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ORIGINAL RESEARCH

Effect of Timing of Staged Percutaneous Coronary Intervention on Clinical Outcomes in Patients With Acute Coronary Syndromes

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BACKGROUND: Complete revascularization reduces cardiovascular events in patients with acute coronary syndromes (ACSs) and multivessel disease. The optimal time point of non–target-vessel percutaneous coronary intervention (PCI) remains a matter of debate. The aim of this study was to investigate the impact of early (<4 weeks) versus late (≥4 weeks) staged PCI of non–target-vessels in patients with ACS scheduled for staged PCI after hospital discharge.

METHODS AND RESULTS: All patients with ACS undergoing planned staged PCI from 2009 to 2017 at Bern University Hospital, Switzerland, were analyzed. Patients with cardiogenic shock, in-hospital staged PCI, staged cardiac surgery, and multiple staged PCIs were excluded. The primary end point was all-cause death, recurrent myocardial infarction and urgent premature non–target-vessel PCI. Of 8657 patients with ACS, staged revascularization was planned in 1764 patients, of whom 1432 patients fulfilled the eligibility criteria. At 1 year, there were no significant differences in the crude or adjusted rates of the primary end point (7.8% early versus 10.8% late, hazard ratio [HR], 0.72 [95% CI, 0.47–1.10], *P*=0.129; adjusted HR, 0.80 [95% CI, 0.50–1.28], *P*=0.346) and its individual components (all-cause death: 1.5% versus 2.9%, HR, 0.52 [95% CI, 0.20–1.33], *P*=0.170; adjusted HR, 0.62 [95% CI, 0.23–1.67], *P*=0.343; recurrent myocardial infarction: 4.2% versus 4.4%, HR, 0.97 [95% CI, 0.475–1.10], *P*=0.924; adjusted HR, 1.03 [95% CI, 0.53–2.01], *P*=0.935; non–target-vessel PCI, 3.9% versus 5.7%, HR, 0.97 [95% CI, 0.53–1.80], *P*=0.928; adjusted HR, 1.19 [95% CI, 0.61–2.34], *P*=0.609).

CONCLUSIONS: In this single-center cohort study of patients with ACS scheduled to undergo staged PCI after hospital discharge, early (<4 weeks) versus late (≥4 weeks) staged PCI was associated with a similar rate of major adverse cardiac events at 1 year follow-up.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02241291.

Key Words: acute coronary syndrome ■ multivessel coronary artery disease ■ staged percutaneous coronary intervention

Multivessel disease (MVD) among patients with acute coronary syndromes (ACSs) is associated with impaired prognosis.[1,2] The existing evidence on both patients with ST-segment–elevation myocardial infarction (STEMI)[3–7] and patients with non–ST-segment–elevation ACS (NSTE-ACS)[8,9] shows more favorable results with complete compared with culprit-lesion–only revascularization. Therefore, the European Society of Cardiology guidelines[10,11] recommend complete revascularization in patients with ACS and MVD.

However, the optimal time point of nonculprit-lesion revascularization remains a matter of ongoing

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CLINICAL PERSPECTIVE

What Is New?

- Among an all-comers acute coronary syndrome population scheduled for staged percutaneous coronary intervention after hospital discharge, similar major adverse cardiac event rates at 1-year follow-up were observed between patients scheduled early (<4 weeks) versus late (≥4 weeks) after index percutaneous coronary intervention.

What Are the Clinical Implications?

- The current study implies, that, if in the judgment of the operator, nonculprit-lesion percutaneous coronary intervention can be deferred until after hospital discharge, it may be safe and effective to perform it early (within <4 weeks) or late (≥4 weeks) from index percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
MVD	multivessel disease
NSTE-ACS	non–ST-segment–elevation acute coronary syndrome

debate.[10,11] In the randomized controlled trials (RCTs) comparing complete versus culprit-lesion–only percutaneous coronary intervention (PCI) among patients with STEMI, nonculprit-lesion revascularization was performed either during the index procedure or before hospital discharge,[3–6] translating to a class IIaA recommendation of these strategies in current European Society of Cardiology guidelines.[10] Among patients with NSTE-ACS, the European Society of Cardiology guidelines provide a class IIbB recommendation for immediate complete revascularization[11] based on 1 RCT showing superior outcomes with immediate complete versus staged in-hospital PCI.[12] However, more emphasis (class IB recommendation) is given to individual patient characteristics to select the appropriate time point of nonculprit-lesion revascularization (ie, clinical presentation, comorbidities, complexity of coronary anatomy, functional significance of all stenoses, ventricular function, revascularization modality, and patient preference).[11]

To date, there are no RCTs comparing different time intervals of staged PCI among patients with ACS. The best available evidence can be derived from the COMPLETE (Complete Versus Culprit-Only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial[7]. In the complete revascularization arm of this large scale RCT, staged PCI had to be performed either during the index hospitalization or after hospital discharge up to 45 days after index PCI.[7] In a pivotal subanalysis,[13] the benefit of complete revascularization over culprit-lesion–only PCI was maintained (ie, no interaction between the time point of staged PCI and primary or key secondary outcomes), regardless of whether staged PCI was performed during index hospitalization (after median 1 day; interquartile range [IQR], 1–3 days) or staged after hospital discharge (after median 23 days; IQR, 12.5–33.5 days). Further data are limited to small observational studies with inconclusive results, and the evidence, especially on staged PCIs scheduled after hospital discharge, is scarce.[14–17]

Therefore, we aimed to investigate the optimal time point of staged PCI after hospital discharge by comparing early (<4 weeks after index PCI) versus late staged PCI (≥4 weeks after index PCI) in patients with ACS and MVD within the large, prospective Cardiobase Bern PCI registry.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population

The Cardiobase Bern PCI registry (NCT02241291) is a prospective, single-center, observational registry of all patients undergoing PCI at Bern University Hospital, Switzerland, established in 2009. There are no exclusion criteria other than age <18 years and inability or unwillingness to provide written informed consent. Baseline, procedural and clinical outcomes are assessed at hospital discharge and 1 year after PCI by an independent clinical events committee. The registry complies with the Declaration of Helsinki and is approved by the institutional ethics committee.

For the purpose of the present study (Figure 1), all patients with ACS included in the Cardiobase Bern PCI registry scheduled to undergo staged PCI within 6 months after index PCI between 2009 and 2017 were analyzed. Whether staged PCI was planned, and if yes, at which time point after index PCI, was derived from the PCI report or discharge letter of the index event. Patients with cardiogenic shock were excluded, as they represent a distinct patient population and the results of the CULPRIT SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial[18] changed guidelines[10,11] and clinical practice. Patients undergoing planned in-hospital PCI were also

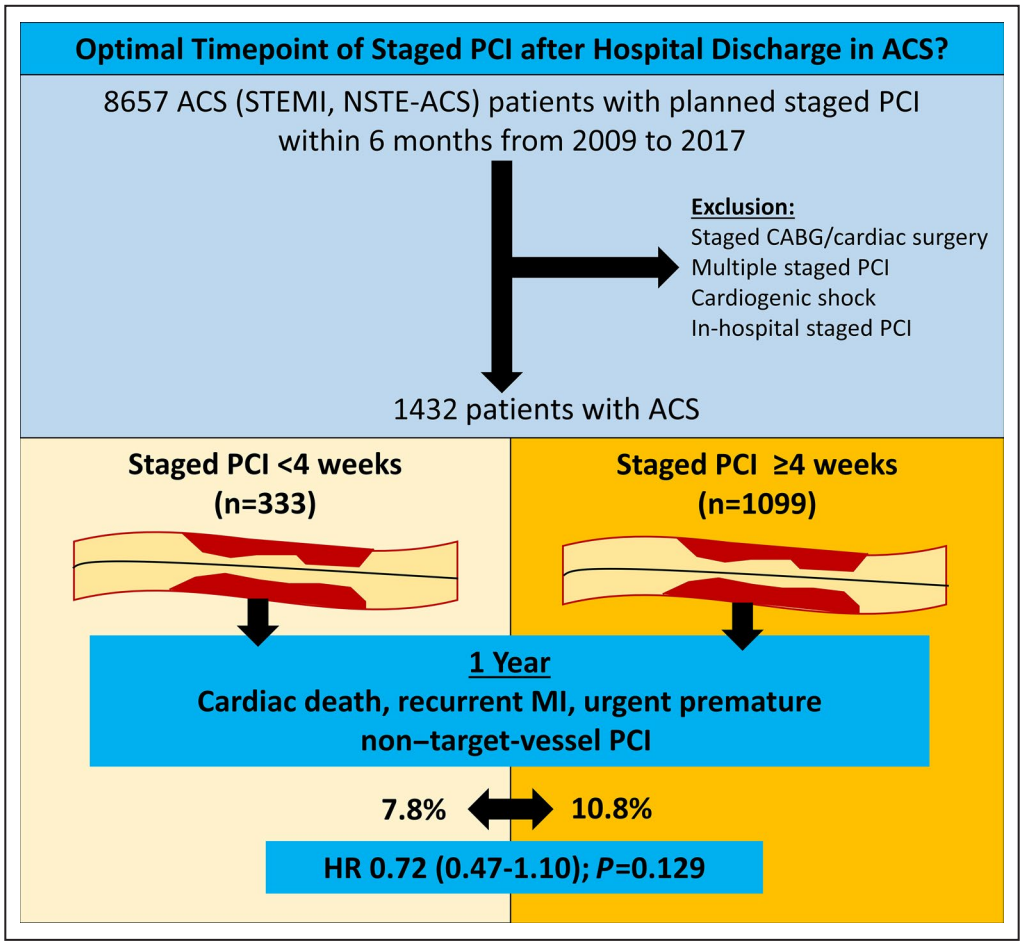

Figure 1. Study design.
ACS indicates acute coronary syndrome, CABG, coronary artery bypass grafting, HR, hazard ratio, MI, myocardial infarction, NSTE-ACS, non–ST-segment–elevation acute coronary syndrome, PCI, percutaneous coronary intervention, and STEMI, ST-segment–elevation myocardial infarction.

excluded from the analysis, as they usually represent a cohort of patients with either severe underlying coronary anatomy requiring urgent intervention or patients who are not willing to return for staged PCI procedures (ie, advanced age or living far away). Finally, patients undergoing staged cardiac surgery or multiple staged PCIs and patients with no information on staged PCI (ie, time point, vessel) were also excluded from the analysis.

