.2% (-0.5, 1.0)	0.56
Any myocardial infarction	1	0.2%	14	3.1%	0.07 (0.01, 0.53)	2.9% (1.2, 4.5)	<0.001
Unplanned ischemia driven revascularization	4	0.9%	17	3.7%	0.23 (0.08, 0.68)*	2.9% (0.9, 4.8)	0.004
Cerebrovascular event	2	0.4%	7	1.5%	0.28 (0.06, 1.36)	1.1% (-0.2, 2.4)	0.09
Probable or definite stent thrombosis	2	0.4%	3	0.7%	0.66 (0.11, 3.97)	0.2% (-0.7, 1.2)	0.65
Target vessel revascularization	4	0.9%	17	3.7%	0.23 (0.08, 0.68)*	2.9% (0.9, 4.8)	0.004
Target lesion revascularization	4	0.9%	15	3.3%	0.26 (0.09, 0.79)*	2.4% (0.6, 4.3)	0.010
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 or 5)	6	1.3%	26	5.7%	0.22 (0.09, 0.54)*	4.4% (2.0, 6.8)	<0.001
Major bleeding (BARC 3 or 5)	1	0.2%	5	1.1%	0.20 (0.02, 1.70)	0.9% (-0.2, 1.9)	0.10

BARC=bleeding academic research consortium. * The cox proportional hazard assumption was not met † Cumulative incidence at 365 days according to the Kaplan-Meier method. ‡ Based on the Kaplan-Meier estimates. A difference in favour of immediate complete revascularizati is presented as a positive value. **§** This P value was tested for superiority of the risk difference.

Table 4. Primary and Secondary Outcomes at 1 Year.

Outcome	Immediate Complete Revascularisation (N=459)		Staged Complete Revascularisation (N=458)		Hazard Ratio (95% CI)	Risk difference (95% CI) ‡	P Valu
	No. events	Percentage †	No. events	Percentage †			
Primary outcome							
All-cause mortality, any myocardial infarction, unplanned ischemia driven revascularization or cerebrovascular event	36	7.9%	46	10.1%	0.75 (0.48, 1.16)*	2.2% (-1.5, 6.0)	0.24
Secondary outcomes							
Cardiovascular mortality or myocardial infarction	14	3.1%	26	5.7%	0.52 (0.27, 1.00)*	2.7% (0.0, 5.3%)	0.052
All-cause mortality	7	1.5%	5	1.1%	1.39 (0.44, 4.38)	-0.4% (-1.9, 1.1)	0.57
Cardiovascular mortality	5	1.1%	4	0.9%	1.24 (0.33, 4.62)	-0.2% (-1.5, 1.1)	0.75
Myocardial infarction	9	2.0%	24	5.3%	0.36 (0.17, 0.78)*	3.3% (0.9, 5.7)	0.008
Unplanned ischemia driven revascularization	19	4.2%	35	7.8%	0.52 (0.30, 0.91)*	3.5% (0.4, 6.6)	0.025
Cerebrovascular event	7	1.6%	8	1.8%	0.86 (0.31, 2.38)*	0.2% (-1.5, 1.9)	0.81
Probable or definite stent thrombosis	2	0.4%	5	1.1%	0.40 (0.08, 2.05)	0.7% (-0.5, 1.8)	0.25
Target vessel revascularization	16	3.6%	33	7.3%	0.47 (0.26, 0.85)*	3.8% (0.8, 6.7)	0.013
Target lesion revascularization	13	2.9%	30	6.7%	0.42 (0.22, 0.80)*	3.8% (1.0, 6.6)	0.007
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 or 5)	30	6.6%	40	8.8%	0.72 (0.45, 1.15)*	2.2% (-1.2, 5.7)	0.21
Major bleeding (BARC 3 or 5)	8	1.8%	9	2.0%	0.88 (0.34, 2.28)	0.2% (-1.5, 2.0)	0.79

