Clinical outcomes in STEMI patients undergoing percutaneous coronary interventions later than 48 hours after symptom onset

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ABSTRACT

Background

Routine revascularisation in patients with ST-segment-elevation myocardial infarction (STEMI) presenting >48hours after symptom onset is not recommended.

Methods

We compared outcomes of STEMI patients undergoing percutaneous coronary intervention (PCI) according to total ischemic time. Patients included in the Bern-PCI registry and the Multicenter Special Program University Medicine ACS (SPUM-ACS) between 2009-2019 were analysed. Based on symptom-to-balloon-time, patients were categorised as early (<12h), late (12-48h) or very late presenters (>48h). Co-primary endpoints were all-cause mortality and target lesion failure (TLF), a composite of cardiac death, target-vessel myocardial infarction and target-lesion revascularisation at one year.

Results

Of 6,589 STEMI patients undergoing PCI, 73.9% were early, 17.2% late and 8.9% very late presenters. Mean age was 63.4 years, 22% were female. At one year, all-cause mortality occurred more frequently in late vs. early (5.8% vs. 4.4%,HR 1.34,95%CI 1.01-1.78,p=0.04) and very late (6.8%) vs. early presenters (HR 1.59, 95%CI 1.12-2.25,p<0.01). There was no excess in mortality comparing very late and late presenters (HR 1.18,95%CI 0.79-1.77,p=0.42). TLF was more frequent in late vs. early (8.3% vs. 6.5%,HR 1.29,95%CI 1.02-1.63,p=0.04) and very late (9.4%) vs. early presenters (HR 1.47,95%CI 1.09-1.97,p=0.01), and similar between very late and late presenters (HR 1.14,95%CI 0.81-1.60,p=0.46). Following adjustment, heart failure, impaired

renal function and previous gastrointestinal bleeding, but not treatment delay were main drivers of outcomes.

Conclusions

PCI >12h after symptom onset was associated with less favourable outcomes, but very late vs. late presenters did not have an excess in events. While benefits seem uncertain, (very) late PCI appeared safe.

KEYWORDS

ST Elevation Myocardial Infarction; Myocardial Revascularisation; Percutaneous Coronary Intervention; Time-to-Treatment

INTRODUCTION

In patients presenting with a ST-segment elevation myocardial infarction (STEMI), the relative benefit of reperfusion decreases proportionally to the treatment delay.[1-4] The 2017 European Society of Cardiology guidelines on the management of STEMI state that routine primary percutaneous coronary intervention (PCI) should be considered 12-48 hours after symptom onset and do not recommend to perform routine revascularisation of occluded infarct-related arteries in asymptomatic STEMI patients presenting >48 hours after symptom onset.[5] The 2021 American College of Cardiology guidelines on coronary artery revascularisation are more restrictive, suggesting that PCI is reasonable to improve outcomes in stable STEMI patients presenting 12-24h after symptom onset, and that PCI should not be performed >24h after symptom onset in asymptomatic stable STEMI patients who have a totally occluded infarct artery.[6] These recommendations are largely based on the Occluded Artery Trial (OAT), the Total Occlusion

Study of Canada 2 trial (TOSCA-2) and the Desobstruction Coronaire en Post-Infarctus trial (DECOPI), which showed no benefit of routine PCI of occluded infarct-related arteries compared to medical therapy after a median of 8-10 days after myocardial infarction (MI).[7-9]

It remains questionable whether the findings of these trials are still valid in the light of contemporary management with newer-generation drug-eluting stents (DES), novel P2Y12-inhibitors, stricter goals for low-density lipoprotein (LDL) reductions and advanced heart-failure therapies.[10-14] Against this, we aimed to compare clinical outcomes in an all-comer population of STEMI patients who underwent early, late or very late PCI.

METHODS

Patient Population

The study population consisted of STEMI patients undergoing PCI, who were prospectively included in the Bern-PCI registry (NCT02241291, n=4,370) and the multicentre Special Program University Medicine - Acute Coronary Syndromes cohort (SPUM-ACS, NCT01000701, n=2,219) between January 2009 and December 2019.