Treatment

PCI was performed according to the recommendations and guidelines[10,11,19,20] valid at the time of presentation. Briefly, unfractionated heparin (initial bolus of 100 IU per kg body weight) was administered during the procedure. Dual antiplatelet therapy (DAPT) consisting of acetylsalicylic acid and a potent P2Y12 inhibitor was initiated before or immediately after the procedure. The recommended DAPT duration was usually 12 months but was modified among patients taking oral anticoagulants. Drug-eluting stents were routinely used. In patients with NSTE-ACS, the culprit lesion was identified according to operators' judgment based on angiographic characteristics (ie, intraluminal filling defects consistent with thrombus, plaque ulceration, plaque irregularity), ECG changes, and echocardiography (if performed).[11,19] For the purpose of this study, all angiographies of all patients with NSTE-ACS were reviewed for culprit-lesion identification by experienced operators from the Corelab (Bern, Switzerland), applying the same criteria as mentioned above.

Timing of Staged PCI

Timing of staged PCI was at the discretion of the operator and defined in the PCI report or hospital discharge letter. Generally, staged procedures were recommended to be performed between 2 and 8 weeks following index PCI by internal guidelines, but the exact timing was left to the operators' discretion. It cannot be excluded, that patient- or lesion-related factors may

have played a role in the scheduling. In the absence of the results of RCTs, we set the comparator groups at a threshold of 4 weeks after index PCI; that is, we aimed to compare clinical outcomes in patients who underwent early staged PCI (within <4 weeks) with patients who underwent late staged PCI (≥4 weeks after index PCI). This time point is supported by a propensity-matched study of patients with STEMI, which reported a reduction in major adverse cardiac events in patients undergoing staged PCI within 1 month as compared with patients undergoing staged PCI after 1 month of the index PCI procedure.[17] Furthermore, we planned to search for another deflection point by considering time from index to planned staged PCI as continuous variable.

Patient Follow-up

Patients were systematically and prospectively followed throughout 1 year to assess death, recurrent myocardial infarction (MI), stroke, repeat revascularization, definite or probable stent thrombosis, and status of medical treatment. A health questionnaire was sent to all living patients with questions on rehospitalization and adverse events, followed by telephone contact in case of missing response. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. For patients who underwent treatment for adverse events at other medical institutions, external medical records, discharge letters, and coronary angiography documentation were systematically collected and reviewed.

Clinical End Points

A clinical event committee consisting of 2 cardiologists (and a third one in case of disagreement) adjudicated all events with use of original source documents.

The primary end point was a composite of all-cause death, recurrent MI, and urgent premature non–target-vessel PCI. Secondary end points were all-cause death, cardiac death, MI, target-vessel MI, non–target-vessel MI, any revascularization, urgent premature non–target-vessel PCI, target-lesion revascularization, definite stent thrombosis, and stroke.

Clinical End Point Definitions

Cardiac death was defined as any death attributable to an immediate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), procedure-related death, or death of unknown cause. Recurrent MI was defined according to a modified historical definition.[21] All MI end points include spontaneous MIs and periprocedural MIs (ie, within 48 hours of the procedure). Target-vessel MI was defined as MI attributed to the culprit vessel intervened at baseline, and non–target-vessel MI was defined as MI attributed to nonculprit vessels at baseline. Urgent premature non–target vessel PCI was defined as urgent PCI in non–target vessels performed earlier than planned because of ≥1 of the following: (1) recurrent MI,[21] (2) unstable angina,[11] (3) worsening congestive heart failure, (4) cardiogenic shock, or (5) symptomatic arrhythmia refractory to medication. This event had to be clearly distinguishable from the staged PCI procedure scheduled at index presentation. Any revascularization was defined as any percutaneous revascularization procedure. Target-lesion revascularization was defined as any clinically indicated revascularization for a stenosis >50% within the stent or the 5-mm borders adjacent to the stent. Stent thrombosis was classified according to the Academic Research Consortium criteria.[22] Stroke was defined as rapid development of clinical signs of focal or global disturbance of cerebral function lasting >24 hours with imaging evidence of an acute, clinically relevant brain lesion.

Statistical Analysis

Continuous variables are expressed as mean±SD, and categorical variables are expressed as counts with percentages. Baseline, procedural, and medication variables were compared between early staged PCI and late staged PCI using Student's *t* tests, chi-square tests, or Fischer's exact tests, as appropriate. For all clinical end points, hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazard models by comparing early versus late planned staged PCI. Patients were censored at the time of an event or end of the planned follow-up at 1 year, whichever occurred first. For the secondary end point urgent premature non–target-vessel PCI, patients were censored at the time of an urgent premature non–target-vessel-PCI or at the time of the planned staged PCI, whichever occurred first. Unadjusted and adjusted clinical outcome analysis was performed. Adjusting covariates were year of enrollment, age (>60 versus ≤60 years), sex, Killip III (Killip IV were excluded), STEMI, left ventricular ejection fraction (≥45% versus <45%), diabetes, and renal failure (ie, glomerular filtration rate <60 mL/min) based on clinical reasoning. The primary end point was also assessed in the following subgroups: STEMI, sex, age (>60 versus ≤60 years), left ventricular ejection fraction (≥45% versus <45%), and diabetes.

The end point urgent premature non–target-vessel PCI was unconventional because time at risk differed between the early and the late staged PCI groups (time at risk=number of days between index PCI and date of planned staged PCI). By definition, an urgent premature non–target-vessel PCI could occur up to 6 months after index PCI in the late staged PCI group, but it could only occur up to 4 weeks after the index PCI in the early staged PCI group. Consequently, the

time-to-event analysis of the composite primary end point was unusual because, for 1 of the 3 components, hazard rates cannot be compared between groups beyond 4 weeks of follow-up. Therefore, as a sensitivity analysis, we also calculated estimates of the risk ratio (RR) for (1) the primary end point across the entire follow-up period, (2) urgent premature non–target-vessel PCI across the entire follow-up period, and (3) urgent premature non–target-vessel PCI across the period ranging from baseline to 4 weeks, such that time at risk was the same in both groups. We used generalized linear models to provide unadjusted and adjusted RRs.

We subsequently performed univariable Cox proportional hazard analysis to test for an association between the primary end point and the variables age >60 years, sex, diabetes, hypertension, smoker, Killip III, renal failure, STEMI, culprit vessel of ACS, left ventricular ejection fraction, stent type (drug-eluting stent versus bare metal stent), previous MI, and early staged PCI (<4 weeks), based on previous studies[14–16] and clinical reasoning. For the multivariable Cox proportional hazards model, a backward selection procedure excluding variables with a *P* value >0.2 was performed.

In addition to the main comparison (ie, <4 versus ≥4 weeks), we ran a restricted cubic splines logistic regression model to plot the probability of the occurrence of the primary end point over time as a continuous variable.

Significance tests were 2-tailed with a significance level set to 0.05. All analyses were performed using Stata 16 (StataCorp, College Station, TX).

RESULTS

Patient Population

Between January 2009 and December 2017, 8657 patients with ACS (STEMI and NSTE-ACS) were consecutively enrolled into the Cardiobase Bern PCI registry. Staged PCI was scheduled in 1764 patients, of whom 1432 patients fulfilled the eligibility criteria and were included in the final analysis. Patients with cardiogenic shock (n=70), early in-hospital staged PCI (n=139), staged coronary artery bypass grafting (n=70), staged cardiac surgery other than coronary artery bypass grafting (n=16), multiple staged PCI (n=45), and patients with no information on staged PCI (ie, scheduled time point, vessel) (n=62) were excluded (Figure 2).

Baseline Characteristics

Baseline clinical characteristics (Table 1), procedural characteristics (Table 2), and medical treatment were well balanced between groups (Table 3, Tables S1 and S2). In NSTE-ACS patients, a culprit lesion was identified in 83.3% (524/629) of patients by the operators performing the index PCI. Among the lesions treated during index PCI, in 99.8% (628/629) of NSTE-ACS patients a presumed culprit lesion was identified by Corelab analysts. Procedural characteristics of culprit-lesion and nonculprit-lesion treatment (according to Corelab adjudication) during index PCI are shown in Table 2.

Intracoronary imaging (ie, intravascular ultrasound or optical coherence tomography) was used for PCI guidance in 0% to 2.4% of patients, depending on the year of enrollment.