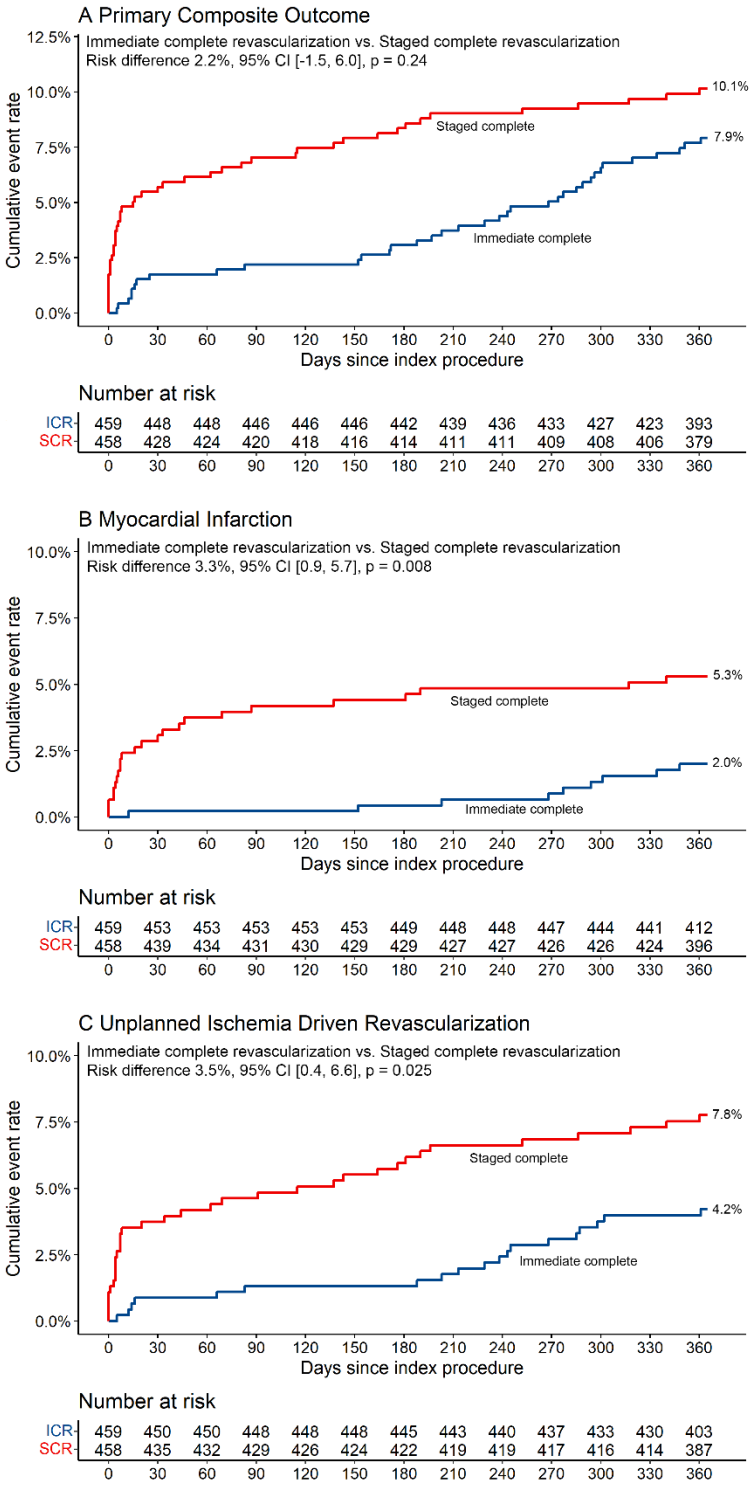
BARC=bleeding academic research consortium. * The cox proportional hazard assumption was not met † Cumulative incidence at 365 days according to the Kaplan-Meier method. ‡ Based on the Kaplan-Meier estimates. A difference in favour of immediate complete revascularization is presented as a positive value. **§** This P value was tested for superiority of the risk difference.

Table 5. Clinical Outcomes Excluding Index and Staged Procedure Related Myocardial Infarctions

Outcome	Immediate Complete Revascularization (N=459)		Staged Complete Revascularization (N=458)		Hazard Ratio (95% CI)	Risk difference (95% CI) ‡	P Value
	No. events	Percentage †	No. events	Percentage †			
All-cause mortality, myocardial infarction, unplanned ischemia driven revascularization or cerebrovascular event	36	7.9%	43	9.5%	0.80 (0.52, 1.25)*	1.6% (-2.1, 5.2)	0.40
Cardiovascular mortality or myocardial infarction	14	3.1%	22	4.9%	0.62 (0.32, 1.21)*	1.8% (-0.8, 4.3)	0.17
Myocardial infarction	9	2.0%	20	4.4%	0.44 (0.20, 0.96)*	2.4% (0.1, 4.7)	0.039
All-cause mortality, myocardial infarction, stroke or major bleeding (BARC 3 and 5)	30	6.6%	37	8.2%	0.78 (0.48, 1.26)	1.6% (-1.8, 5.0)	0.37

BARC=bleeding academic research consortium. * The cox proportional hazard assumption was not met † Cumulative incidence at 365 days according to the Kaplan-Meier method. ‡ Based on the Kaplan-Meier estimates. A difference in favour of immediate complete revascularization is presented as a positive value. § This P value was tested for superiority of the risk difference.