All consecutive patients undergoing PCI at Bern University Hospital, Bern, Switzerland are routinely and prospectively enrolled in the Bern-PCI registry since January 2009, with no formal exclusion criteria.[15,16]

SPUM-ACS is a multicentre observational cohort study of patients presenting with ACS, conducted at four Swiss university hospitals (Bern, Geneva, Lausanne and Zurich). Inclusion criteria were a diagnosis of an acute coronary syndrome (ACS) and age greater than 18 years. Exclusion criteria comprised severe physical disability, inability to comprehend the study, and a life expectancy of less than one year.[16,17]

Patients enrolled in both registries were identified and analysed accordingly. STEMI was defined as the presence of typical symptoms suggestive of myocardial ischemia, new ST-segment elevations measuring ≥0.1mV in ≥2 contiguous leads (≥0.2mV in V2 to V3 leads) or a new left bundle branch block, and elevation of cardiac enzymes (cardiac troponin I/T, creatine kinase [CK] or CK myocardial-band [CK-MB]).

Patients in cardiogenic shock (i.e. Killip class IV), with resuscitation prior to hospital arrival or requiring hemodynamical support (vasopressors, mechanical circulatory support) were excluded from the current analysis.

Treatment delay

Exact symptom onset-, door- and balloon-times were only recorded in patients presenting within 24h. In the remainder of patients, total ischemic times (symptom onset-to-balloon times), were recorded in the categories >24-48h, >48-72h, >72h-7 days and >7 days. In line with the study protocols of the Bern-PCI and SPUM-ACS registries as well as the current European Society of Cardiology Guidelines on the management of STEMI[5], early presenters were defined as those coming with a delay of ≤12h. These patients were compared to those treated >12-48h after symptom onset (late presenters) or >48h after symptom onset (very late presenters). The study conforms to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by all institution's human research committee (institutional ethics committees Bern, Geneva, Lausanne, Zurich). All patients provided written informed consent.

Index PCI

PCI was performed in accordance with the guidelines current at the time of enrolment.[18,19] Unfractionated heparin (at least 5,000 IU or an initial bolus of 100 IU per kg body weight) was

used for procedural anticoagulation with the aim of maintaining an activated clotting time of >250 ms. The periprocedural use of glycoprotein IIb/IIIa inhibitors was left at the discretion of the operator. Dual antiplatelet therapy (DAPT) consisting of acetylsalicylic acid and a P2Y12-inhibitor was initiated before, at the time of, or immediately after the procedure. Prasugrel was introduced as of September 2009, and ticagrelor as of November 2011. The routinely recommended DAPT duration was 12 months. Secondary preventions drugs such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin-receptor-neprilysin-inhibitors (ARNIs), beta-blockers and LDL-lowering drugs were administered at the discretion of the treating physicians and in accordance with the guidelines at that time.[18-20]

Clinical Endpoints

Clinical events were adjudicated by an independent clinical events committee for both registries. Because the Bern University Hospital had the leading role for coordination and execution of these studies, outcome definitions were identical and event adjudication was done in a consistent fashion for all patients.

The co-primary endpoints were all-cause mortality and target lesion failure (TLF), defined as cardiac death, recurrent target vessel myocardial infarction (MI) or target lesion revascularisation (TLR) at one year. Secondary endpoints were the composite of cardiac death, MI or stroke, the composite of cardiac death, MI, stroke or Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding, and the individual components of these endpoints after one year. Detailed endpoint definitions are provided in the **Supplementary Appendix**.

Statistical analysis

Descriptive discrete characteristics are expressed as counts and percentages, and differences between groups were determined by the χ^2 test or the Fisher´s exact test. Continuous variables, normally distributed variables are expressed as means and standard deviations (SD), unless otherwise specified. Differences were examined using the *t* test or the Mann-Whitney-U test, where appropriate. The level of significance used for all tests was a two-sided $p<0.05$.

Primary and secondary outcomes were analysed using a Cox proportional-hazards model, comparing the reference group of early presenters to late and very late presenters, respectively. Multivariate adjustments were not performed for the primary analysis in order to reflect outcomes associated with late presentation. A multivariable Cox proportional-hazards model was chosen to adjust for clinically and prognostically relevant baseline differences. The following co-variables were considered for adjustment: Total ischemic time (<12h, 12-48h, >48h), age, gender, body mass index, smoking, hypertension, diabetes mellitus, hypercholesterolemia, previous MI, previous PCI, previous CABG, family history for coronary artery disease, peripheral artery disease, history of stroke or transient ischemic attack, history of gastrointestinal (GI) bleeding, impaired renal function (estimated glomerular filtration rate, GFR <60m/min), known heart failure (left ventricular ejection fraction, LVEF, ≤30%), congestive heart failure at presentation (Killip I-III), and treatment of ≥3 lesions. Co-primary endpoints (all-cause mortality, TLF) and composite secondary endpoints were selected for multivariable assessments. Results of the Cox proportional-hazard models are presented as hazard ratios (HR) with 95% confidence intervals (CIs).