Scheduled Time Point of Staged PCI

The time point of staged PCIs ranged from 5 to 180 (median, 28; IQR, 28–42) days after the index PCI with similar distribution among patients with STEMI and patients with NSTE-ACS. In 23.3% (n=333) of patients, staged PCI was planned early (<4 weeks [within 27 days]) and in 76.7% (n=1099) of patients late (≥4 weeks [≥28 days]) after the index PCI (Figure 3). There was a gradual shortening of time to staged PCI over the entire study period from 60 median (IQR, 28–90) days among patients enrolled in 2009 to 28 median (IQR, 21–28) days among patients enrolled in 2017 (Figure S1). To account for these changes, outcome analyses were adjusted for year of enrollment.

Clinical Outcomes

Clinical outcomes throughout 1 year are summarized in Table 4. The primary end point all-cause death, recurrent MI, or urgent premature non–target-vessel PCI occurred in 7.8% in the early versus 10.8% in the late staged PCI group (HR, 0.72 [95% CI, 0.47–1.10]; *P*=0.129) (Figure 4). There were no significant differences in the rates of any of the component of the primary end point (Table 4, Figure 4) or in the rates of other secondary end points (Table 4). The incidence risk of the primary end point also did not differ between late versus early staged PCI groups (unadjusted RR, 0.72 [95% CI, 0.48–1.08], *P*=0.115; adjusted RR, 0.78 [95% CI, 0.50–1.22], *P*=0.285) (Table S3).

Adjusted analyses for year of enrollment, age, sex, left ventricular ejection fraction, Killip III, STEMI, diabetes, and renal failure provided similar results (Table 4 and Table S4).

Results were consistent analyzing patients with STEMI or NSTE-ACS, separately, except for crude rates of non–target vessel MI among patients with NSTE-ACS, which occurred significantly more frequently in the early staged PCI group as compared with the late staged PCI group (3.7% early versus 1.1% late; HR, 3.53 [95% CI, 1.08–11.55], *P*=0.037). However, this difference was no longer present after adjustment for the covariates mentioned above (Table S5).

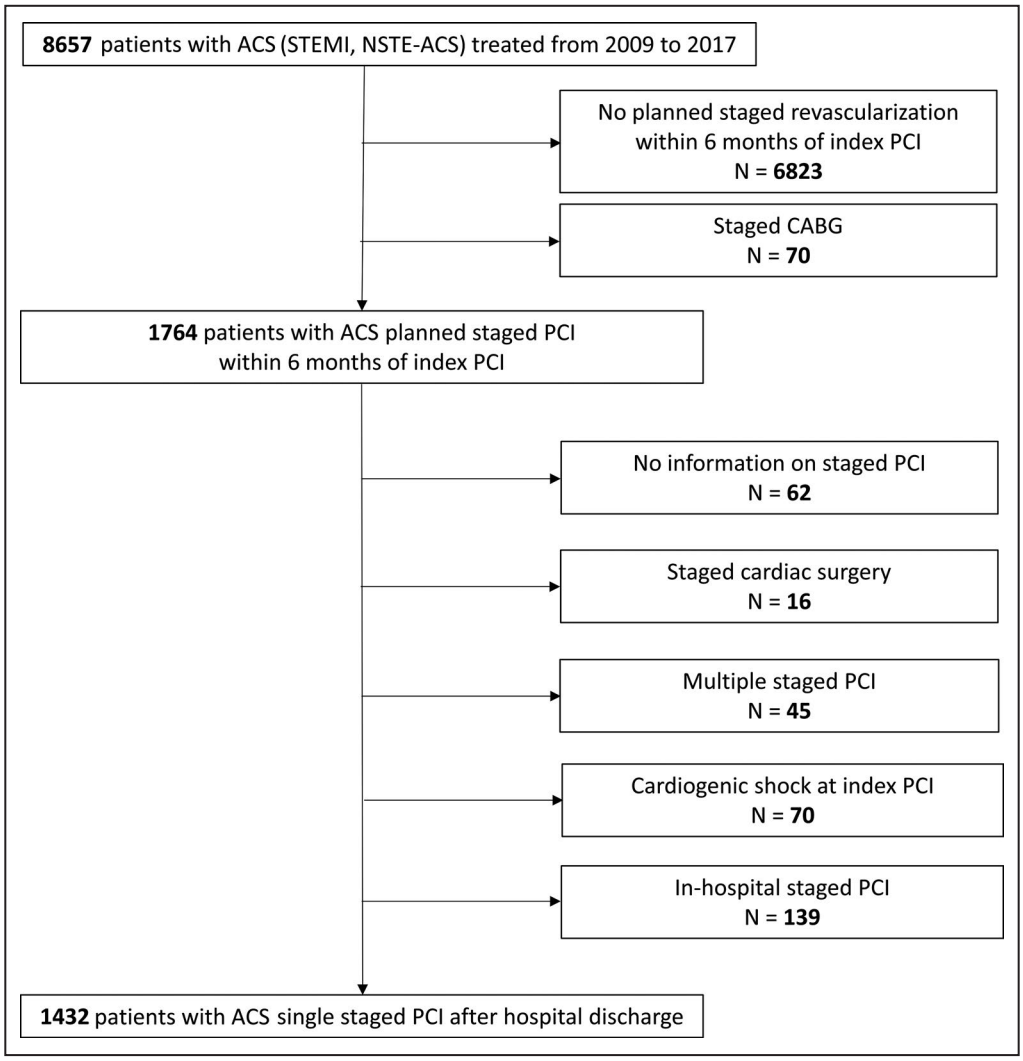

Figure 2. Patient flowchart.
ACS indicates acute coronary syndrome, CABG, coronary artery bypass grafting, NSTE-ACS, non–ST-segment–elevation acute coronary syndrome, PCI, percutaneous coronary intervention, and STEMI, ST-segment–elevation myocardial infarction.

The sensitivity analysis on the incidence risk of urgent non–target-vessel PCI showed no significant difference between early and late staged PCI groups across the entire follow-up period (unadjusted RR, 0.68 [95% CI, 0.38–1.22], *P*=0.198; adjusted RR, 0.86 [95% CI, 0.46–1.63], *P*=0.651). The risk also did not differ when considering only the period from baseline up to 28 days (early staged PCI: 3.9%; late staged PCI group: 4.8%; unadjusted RR, 0.81 [95% CI, 0.45–1.47], *P*=0.486; adjusted RR, 1.01 [95% CI, 0.53–1.93], *P*=0.967). The incidence risk for the group still at risk (late staged PCI group) between 29 and 60 days was 2.5% (Figure 4D). After 60 days, very few patients were still at risk for this end point, as most had already received their staged PCI.

Comparing only events up to the date of the planned staged PCI, there were also no significant differences with respect to the primary end point (4.5% in the early versus 6.8% in the late staged PCI group; unadjusted HR, 0.89 [95% CI, 0.50–1.56], *P*=0.681; adjusted HR, 1.11 [95% CI, 0.60–2.05], *P*=0.739) or all-cause death or recurrent MI alone (Table S6). Adjusted variables were the same as for all other adjusted outcome analyses.

The results from the sensitivity analysis considering time as a continuous variable indicate that the expected probability of the primary end point peaks at 66 days from the index PCI (Figure S2).

Indication for Urgent Premature Non–Target-Vessel PCI

The indications for urgent premature non–target-vessel PCI are displayed in Table S7. In the early staged PCI group, urgent premature non–target-vessel PCI was mainly related to unstable angina (53.8%, n=7) or

Table 1. Clinical Characteristics

	Early staged PCI (n=333)	Late staged PCI (n=1099)	*P* value
Age, y	65.4±11.9	65.5±11.3	0.921
Female	58 (17.4)	242 (22.0)	0.077
BMI, kg/m^2	27.4±4.4	27.3±4.3	0.640
Smoker	123 (36.9)	401 (36.5)	0.948
Hypercholesterolemia	185 (55.6)	569 (51.8)	0.259
Hypertension	192 (57.7)	666 (60.6)	0.339
Diabetes	56 (16.8)	218 (19.8)	0.234
Family history of CAD	92 (27.6)	257 (23.4)	0.126
Previous MI	25 (7.5)	81 (7.4)	0.906
Previous PCI	33 (9.9)	109 (9.9)	1.000
Previous CABG	8 (2.4)	32 (2.9)	0.708
Left ventricular function, %	50.1±12.0	49.8±11.4	0.700
Indication			0.069
Unstable angina	20 (6.0)	51 (4.6)	
NSTEMI	144 (43.2)	414 (37.7)	
STEMI	169 (50.8)	634 (57.7)	
Congestive heart failure			0.599
Killip I	279 (83.8)	941 (85.6)	
Killip II	39 (11.7)	119 (10.8)	
Killip III	15 (4.5)	39 (3.6)	
Renal failure (GFR <60 mL/min)	52 (15.6)	172 (15.7)	0.931
Renal failure requiring dialysis	4 (1.2)	15 (1.4)	1.000
Peripheral arterial disease	8 (2.4)	50 (4.6)	0.083
History of stroke or TIA	9 (2.7)	55 (5.0)	0.095
History of GI bleeding	5 (1.5)	13 (1.2)	0.585
History of malignancy	29 (8.7)	91 (8.3)	0.822
Chronic obstructive pulmonary disease (COPD)	18 (5.4)	57 (5.2)	0.889
Anemia*	43 (12.9)	168 (15.3)	0.465

Values are n (%) or mean±standard deviations. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD: chronic obstructive pulmonary disease; GFR, glomerular filtration rate; GI, gastrointestinal; IABP, intra-aortic balloon pump; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack.