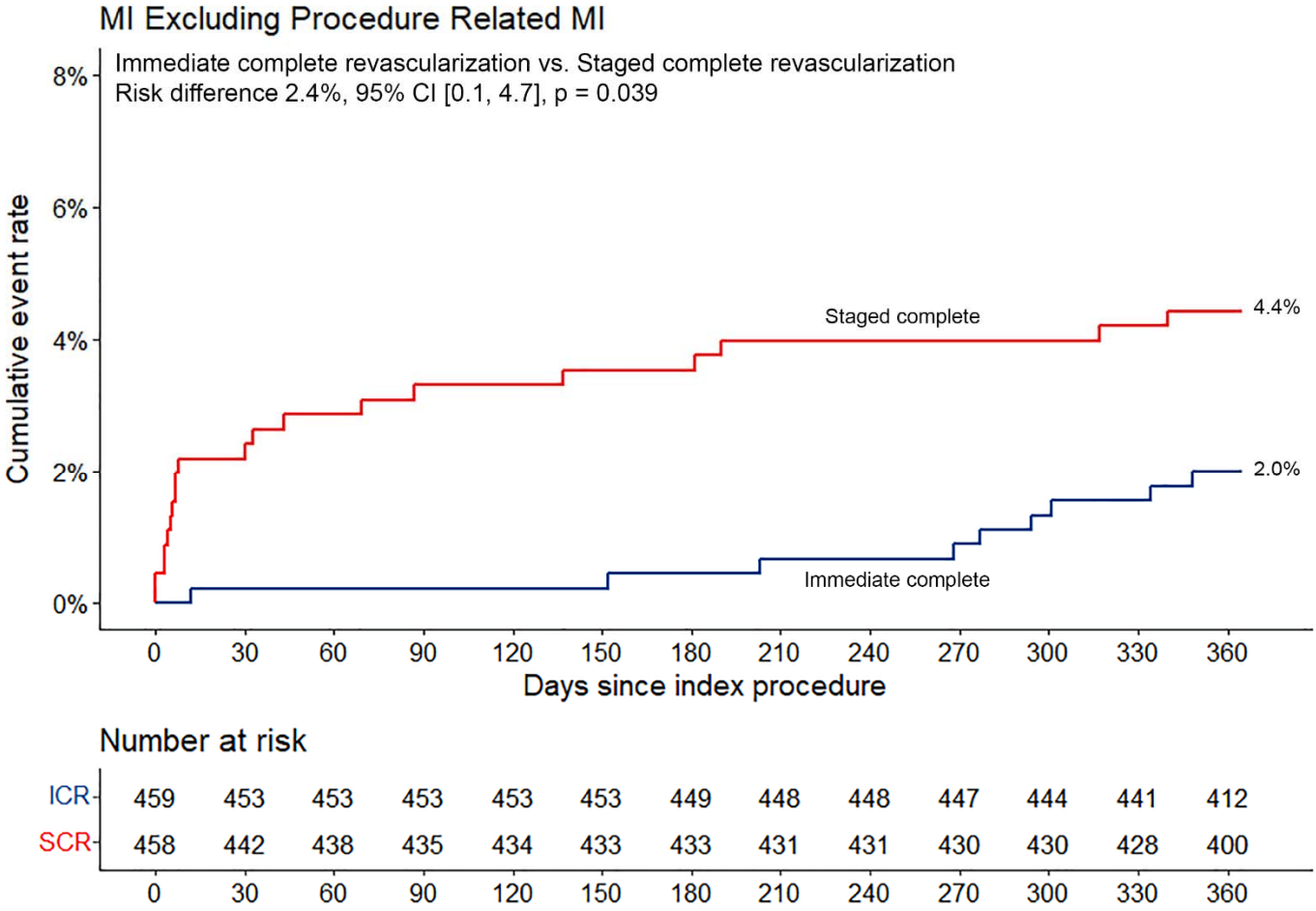
Figure 1. Outcomes



Caption: The primary outcome is a composite of all-cause mortality, myocardial infarction, unplanned ischemia driven revascularization and cerebrovascular events. A difference in favour