Subgroup analysis for the co-primary endpoints was performed to account for potential sex-related differences and investigate previously studied sub-groups of clinical interest (proximal vs. non-proximal lesion localisation, TIMI flow pre PCI 0-1 vs. >1, LVEF ≤35% vs. >35%, Killip class

I vs. II-III). Subgroup analyses are presented as Kaplan-Meier failure rates with 95% CIs and p-values for interaction.

Statistical analyses were performed by the Clinical Trials Unit of the University of Bern (Bern, Switzerland), with Stata version 15.1 (StataCorp, College Station, Texas, United States) and R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). One author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The data underlying this article will be shared on reasonable request to the corresponding author.

RESULTS

The cohort consisted of 6,589 patients presenting with STEMI and undergoing PCI, who were included in the Bern-PCI registry between 2009-2019 and in the SPUM-ACS study between 2009-2017. Patients with Killip class IV at presentation (cardiogenic shock), use of mechanical circulatory support or vasopressors (n=995) and those with missing or uncertain information with respect to symptom-to-balloon time (n=193) were excluded **(Figure 1)**. In total, 4,868 (73.9%) were classified as early presenters, 1,134 (17.2%) as late presenters and 587 (8.9%) as very late presenters. In the very late presenting group, total ischemic time was 48-72h in 255 (43.4%), 72h-7days in 213 (36.3%) and >7days in 119 (20.3%) patients.

Patient Characteristics

Clinical and procedural characteristics are presented in **Table 1** and **Table S1**.

Compared to early presenters, patients presenting very late or late were older (66.2±13.2 vs. 65.3±13.1 vs. 62.7±12.7 years, respectively; p<0.01 and p<0.01), more frequently female (24% vs. 29% vs. 20%; p=0.04 and p<0.01), and had a higher prevalence of risk factors with respect to

arterial hypertension (57% vs. 56% vs. 49%; p<0.01 and p<0.01) and diabetes (22% vs. 19% vs. 13%; p<0.01 and p<0.01). Mean left ventricular ejection fraction was lower in very late and late presenters (45.0% vs. 46.0% vs. 47.2%, p<0.01 and p<0.01). Early presenters more frequently had a previous PCI compared to those patients presenting late or very late (7% vs. 7% vs. 10%; p<0.01 and p=0.04).

Procedural characteristics were similar between the groups with respect to the treated vessel, type of intervention (PCI with or without stent implantation) and the number of stents implanted in the culprit vessel (mean 1.40 ± 0.68, p=0.15 and p=0.07, **Table S1**). TIMI flow grades prior to PCI were similar in late vs. early presenters (p=0.57), while very late presenters less frequently had TIMI 0 flow in the infarct artery compared to early presenters (54% vs. 60%, p<0.01).

Antiplatelet therapies and secondary prevention medications are presented in **Table S2**. Clopidogrel instead of novel P2Y12-inhibitors (35% vs. 28% vs. 21%, p<0.01 and p<0.01) as well as oral anticoagulants (12% vs. 8% vs. 6%, p<0.01 and p<0.01) were more often prescribed in very late and late presenters, respectively.

Primary and Secondary Outcomes

All-cause mortality and TLF occurred in 303 (4.6%) and 439 (6.7%) patients after 1 year of follow-up, respectively. Cumulative time-to-event curves for these outcomes stratified by treatment delays are presented in **Figures 2** and **3**.