*Anemia was defined as hemoglobin <130 g/L in men and <120 g/L in women.

recurrent MI (30.8%, n=4), and in the late staged PCI group, to unstable angina (54.0%, n=34) or congestive heart failure (20.6%, n=13) (*P*=0.50 for any between-group differences).

Multivariable Cox Proportional Hazards Models

Following a backward selection procedure excluding variables with a *P* value >0.2 in the univariable Cox proportional hazards model, the variables Killip III, renal failure, left main, and early staged PCI remained for the multivariable analysis. Of these, Killip III (HR, 2.36 [95% CI,1.23–4.55], *P*=0.010) and renal failure (ie, glomerular filtration rate <60 mL/min) (HR, 1.91 [95% CI, 1.27–2.87], *P*=0.002) were significantly associated with a higher rate of the primary end point (Table 5).

Subgroup Analyses

The results were consistent across all major clinical subgroups, including clinical presentation (STEMI versus NSTE-ACS), age, sex, and diabetes (Figure 5).

DISCUSSION

In this cohort study, among ACS patients with MVD scheduled to undergo staged PCI after hospital discharge, early (<4 weeks after index PCI) as compared with late staged PCI (≥4 weeks after index PCI) was associated with a similar rate of major adverse cardiac events and its individual components at 1 year follow-up.

Timing of Staged PCI in Patients With STEMI

In the complete revascularization arm of the COMPLETE trial, where staged PCI had to be performed either during the index hospitalization (median, 1 day; IQR 1–3 days) or after hospital discharge within 45 days (median, 23 days; IQR, 12.5–33.5 days) from index PCI,[7] the benefit of complete revascularization as compared with culprit-lesion–only PCI in terms of cardiovascular death/MI and cardiovascular death/MI/ischemia-driven revascularization was consistently observed, irrespective of the timing of staged PCI.[13] The results of the COMPLETE trial are fully consistent with our results. This contrasts the evidence from previous small observational studies, which suggested that staged PCI should preferentially be performed within 30 days,[17] 2 weeks,[14,15] or even 1 week[16] after the index presentation, as this was associated with better outcomes[14,15,17] or had emerged as an independent predictor of a reduced 3-year major adverse cardiac event rate.[16] As suggested previously,[13] the lack of an effect of timing of staged PCI on patient outcomes could be explained by the following: (1) Early events after STEMI are rather related to infarct size, severity, and the outcome of the culprit-lesion PCI, and thus, these events may occur equally frequently in patients with earlier or later planned staged PCI. (2) After this initial phase, a potential impact of the time point of staged PCI could emerge; however, the use of evidence-based medical therapy including DAPT could protect from thrombotic nonculprit-lesion events before a planned staged PCI (99% any DAPT and 77% potent DAPT with ticagrelor or prasugrel in this cohort; in the COMPLETE trial, >99% any DAPT

Table 2. Procedural Characteristics of Index PCI

All patients	Early staged PCI (n=333)	Late staged PCI (n=1099)	*P* value
Number of vessels			0.253
1	267 (80.2)	911 (82.9)	
2–3	66 (19.8)	188 (17.1)	
Number of lesions			0.192
1	170 (51.1)	633 (57.6)	
2	113 (33.9)	322 (29.3)	
3	42 (12.6)	117 (10.6)	
≥4	8 (2.4)	27 (2.5)	
Culprit lesions	**Early staged PCI (n=354)**	**Late staged PCI (n=1167)**	***P* value**
Target vessel			0.503
Left main	8 (2.3)	14 (1.2)	
Left anterior descending	132 (37.3)	413 (35.4)	
Left circumflex	82 (23.2)	276 (23.7)	
Right coronary artery	129 (36.4)	447 (38.3)	
Bypass graft (any)	3 (0.8)	17 (1.5)	
Type of intervention			0.400
Implantation of stent(s)	343 (96.9)	1140 (97.7)	
Balloon dilatation only	11 (3.1)	27 (2.3)	
Baseline TIMI flow			0.159
0 or 1	171 (48.3)	631 (54.1)	
2	61 (17.2)	195 (16.7)	
3	121 (34.2)	337 (28.9)	
Post-TIMI flow			0.604
0 or 1	3 (0.8)	5 (0.4)	
2	7 (2.0)	27 (2.3)	
3	343 (96.9)	1133 (97.1)	
Restenotic lesion	19 (5.4)	50 (4.3)	0.408
Chronic total occlusion	7 (2.0)	25 (2.1)	0.864
Thrombus aspiration	67 (18.9)	271 (23.2)	0.399
Total number of stents implanted			0.257
1	202 (57.1)	710 (60.8)	
2	102 (28.8)	327 (28.0)	
≥3	50 (14.1)	130 (11.1)	
Total stent length, mm	32.0 [23.0, 48.0]	30.0 [22.0, 45.5]	0.094
Mean stent diameter, mm	2.99±0.45	2.99±0.48	0.928
Maximum pressure, atm	14.1±3.6	14.2±3.6	0.713
Treatment of a bifurcation	56 (15.8)	204 (17.5)	0.399
Overlapping stents	139 (39.3)	404 (34.6)	0.093
Nonculprit lesions	**Early staged PCI (n=205)**	**Late staged PCI (n=582)**	***P* value**
Target vessel			0.235
Left main	5 (2.4)	13 (2.2)	
Left anterior descending	68 (33.2)	204 (35.1)	
Left circumflex	62 (30.2)	130 (22.3)	
Right coronary artery	69 (33.7)	232 (39.9)	
Bypass graft (any)	1 (0.5)	3 (0.5)	

(*Continued*)

Table 2. Continued

Nonculprit lesions	Early staged PCI (n=205)	Late staged PCI (n=582)	*P* value
Type of intervention			0.810
Implantation of stent(s)	192 (93.7)	547 (94.0)	
Balloon dilatation only	13 (6.3)	34 (5.8)	
Baseline TIMI flow			0.065
0 or 1	31 (15.1)	108 (18.6)	
2	26 (12.7)	113 (19.4)	
3	146 (71.2)	356 (61.2)	
Post-TIMI flow			0.347
0 or 1	2 (1.0)	5 (0.9)	
2	1 (0.5)	13 (2.2)	
3	200 (97.6)	560 (96.2)	
Restenotic lesion	2 (1.0)	9 (1.6)	0.562
Chronic total occlusion	4 (2.0)	10 (1.7)	0.834
Thrombus aspiration	4 (2.0)	18 (3.1)	0.940
Total number of stents implanted			0.710
1	155 (75.6)	438 (75.3)	
2	29 (14.1)	93 (16.0)	
≥3	21 (10.2)	51 (8.8)	
Total stent length, mm	22.0 [15.0, 31.0]	22.0 [15.0, 31.0]	0.248
Mean stent diameter, mm	2.83±0.54	2.88±0.51	0.259
Maximum pressure, atm	13.3±3.6	13.8±3.4	0.128
Treatment of a bifurcation	27 (13.2)	96 (16.5)	0.940
Overlapping stents, n (%)	42 (20.5)	127 (21.8)	0.721

Values are n (%), mean±standard deviation, or median [interquartile range]. DES indicates drug eluting stent, PCI, percutaneous coronary intervention; and TIMI, thrombolysis in myocardial infarction.

and 75% potent DAPT). Within the investigated time frames, this appears to be equally effective in patients with earlier or later planned staged PCI.

Timing of Staged PCI in NSTE-ACS Patients

With respect to NSTE-ACS, one propensity-matched study showed similar mortality in patients undergoing staged PCI during the index hospitalization versus staged PCI within 60 days of hospital discharge.[23] Even though these results cannot be directly compared with our data, since this analysis focused exclusively on patients with staged PCI after hospital discharge, the observation of a similar mortality rate in the earlier versus the later staged PCI group is consistent. Other data on NSTE-ACS patients are limited to studies comparing immediate complete revascularization versus staged PCI[12,24] and reported conflicting results. Whereas in a propensity-matched study, staged PCI (within median 5 days) versus immediate revascularization was more favorable with respect to cardiac death/MI,[24] in the Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients RCT, a reduced rate of

Table 3. Medication at Hospital Discharge

	Early staged PCI (n=333)	Late staged PCI (n=1099)	*P* value
Aspirin	330 (99.1)	1084 (98.6)	0.388
Potent P2Y12 inhibitor (prasugrel or ticagrelor)	260 (78.1)	841 (76.5)	0.552
Clopidogrel	72 (21.6)	255 (23.2)	0.602
Any DAPT	330 (99.1)	1082 (98.5)	0.274
Oral anticoagulation (vitamin K antagonists or NOAC)	27 (8.1)	65 (5.9)	0.160
Statin	317 (95.2)	1051 (95.6)	0.878

Values are n (%). DAPT indicates dual antiplatelet therapy; NOAC, novel oral anticoagulant; and PCI, percutaneous coronary intervention.