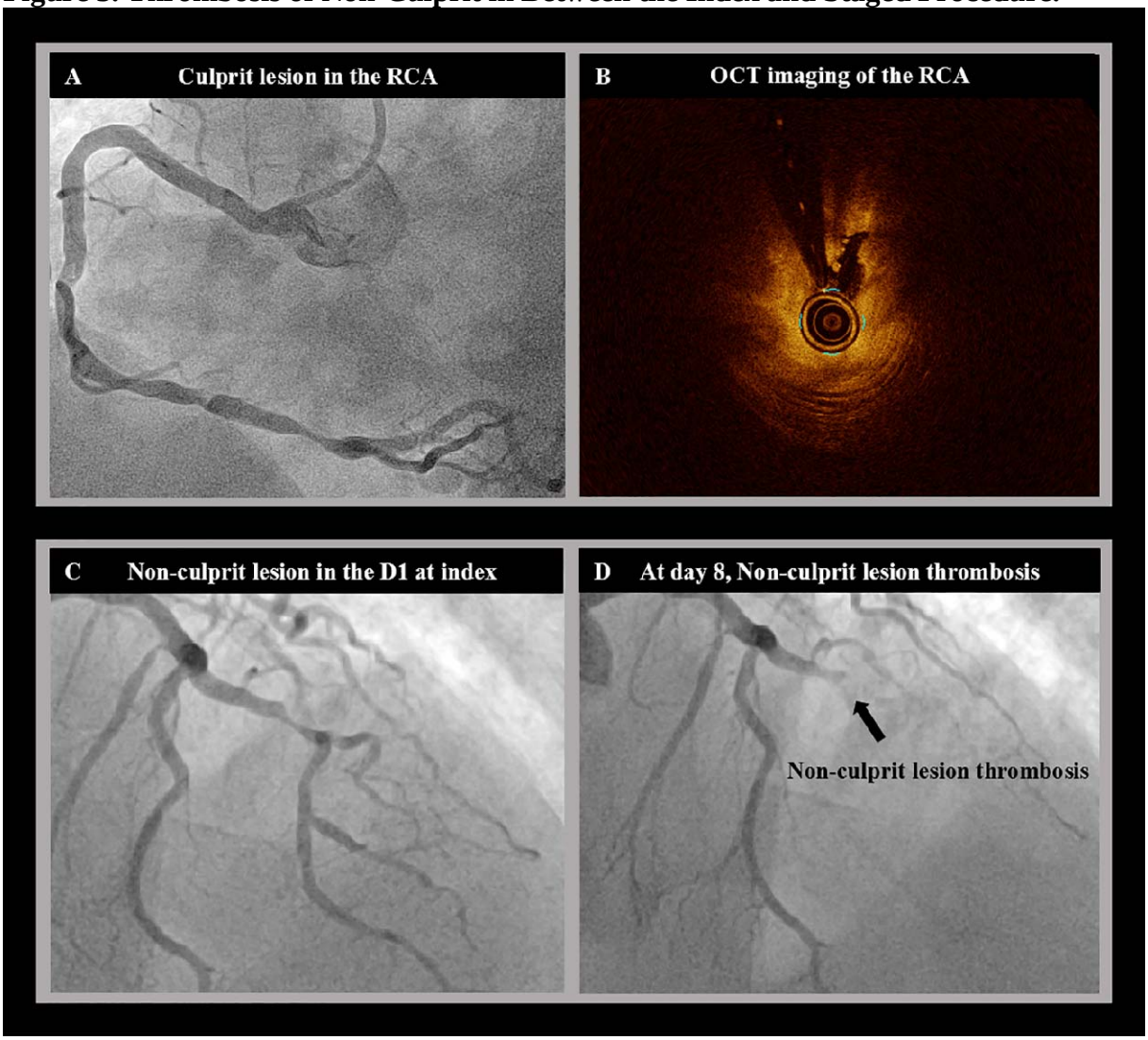
of immediate complete revascularization is presented as a positive value. ICR indicates immediate complete revascularization; SCR, staged complete revascularization.

Figure 2. Myocardial Infarction Excluding Procedure Related Myocardial Infarctions



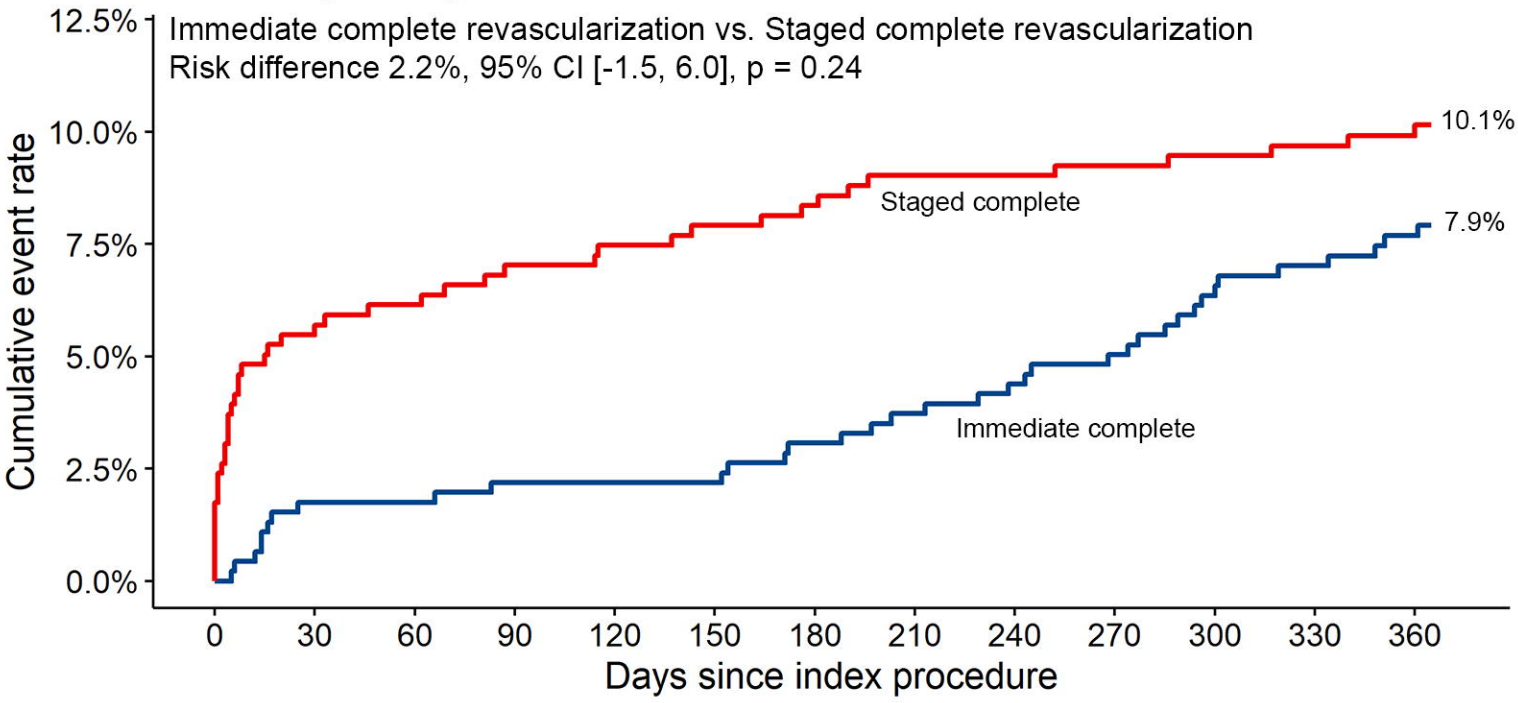
Caption: Type 4a myocardial infarctions related to the index and staged procedure were excluded from the analysis. A difference in favour of immediate complete revascularization is presented as a positive value. ICR indicates immediate complete revascularization; SCR, staged complete revascularization.