Rates of all-cause mortality were higher in late vs. early presenters (5.8% vs. 4.4%, HR 1.34, 95% CI 1.01-1.78, p=0.04) as well as very late (6.8%) vs. early presenters (HR 1.59, 95% CI 1.12-2.25, p<0.01, **Figure 2**). There were no significant differences in all-cause mortality comparing very late vs. late presenters (HR 1.18, 95% CI 0.79-1.77, p=0.42)

TLF occurred more frequently in late vs. early presenters (8.3% vs. 6.5%, HR 1.29, 95% CI 1.02-1.63, p=0.04) and very late (9.4%) vs. early presenters (HR 1.47, 95% CI 1.09-1.97, p=0.01**, Figure 3**). Differences in TLF were primarily driven by higher rates of cardiac death, but not recurrent target vessel MI or target lesion revascularisation (**Table 2**). The incidence of TLF was similar between very late and late presenters. (HR 1.14, 95% CI 0.81-1.60, p=0.46).

Rates of the composite of cardiac death, MI and stroke were similar in patients presenting late vs. early (HR 7.9% vs. 7.1%, HR 1.11, 95% CI 0.87-1.41, p=0.40) or very late (8.8%) vs. early (HR 1.25, 95% CI 0.92-1.68, p=0.15). An excess in cardiac death was counterbalanced by numerically lower rates of stroke in late and very late presenters (1.6% vs. 1.0% vs. 0.9%), which contributed to overall non-significant differences in this composite endpoint between groups (**Table 2, Figure S1**).

Rates of the composite of cardiac death, MI, stroke or BARC 3 or 5 bleeding were similar between groups (**Table 2, Figure S2**). Rates of definite stent thrombosis at one year were similar between groups (1.3%, 1.2% and 1.5%, p=0.69 and p=0.87).

Main results were consistent when accounting for competing risk with non-cardiac death (Table S3). After adjustment for clinical characteristics, treatment delay was not independently associated with all-cause mortality, TLF, the composite of cardiac death, MI or stroke, or the composite of cardiac death, MI, stroke or BARC 3 or 5 bleeding. The multivariable models for

the respective endpoints are presented in **Tables S4-S7**. Among these endpoints, congestive heart failure (Killip class >1) or severely reduced LVEF ≤30%, impaired renal function (GFR <60ml/min), and a history of GI bleeding were main independent drivers of outcomes.

Subgroup analysis

With respect to all-cause death, results were consistent in women, patients with proximal localisation of the target lesion, totally occluded infarct related arteries, LVEF ≤35% and Killip class II or III at presentation (p for interaction >0.05 for each, **Figure S3**).

Very late presenters with an LVEF ≤35% had an excess in the rates of TLF (p for interaction <0.01, primarily driven by cardiac death with p for interaction 0.07, **Table S8**). Results were consistent in the remaining subgroups, particularly in patients with totally occluded infarct related arteries (p for interaction >0.05, **Figure S4**).

DISCUSSION

In this large "real-world" cohort of STEMI patients undergoing PCI, late or very late presentation compared to early presentation was associated with higher rates of all-cause mortality, TLF and cardiac death after one year. The incidence of hard clinical outcomes was similar when comparing patients treated very late (>48h) vs. late (12-48h) after symptom onset. Results were consistent in patients with a total occlusion of the infarct related artery.

After adjustment for prognostically relevant characteristics, treatment delay was not independently associated with events. We attribute this finding to the sample size of (very) late presenting patients and the prognostically relevant co-variables with significant competing impact on outcomes. Main independent drivers of outcomes in this cohort were the presence of congestive heart failure or severely reduced left ventricular ejection fraction, impaired renal

function, and a history of GI bleeding. Numerically lower rates of stroke in late and very late presenters, as well as similar rates of stent thrombosis and BARC 3-5 bleeding imply that (very) late PCI did not come at the cost of potentially treatment-related complications.

Our data therefore suggest that in STEMI patients who are selected for an invasive management, PCI performed in a contemporary setting appeared to be safe even beyond the >48h limit. Alternatively, the usefulness of PCI in late presenters (12-48h after symptom onset) could be called into question, however available data strongly point towards a benefit of PCI over conservative management in terms of reduced infarct sizes, more favourable patterns of left ventricular remodelling and lower rates of mortality.[21-26] Contemporary data on very late presenters are particularly scarce.[21-25] In KAMIR-NIH, 2-year rates of all-cause death and MACE were 12.5% and 13.4% in late presenters (n=599), and 13.6% and 11.3% in very later presenters (n=265), respectively.[27] In line with our data, very late presenters were older, had higher NT-pro-BNP levels, worse renal function and worse LVEF, but even unadjusted crude outcomes were not substantially worse in these very late presenters, all undergoing PCI.[27]