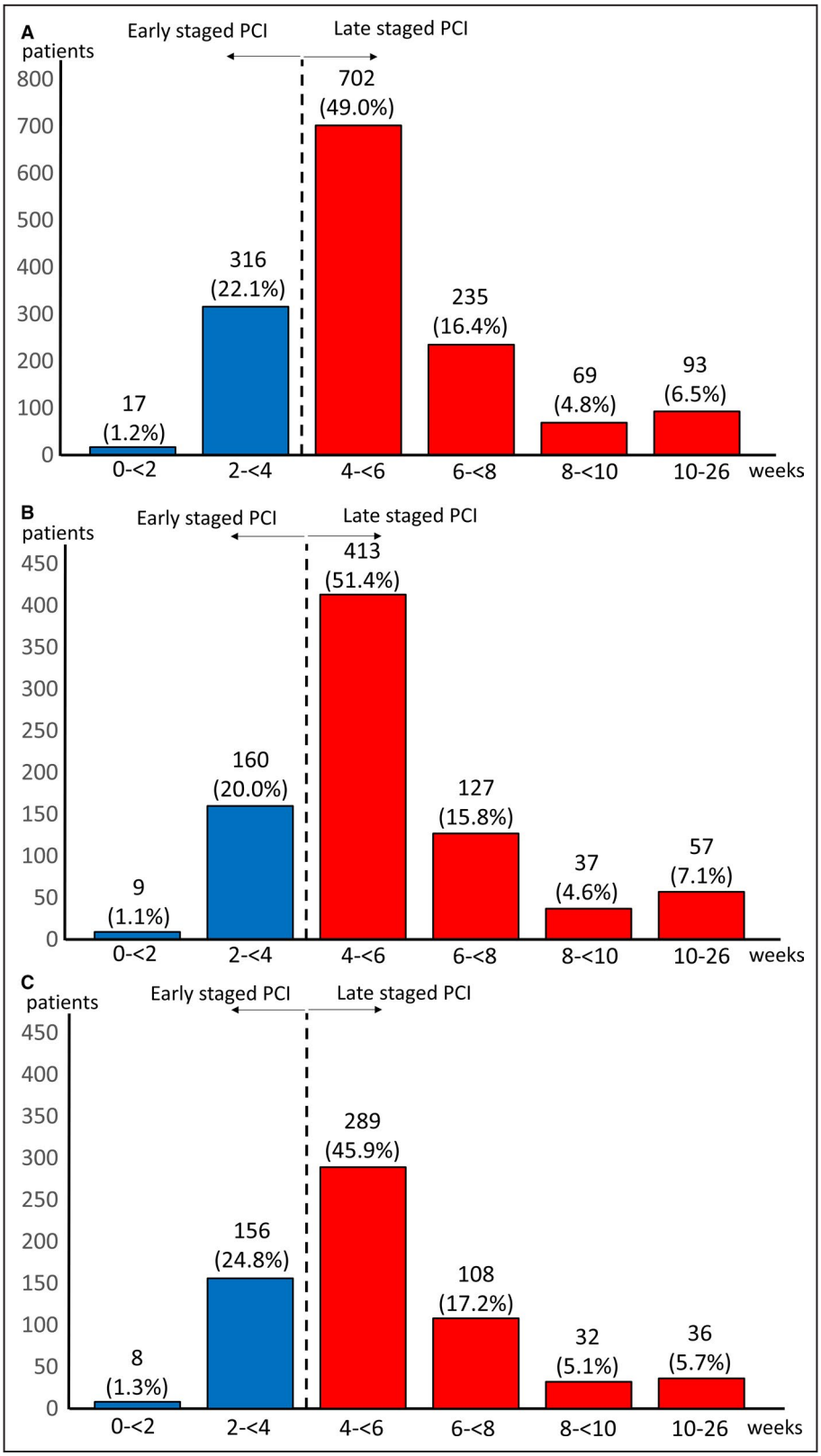

Figure 3. Distribution of scheduled duration between index and staged PCI.
A, All patients, (**B**) patients with STEMI, and (**C**) patients with NSTE-ACS. NSTE-ACS indicates non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Table 4. Clinical Outcomes at 1 Year

	Early staged PCI (n=333)	Late staged PCI (n=1099)	HR (95% CI)	*P* value
All-cause death, recurrent MI, urgent premature non–target-vessel PCI	26 (7.8)	119 (10.8)	0.72 (0.47–1.10)	0.129
All-cause death, recurrent MI, urgent premature non–target-vessel PCI, adjusted	26 (7.8)	119 (10.8)	0.80 (0.50–1.28)	0.346
All-cause death	5 (1.5)	32 (2.9)	0.52 (0.20–1.33)	0.170
Cardiac death	3 (0.9)	17 (1.6)	0.58 (0.17–1.99)	0.391
Recurrent MI (any)	14 (4.2)	48 (4.4)	0.97 (0.54–1.76)	0.924
Cardiac death or MI	15 (4.5)	58 (5.3)	0.86 (0.49–1.52)	0.605
Target-vessel MI	4 (1.2)	20 (1.8)	0.66 (0.23–1.93)	0.448
Non–target-vessel MI	7 (2.1)	17 (1.6)	1.37 (0.57–3.31)	0.480
Revascularization (any)	32 (9.6)	118 (10.7)	0.90 (0.61–1.33)	0.608
Urgent premature non–target-vessel PCI	13 (3.9)	63 (5.7)	0.97 (0.53–1.80)	0.928
Target-lesion revascularization	11 (3.3)	47 (4.3)	0.77 (0.40–1.49)	0.445
Stent thrombosis (definite/probable)	8 (2.4)	29 (2.6)	0.91 (0.42–2.00)	0.822
Stent thrombosis (definite)	5 (1.5)	16 (1.5)	1.03 (0.38–2.82)	0.947

Values are n (%) or HR with 95% CI. HR indicates hazard ratio; MI, myocardial infarction, and PCI, percutaneous coronary intervention.

Adjusted covariates are year of inclusion, age (>60 vs ≤60 y), sex, left ventricular ejection fraction (≥45% vs <45%), Killip III, ST-segment–elevation myocardial infarction, diabetes, and renal failure (ie, glomerular filtration rate <60 mL/min).

major adverse cardiac events in favor of immediate complete revascularization as compared with staged PCI during index hospitalization was reported.[12] The results of the Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients RCT have translated to a class IIbB recommendation for immediate complete

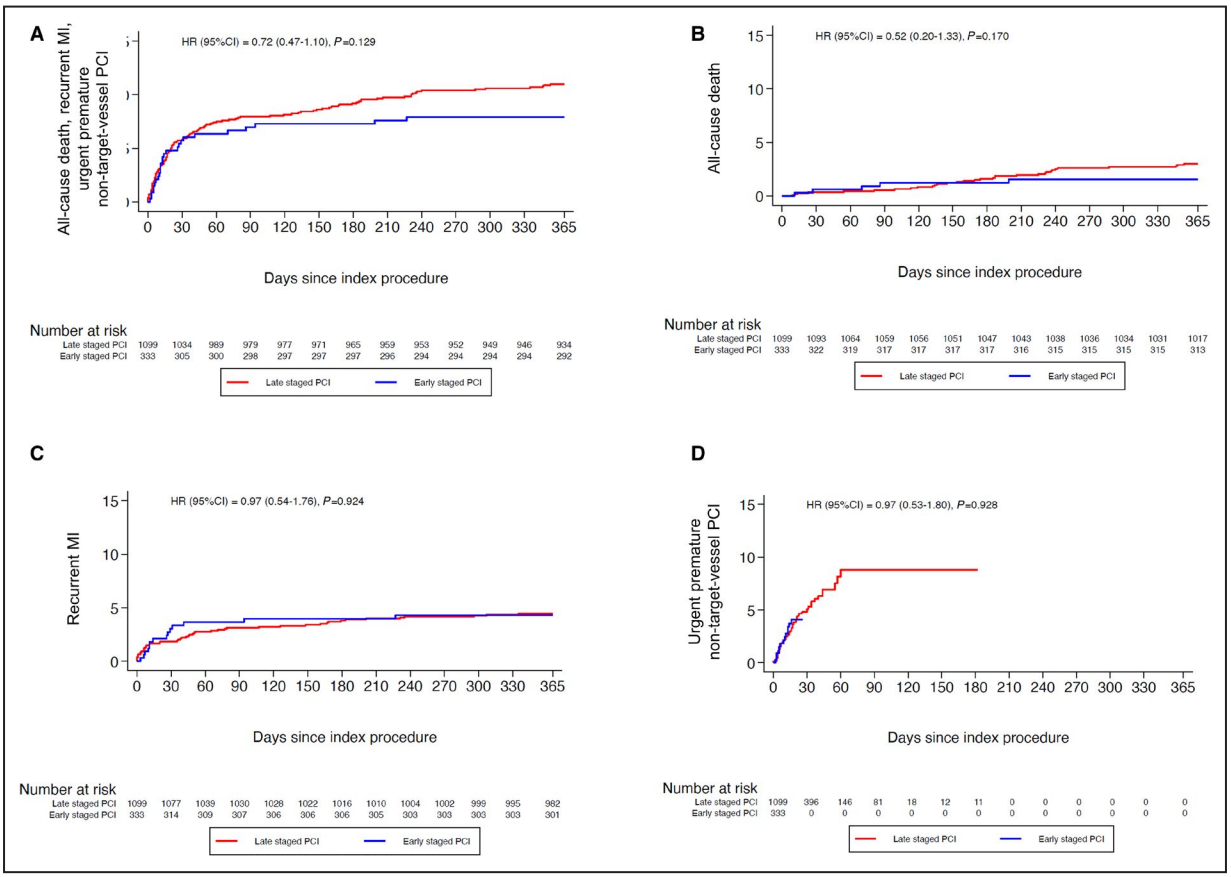

Figure 4. Kaplan-Meier curves of the primary end point and its components.
Kaplan-Meier curves of (**A**) primary end point, (**B**) all-cause death, (**C**) recurrent MI, (**D**) urgent premature non–target-vessel PCI. HR, indicates hazard ratio; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Table 5. Univariable and Multivariable Cox Proportional Hazards Models for the Primary End Point