Figure 3. Thrombosis of Non-Culprit in Between the Index and Staged Procedure.



Caption: A patient in their 70s presented with a NSTEMI. Coronary angiogram revealed subtotal lesions in the RCA (panel A), a significant lesion in the diagonal branch (panel C) and in-stent restenosis of the LCX. After intravascular imaging the lesion in the RCA was identified as the culprit lesion (panel B).
The patient was randomized to staged complete revascularization. The RCA was treated successfully and non-culprit lesion treatment was planned after 14 days.
At day 8 post index PCI, the patient presented at the emergency due to chest pain. New coronary angiography showed that the significant non-culprit lesion in the diagonal had evolved into a thrombotic occlusion (panel D).
D1 indicates first diagonal; LCX, left circumflex artery; NSTEMI, non-ST-elevation myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RCA, right coronary artery.

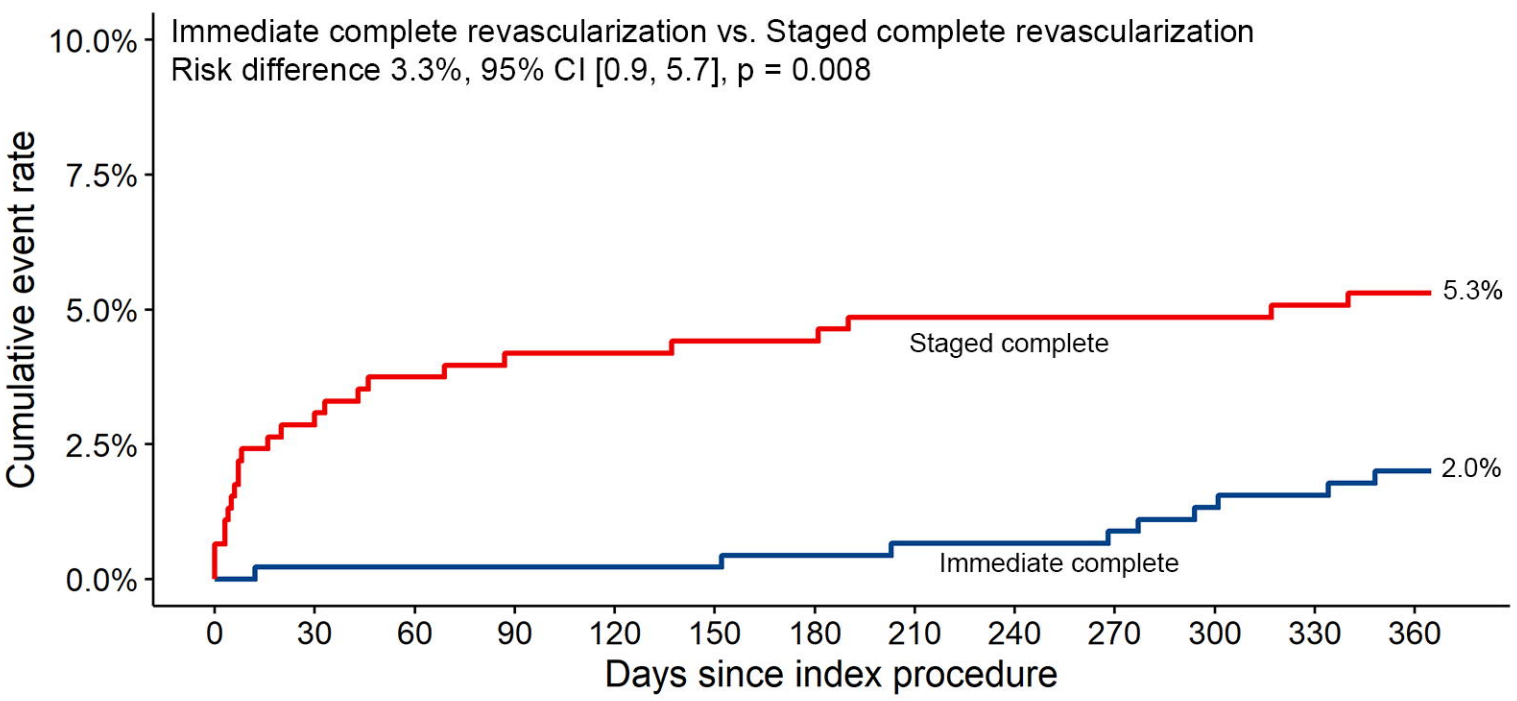
A Primary Composite Outcome



Number at risk

	0	30	60	90	120	150	180	210	240	270	300	330	360
ICR	459	448	448	446	446	446	442	439	436	433	427	423	393
SCR	458	428	424	420	418	416	414	411	411	409	408	406	379

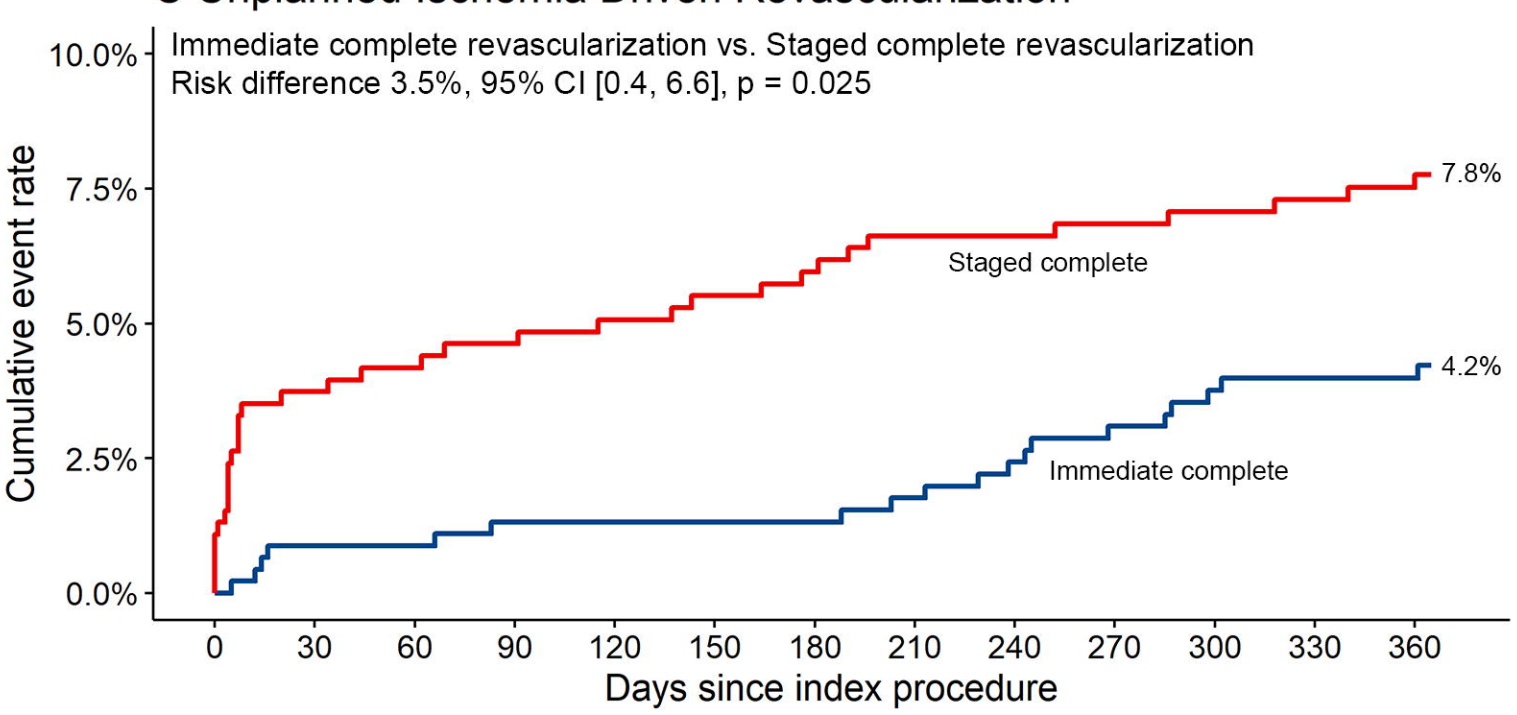
B Myocardial Infarction



Number at risk

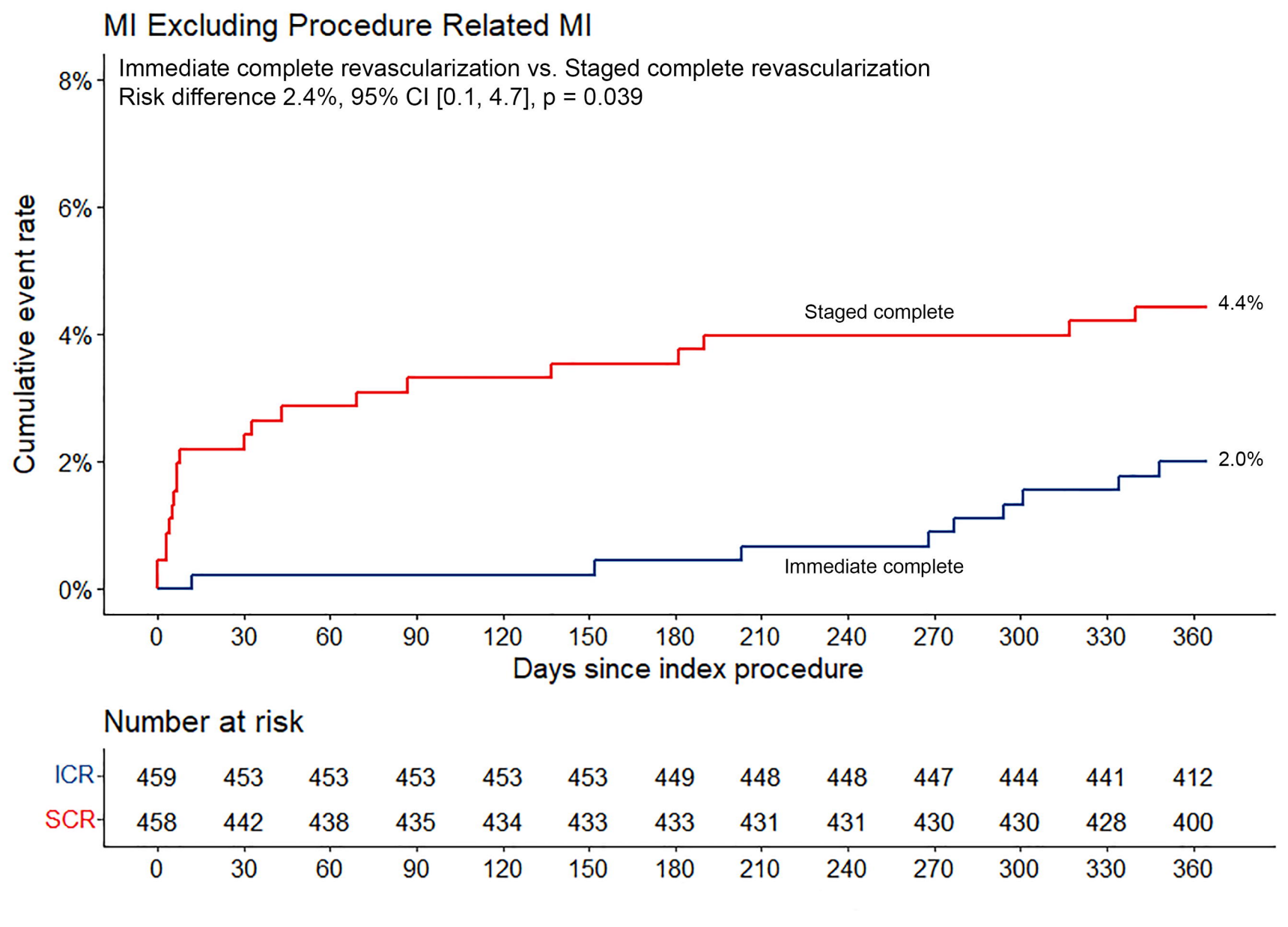
	0	30	60	90	120	150	180	210	240	270	300	330	360
ICR	459	453	453	453	453	453	449	448	448	447	444	441	412
SCR	458	439	434	431	430	429	429	427	427	426	426	424	396