	Univariable analysis		Multivariable analysis (n=1262)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age >60 y	1.35 (0.94–1.96) n=1432	0.105		
Sex, female vs male	0.85 (0.56–1.29) n=1432	0.446		
Diabetes	1.19 (0.80–1.76) n=1431	0.382		
Hypertension	1.23 (0.88–1.73) n=1431	0.231		
Smoker	0.75 (0.53–1.07) n=1424	0.109		
Killip III	2.63 (1.49–4.65) n=1432	0.001	2.36 (1.23–4.55)	0.010
Renal failure, GFR <60 mL/min	1.95 (1.34–2.86) n=1326	0.001	1.91 (1.27–2.87)	0.002
STEMI	0.86 (0.62–1.20) n=1432	0.380		
Left main artery	0.24 (0.03–1.72) n=1432	0.156	0.24 (0.03–1.72)	0.156
Left anterior descending artery	0.88 (0.63–1.22) n=1432	0.437		
Left circumflex artery	0.97 (0.68–1.39) n=1432	0.876		
Right coronary artery	1.13 (0.81–1.56) n=1432	0.474		
Drug eluting stent, any	1.21 (0.39–3.81) n=1420	0.740		
LVEF, per 10% increase	0.98 (0.97–1.00) n=1384	0.031		
Previous MI	1.01 (0.55–1.87) n=1428	0.966		
Early staged PCI (<4 weeks)	0.72 (0.47–1.10) n=1432	0.129	0.74 (0.47–1.17)	0.197

Results of univariable and multivariable Cox proportional hazard models for the primary end point (all-cause death, recurrent MI, urgent premature non-target-vessel PCI). The multivariable model was performed following a backward selection procedure excluding variables with *P* value >0.2. GFR indicates glomerular filtration rate, HR, hazard ratio, LVEF, left ventricular ejection fraction, MI, myocardial infarction, PCI, percutaneous coronary intervention, STEMI, ST-segment–elevation myocardial infarction.

revascularization in NSTE-ACS in the current European Society of Cardiology guidelines.[11] However, RCT data for different time intervals of staged PCI are not available in patients with NSTE-ACS.

Early (<4 Weeks) Versus Late (≥4 Weeks) Staged PCI in Patients With ACS

The clinical implications of this cohort study may be that if, in the judgment of the operator, nonculprit-lesion PCI can be deferred until after hospital discharge, it is safe and effective to perform it early (within <4 weeks) or late (≥4 weeks from index PCI). However, there was only a small number of patients (11.3%, 162/1432) who underwent staged PCI beyond a time point of 8 weeks, so that the results of these late staged PCIs are subject to imprecision and should be interpreted with caution.

Furthermore, in the late staged PCI group, there were 2.5% of patients with an urgent premature non–target-vessel PCI occurring between days 29 and 60. Aiming at a reduction of urgent recurrent PCIs (beyond detecting a statistically significant between-group difference), this would imply, that, to avoid 1 urgent premature non–target-vessel PCI in the late staged PCI group (ie, ≥4 weeks), 40 additional patients should be treated within <4 weeks.

Notably, our results do not pertain to higher-risk patients with the need for in-hospital staged PCI, as per judgment of the operator. In the Cardiobase Bern PCI registry, this concerns a minority (7.8%, 139/1764) of patients with ACS.

Numerical but statistically nonsignificant differences were observed between the early and the late group with respect to the indications for urgent premature non–target-vessel PCI. Whereas in the early

Primary end point (cardiac death, recurrent MI, urgent premature non–target-vessel PCI)	Early staged PCI	Late staged PCI	HR (95% CI)	*P* value	*P* value interaction
STEMI					0.58
Yes	11/169	65/634	0.63 (0.33-1.19)	0.15	
No	15/164	54/465	0.80 (0.45-1.41)	0.44	
Sex					0.24
Female	2/58	25/242	0.32 (0.08-1.37)	0.13	
Male	24/275	94/857	0.80 (0.51-1.25)	0.33	
Age >60 years					0.19
yes	16/216	90/739	0.60 (0.35-1.02)	0.06	
No	10/117	29/360	1.08 (0.53-2.22)	0.82	
LVEF ≥45%					0.78
Yes	17/235	77/783	0.74 (0.44-1.25)	0.26	
No	7/85	35/281	0.64 (0.29-1.44)	0.28	
Diabetes					0.10
Yes	2/56	30/218	0.24 (0.06-1.02)	0.05	
No	24/277	89/880	0.87 (0.55-1.36)	0.53	

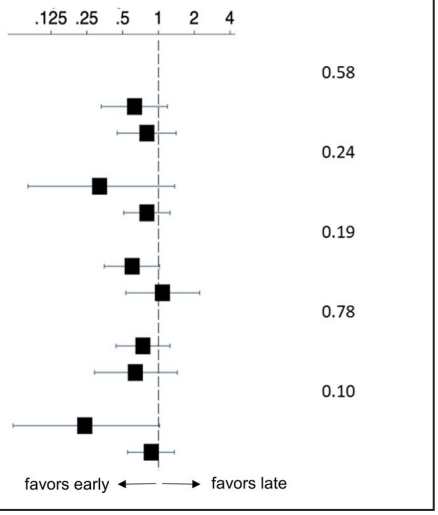

Figure 5. Subgroup analyses for the primary end point.
Reported are numbers of first events and hazard ratios (HR) with 95% CI. LVEF indicates left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

staged PCI group, urgent premature non–target-vessel PCI was indicated mostly because of recurrent ACS (84.6%) (unstable angina, 53.8%; or MI, 30.8%), in the late staged PCI group, indications were mainly unstable angina (54.0%) or congestive heart failure (20.6%).

We are not aware of any RCT to compare different time intervals of staged PCI after hospital discharge and thus, the current data addresses a knowledge gap that is not foreseen to be covered by RCT data in the future.

Limitations

The findings of the present study need to be considered in the context of several limitations:

1. It is a single-center, observational, retrospective, nonrandomized study with modest sample size, limiting generalizability.
2. The follow-up duration of 1 year is relatively short, and it is possible that a late benefit of either of the strategies was missed by the current study.
3. The observed CIs were wide, and the study might be underpowered and could therefore have missed existing differences in the end points assessed.
4. Patients with in-hospital staged PCI, staged coronary artery bypass grafting, cardiogenic shock, and multiple staged PCI were excluded from the analysis, and therefore, results cannot be applied to these higher-risk populations.
5. Between 2009 and 2017, PCI practice was subject to relevant improvements, which may affect outcomes. However, we have accounted for this by adjusting for year of inclusion with no effect on the study results.
6. Even though a culprit lesion was identified and treated in 99.8% of patients with NSTE-ACS during the index PCI, multiple vulnerable plaques are present in up to 40% of patients,[11] rendering possible that the true culprit lesion was left untreated during the index PCI in some patients. This could result in more early events in patients with NSTE-ACS. However, it can be assumed that this potential bias was reduced by excluding patients undergoing in-hospital staged PCI, as these include the patients with the highest-risk lesions, which are the lesions most likely to lead to confusion between culprit and nonculprit lesion.
7. Within the scope of the present study, we do not provide data on angiographic characteristics (eg, stenosis diameter, lesion complexity) or functional significance of the nonculprit-lesion scheduled for staged PCI.
8. We did not assess renal failure related to the staged PCI, and thus the impact of the earlier versus the later staged PCI strategy with respect to renal failure remains unknown.

CONCLUSIONS

In patients with both ACS and MVD scheduled to undergo staged PCI after hospital discharge, early (<4 weeks) compared with late staged PCI (≥4 weeks) was associated with a similar rate of the primary end point all-cause death, recurrent MI, urgent premature non–target-vessel PCI in this single center and all-comer population.

ARTICLE INFORMATION

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Supplementary Material

Table S1–S7
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Medication During Index PCI.

	Early staged PCI (n=333)	Late staged PCI (n=1099)	P value
Aspirin, n (%)			0.757
Loading dose	269 (80.8)	894 (81.3)	
Already on Aspirin	63 (18.9)	196 (17.8)	
Potent P2Y12 inhibitor (Prasugrel/Ticagrelor), n (%)			1.000
Loading dose	259 (77.8)	831 (75.6)	
Already on potent P2Y12 inhibitor	1 (0.3)	4 (0.4)	
Clopidogrel, n (%)			0.128
Loading dose	93 (27.9)	408 (37.1)	
Already on any P2Y12 inhibitor	11 (3.3)	26 (2.4)	
GP IIb/IIIa inhibitor, n (%)	172 (15.7)	46 (13.8)	0.434
Unfractionated Heparin, n (%)	329 (98.8)	1084 (98.6)	1.000

Values are n (%). GP IIb/IIIa = glycoprotein IIb/IIIa, PCI = percutaneous coronary intervention.

Table S2. Medication at 1 Year after Index PCI.