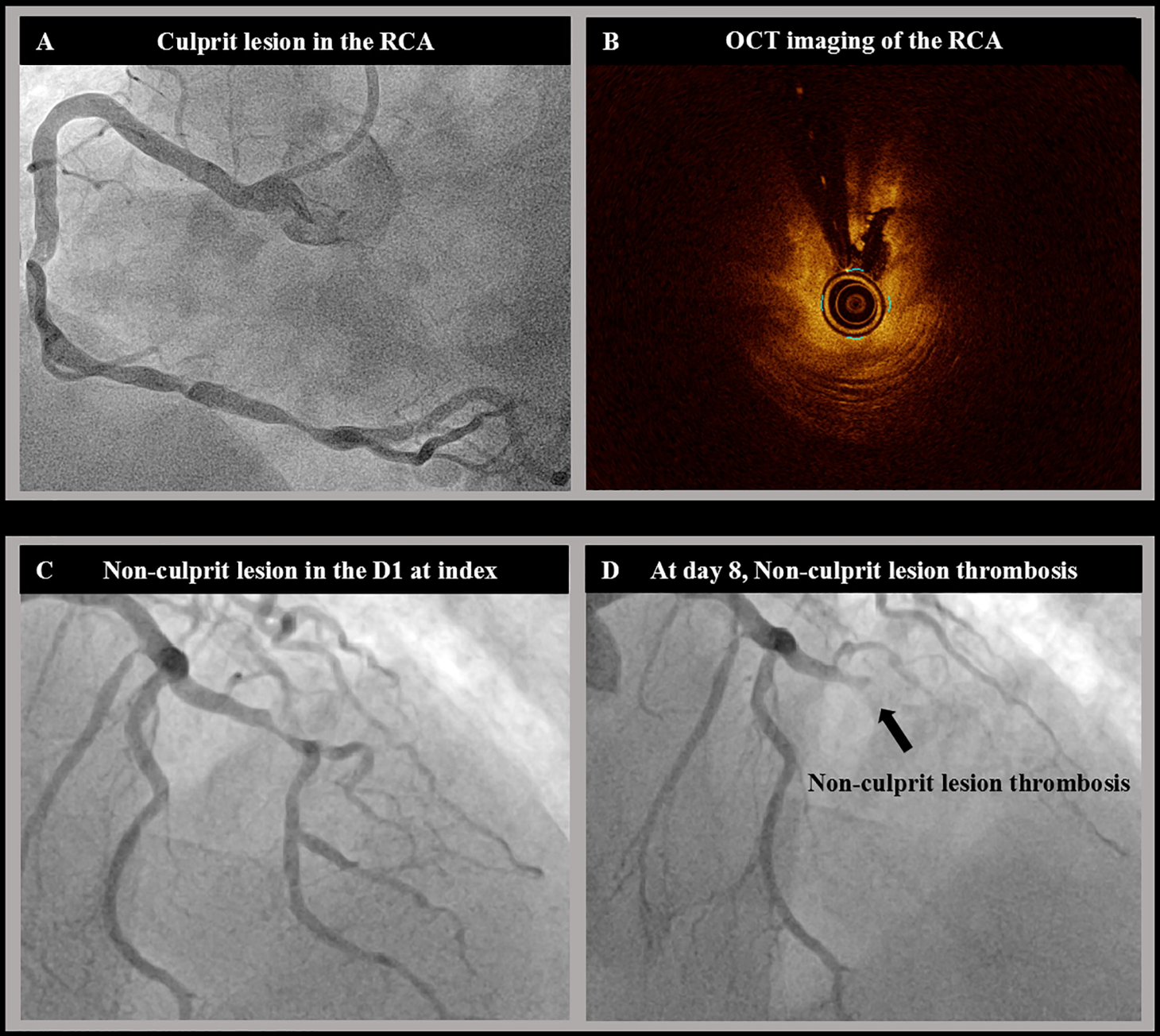
C Unplanned Ischemia Driven Revascularization



Number at risk

	0	30	60	90	120	150	180	210	240	270	300	330	360
ICR	459	450	450	448	448	448	445	443	440	437	433	430	403
SCR	458	435	432	429	426	424	422	419	419	417	416	414	387


MI Excluding Procedure Related MI
Immediate complete revascularization vs. Staged complete revascularization
Risk difference 2.4%, 95% CI [0.1, 4.7], p = 0.039
Cumulative event rate
8%
6%
4%
2%
0%
Staged complete
4.4%
Immediate complete
2.0%
0
30
60
90
120
150
180
210
240
270
300
330
360
Days since index procedure
Number at risk
ICR 459 453 453 453 453 453 449 448 448 447 444 441 412
SCR 458 442 438 435 434 433 433 431 431 430 430 428 400
0
30
60
90
120
150
180
210
240
270
300
330
360


A
Culprit lesion in the RCA
B
OCT imaging of the RCA
C
Non-culprit lesion in the D1 at index
D
At day 8, Non-culprit lesion thrombosis
Non-culprit lesion thrombosis