	Early staged PCI (n=333)	Late staged PCI (n=1099)	P Value
Aspirin, n (%)	271 (81.4)	935 (85.1)	0.031
Potent P2Y12 inhibitor (Prasugrel or Ticagrelor), n (%)	208 (62.5)	660 (60.1)	0.443
Clopidogrel, n (%)	59 (17.7)	219 (19.9)	0.423
Any DAPT, n (%)	240 (72.1)	823 (74.9)	0.270
Oral anticoagulation (vitamin K antagonists or NOAC), n (%)	30 (9.0)	82 (7.5)	0.350
Statin, n (%)	266 (79.9)	907 (82.5)	0.149

Values are n (%). DAPT = dual antiplatelet therapy. NOAC = novel oral anticoagulant.

PCI = percutaneous coronary intervention.

Table S3. Risk Ratios for the Primary Endpoint and Urgent Premature Non-target-vessel PCI.

	Risk Ratio (95% CI)	P value	Risk Ratio$_{adj}$ 95% CI	P value
All-cause death, recurrent MI, urgent premature non-target-vessel PCI, n (%)	0.72 (0.48-1.08)	0.115	0.78 (0.50-1.22)	0.285
Urgent premature non-target-vessel PCI, n (%)	0.68 (0.38-1.22)	0.198	0.86 (0.46-1.63)	0.651

Risk ratios from generalized linear models (GLMs). Adjusted covariates are: year of inclusion, age (>60 vs. ≤60 years), sex, left ventricular ejection fraction (≥45% vs. <45%), Killip III, STEMI, diabetes mellitus, and renal failure (i.e. glomerular filtration rate <60 ml/min). Adj = adjusted, CI = confidence interval, MI = myocardial infarction, PCI = percutaneous coronary intervention. STEMI = ST-segment-elevation myocardial infarction.

Table S4. Adjusted and Unadjusted Clinical Outcomes at 1 Year.

	Early staged PCI (n=333)	Late staged PCI (n=1099)	HR (95% CI)	P value	HR_{adj} (95% CI)	P $value_{adj}$
All-cause death, recurrent MI, urgent premature non-target-vessel PCI, n (%)	26 (7.8)	119 (10.8)	0.72 (0.47-1.10)	0.129	0.80 (0.50-1.28)	0.346
All-cause death, n (%)	5 (1.5)	32 (2.9)	0.52 (0.20-1.33)	0.170	0.62 (0.23-1.67)	0.343
Cardiac death, n (%)	3 (0.9)	17 (1.6)	0.58 (0.17-1.99)	0.391	0.79 (0.21-2.91)	0.723
Recurrent MI (any), n (%)	14 (4.2)	48 (4.4)	0.97 (0.54-1.76)	0.924	1.03 (0.53-2.01)	0.935
Cardiac death or MI, n (%)	15 (4.5)	58 (5.3)	0.86 (0.49-1.52)	0.605	0.89 (0.47-1.67)	0.707
Target-vessel MI, n (%)	4 (1.2)	20 (1.8)	0.66 (0.23-1.93)	0.448	0.90 (0.29-2.77)	0.857
Non-target-vessel MI, n (%)	7 (2.1)	17 (1.6)	1.37 (0.57-3.31)	0.480	0.97 (0.33-2.81)	0.950
Revascularization (any), n (%)	32 (9.6)	118 (10.7)	0.90 (0.61-1.33)	0.608	1.04 (0.68-1.60)	0.842

Urgent premature non-target-vessel PCI, n (%)	13 (3.9)	63 (5.7)	0.97 (0.53-1.80)	0.928	1.19 (0.61-2.34)	0.609
Target-lesion revascularization, n (%)	11 (3.3)	47 (4.3)	0.77 (0.40-1.49)	0.445	1.03 (0.50-2.11)	0.944
Stent thrombosis (definite/probable), n (%)	8 (2.4)	29 (2.6)	0.91 (0.42-2.00)	0.822	0.92 (0.37-2.33)	0.866
Stent thrombosis (definite), n (%)	5 (1.5)	16 (1.5)	1.03 (0.38-2.82)	0.947	0.76 (0.21-2.75)	0.670

Values are n (%) or hazard ratio (HR) with 95% confidence intervals (CI). Adjusted covariates are: year of inclusion, age (>60 vs. ≤60 years), sex, left ventricular ejection fraction (≥45% vs. <45%), Killip III, STEMI, diabetes mellitus, and renal failure (i.e. glomerular filtration rate <60 ml/min). adj= adjusted, MI = myocardial infarction, PCI = percutaneous coronary intervention.

Table S5. Clinical Outcomes at 1 Year among STEMI and NSTE-ACS.

STEMI patients (n=803)	Early staged PCI (n=169)	Late staged PCI (n=634)	HR (95% CI)	P value	HR_{adj} (95% CI)	P $value_{adj}$
All-cause death, recurrent MI, urgent premature non-target-vessel PCI, n (%)	11 (6.5)	65 (10.3)	0.63 (0.33-1.19)	0.153	0.70 (0.35-1.42)	0.327
All-cause death, n (%)	1 (0.6)	14 (2.2)	0.26 (0.03-2.00)	0.196	0.30 (0.04-2.51)	0.266
Cardiac death, n (%)	1 (0.6)	10 (1.6)	0.37 (0.05-2.87)	0.340	0.34 (0.04-2.92)	0.324
Recurrent MI (any), n (%)	2 (1.2)	28 (4.4)	0.26 (0.06-1.10)	0.068	0.35 (0.08-1.53)	0.165
Cardiac death or MI, n (%)	3 (1.8)	34 (5.4)	0.32 (0.10-1.05)	0.060	0.38 (0.11-1.29)	0.122
Target-vessel MI, n (%)	0 (0.0)	9 (1.4)				
Non-target-vessel MI, n (%)	1 (0.6)	12 (1.9)	0.31 (0.04-2.37)	0.258	0.41 (0.05-3.35)	0.404
Revascularization (any), n (%)	15 (8.9)	65 (10.3)	0.86 (0.49-1.50)	0.590	0.98 (0.54-1.80)	0.959
Urgent premature non-target-vessel	8 (4.7)	35 (5.5)	1.16 (0.53-2.54)	0.714	1.19 (0.49-2.87)	0.699

PCI, n (%)						
Target-lesion revascularization, n (%)	5 (3.0)	22 (3.5)	0.84 (0.32-2.22)	0.728	0.93 (0.30-2.87)	0.895
Stent thrombosis (definite/probable), n (%)	2 (1.2)	16 (2.5)	0.46 (0.11-2.02)	0.307	0.31 (0.04-2.43)	0.263
Stent thrombosis (definite), n (%)	2 (1.2)	12 (1.9)	0.62 (0.14-2.77)	0.532	0.40 (0.05-3.36)	0.401
NSTE-ACS patients (n=629)	Early staged PCI (n=164)	Late staged PCI (n=465)	HR (95% CI)	P value	HR_{adj} (95% CI)	P $value_{adj}$
All-cause death, recurrent MI, urgent premature non-target-vessel PCI, n (%)	15 (9.2)	54 (11.6)	0.80 (0.45-1.41)	0.439	0.84 (0.44-1.61)	0.607
All-cause death, n (%)	4 (2.4)	18 (3.9)	0.65 (0.22-1.92)	0.434	0.79 (0.24-2.58)	0.693
Cardiac death, n (%)	2 (1.2)	7 (1.5)	0.83 (0.17-4.00)	0.817	1.23 (0.20-7.62)	0.821
Recurrent MI (any), n (%)	12 (7.3)	20 (4.3)	1.76 (0.86-3.61)	0.121	1.91 (0.82-4.43)	0.134
Cardiac death or MI, n (%)	12 (7.3)	24 (5.2)	1.47 (0.74-2.95)	0.273	1.51 (0.68-3.37)	0.314
Target-vessel MI, n (%)	4 (2.4)	11 (2.4)	1.04 (0.33-3.28)	0.942	1.56 (0.44-5.50)	0.486

Non-target-vessel MI, n (%)	6 (3.7)	5 (1.1)	3.53 (1.08-11.55)	0.037	3.24 (0.64-16.29)	0.154
Revascularization (any), n (%)	17 (10.4)	53 (11.4)	0.94 (0.54-1.62)	0.813	1.03 (0.56-1.89)	0.931
Urgent premature non-target-vessel PCI, n (%)	5 (3.1)	28 (6.0)	0.78 (0.29-2.07)	0.614	1.22 (0.42-3.57)	0.713
Target-lesion revascularization, n (%)	6 (3.7)	25 (5.4)	0.69 (0.28-1.69)	0.422	0.98 (0.37-2.57)	0.964
Stent thrombosis (definite/probable), n (%)	6 (3.7)	13 (2.8)	1.33 (0.51-3.50)	0.562	1.67 (0.54-5.18)	0.373
Stent thrombosis (definite), n (%)	3 (1.8)	4 (0.9)	2.15 (0.48-9.59)	0.318	2.03 (0.26-15.69)	0.498

Values are n (%) or hazard ratio (HR) with 95% confidence intervals (CI). Adjusted covariates are: year of inclusion, age (>60 vs. ≤60 years), sex, left ventricular ejection fraction (≥45% vs. <45%), Killip III, STEMI, diabetes mellitus, and renal failure (i.e. glomerular filtration rate <60 ml/min). adj= adjusted, NSTE-ACS = Non-ST-elevation acute coronary syndrome, MI = myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction.

Table S6. Clinical Events up to Planned Staged PCI.

	Early staged PCI (n=333)	Late staged PCI (n=1099)	HR (95% CI)	P value	HR_{adj} (95% CI)	P $value_{adj}$
All-cause death, recurrent MI, urgent premature non-target-vessel PCI, n (%)	15 (4.5%)	75 (6.8%)	0.89 (0.50-1.56)	0.681	1.11 (0.60-2.05)	0.739
All-cause death, n (%)	0 (0.0%)	8 (0.7%)	-	-	-	-
Recurrent MI (any), n (%)	6 (1.8%)	24 (2.2%)	1.01 (0.41-2.51)	0.983	1.29 (0.49-3.37)	0.606

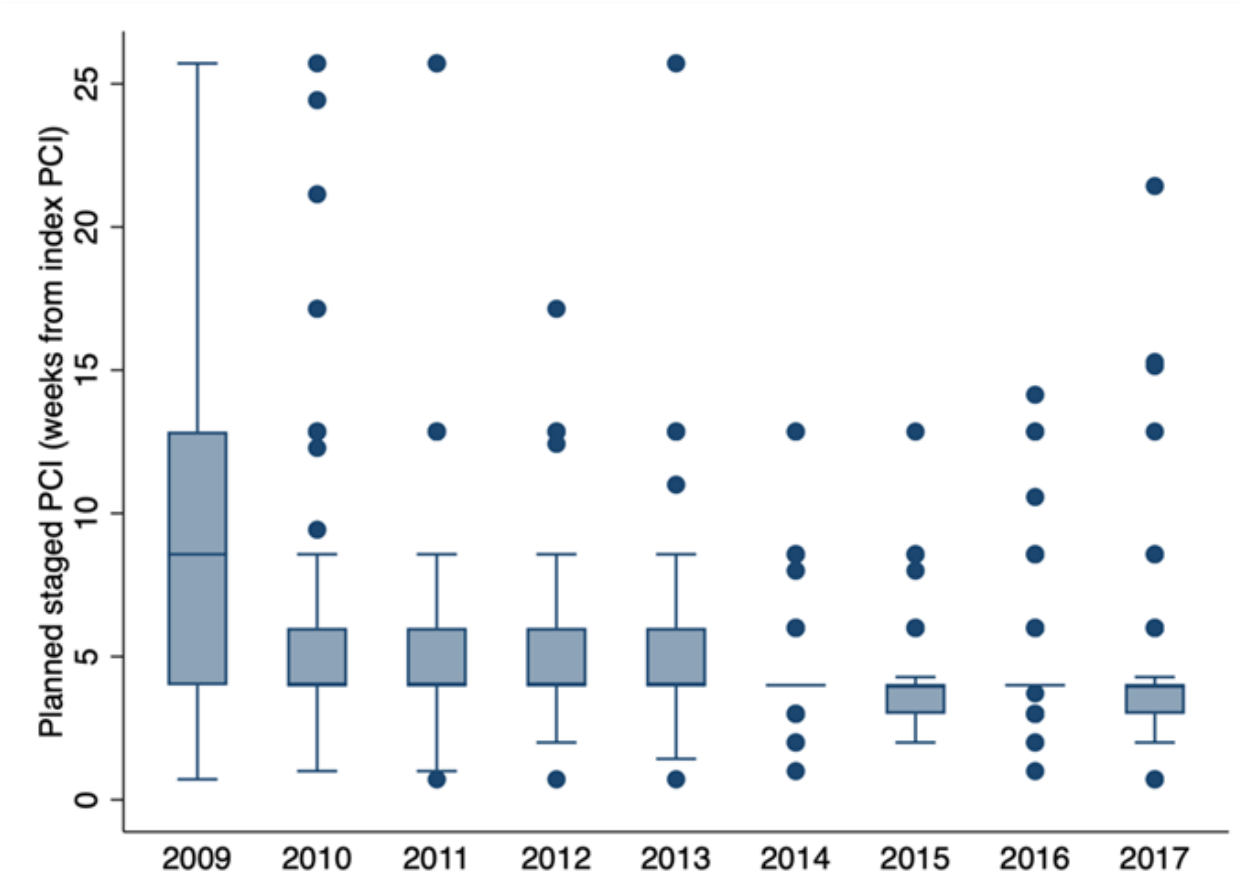
Values are n (%) or hazard ratio (HR) with 95% confidence intervals (CI) from Cox proportional hazards models considering only events up to the date of the planned staged PCI. Adjusted covariates are: year of inclusion, age (>60 vs. ≤60 years), sex, left ventricular ejection fraction (≥45% vs. <45%), Killip III, STEMI, diabetes mellitus, and renal failure (i.e. glomerular filtration rate <60 ml/min). adj= adjusted, MI = myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment-elevation myocardial infarction.

Table S7. Indication for Urgent Premature Non-target-vessel PCI.

Indication for urgent premature non-target-vessel PCI	Early staged PCI (n=13)	Late staged PCI (n=63)	P value
			0.50
Recurrent MI, n (%)	4 (30.8)	10 (15.9)	
Unstable angina, n (%)	7 (53.8)	34 (54.0)	
Congestive heart failure, n (%)	1 (7.7)	13 (20.6)	
Cardiogenic shock, n (%)	0 (0.0)	3 (4.8)	
Arrhythmia, n (%)	1 (7.7)	3 (4.8)	

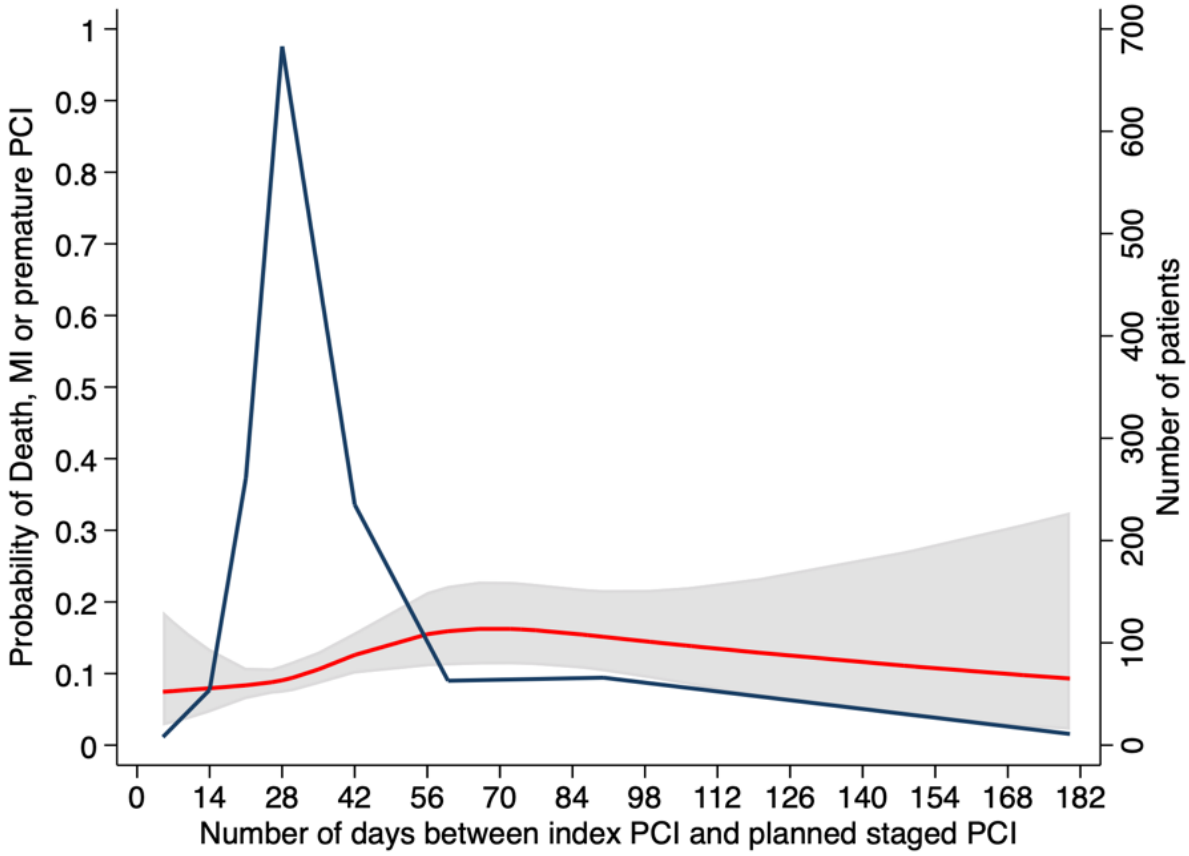
Values are n (%). MI = myocardial infarction, PCI = percutaneous coronary intervention.

Figure S1. Time from Index to Planned Staged PCI per Year of Enrolment.



Distribution of time (in weeks) from index to planned staged PCI per year of enrolment. PCI = percutaneous coronary intervention.

Figure S2. Expected Probability of the Primary Endpoint over Time.



The red line shows the expected probability of occurrence of the primary endpoint in relation to the number of days between index PCI and planned staged PCI, based on a restricted cubic splines logistic regression. The associated 95% confidence intervals are displayed in gray. The blue line shows the number of patients according to the number of days between index PCI and planned staged PCI. MI = myocardial infarction, PCI = percutaneous coronary intervention.