It has been established that in acute myocardial infarction, fully salvageable myocardium is a function of time with a narrow window as low as <3 hours. [28-30] In contrast, even in patients with totally occluded infarct arteries, substantial (>50%) myocardial salvage could be achieved with late reperfusion after 12-72h.[25] Pre-formed coronary collaterals which are able to prevent myocardial ischemia have been shown to be present in approximately 25-30% of patients[31-33], potentially resulting in myocardial stunning (i.e. reversible post-ischemic contractile dysfunction) or short-term hibernation for up to 24 hours (i.e. matched reduction of blood flow and contractile dysfunction) – thus, room for recovery.[29,30,34,35] Very late presenters with an LVEF ≤35% had excess rates of TLF. As recently shown in the REVIVED-BCIS2 trial, patients with extensive

coronary artery disease and a LVEF ≤35% did not benefit from revascularisation, even in the presence of demonstrable viability.[36]

Trials upon which the current guidelines recommendations are based on, namely the OAT, TOSCA-2 and DECOPI trials randomised patients at a median of 8-10 days after MI.[7-9] Patients were enrolled between 1998-2005, the OAT and TOSCA-2 trials additionally required a criterion of increased risk (ejection fraction of less than 50% or proximal occlusion of a major epicardial vessel), and patients were mainly treated with bare-metal stents or balloon angioplasty.[7,8,37] In the OAT trial, 32% of screened patients were randomised into the trial, which underlines that these above-mentioned characteristics are not encountered frequently in patients admitted for a subacute STEMI. Accordingly, European and American guidelines, which discourage from routine revascularisation 48 or even 24h after symptom onset refer to a subset of (asymptomatic) subacute STEMI patients rather than all-comers with long delays.[5,6] Also in the light of contemporary medical treatments, including novel $P2Y_{12}$-inhibitors[11,12], stricter goals for LDL cholesterol reductions[13], advanced heart failure therapies[14], neprilysin inhibitors[38], sodium-glucose co-transporter 2 inhibitors[39], device therapy[40], as well as improved interventional strategies (newer generation DES[41-43], intravascular imaging-guided PCI[44-48]), the applicability of these trial findings remain questionable.

Strengths and Limitations

Our study was not able to directly assess the benefits of PCI over conservative management. Patients in cardiogenic shock at presentation and those who were either treated conservatively or deferred from primary PCI after angiography were not captured in this analysis. Based on subjective impression from the reported timeframe, angiography and/or PCI was infrequently (i.e.

<5%) withheld in STEMI patients. Exact data allowing a precise assessment of selection bias were not available. Bias might have been introduced by physicians prompting late or very late PCI due to heart failure, arrhythmias, or recurrent symptoms. These details were not recorded in the databases. Exact symptom-, door- and balloon-times were only assessed in patients within 24h of symptom onset. Due to the 24/7 service at the enrolling centres, all patients with electrocardiographic signs of STEMI were offered rapid invasive management, usually below 120 minutes after admission. Thus, categorisation according to total ischemic time can be regarded as virtually identical to previously reported pre-hospital delays (symptom-to-door times). The observational nature of this analysis cannot infer causality and only describes observed outcomes stratified by total ischemic time. Therefore, our data have to be regarded as hypothesis generating with respect to the favourable outcomes after very late primary PCI. The prospective follow-up with a 93% follow-up rate and central independent event adjudication deserves mentioning.

CONCLUSIONS

STEMI patients in whom PCI was performed >12h after symptom onset had a higher incidence of adverse events. Following adjustment, heart failure, impaired renal function and history of GI bleeding but not treatment delay remained independently associated with clinical outcomes. Very late vs. late PCI was not associated with an excess in events, also with respect to potentially treatment related adverse outcomes such as stroke, major bleeding or stent thrombosis. While the study was not able to provide insights regarding the benefits over conservative treatment, (very) late PCI appeared to be safe.

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FIGURES LEGENDS

FIGURE 1

Patient recruitment flow-chart. Legend: IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

FIGURE 2

Kaplan-Meier cumulative event curves for all-cause mortality in patients with ST-segment elevation myocardial infarction who underwent PCI early (≤12h) vs. late (>12h-48h) vs. very late (>48h) after symptom onset. Legend: CI: confidence interval; HR: hazard ratio

FIGURE 3

Kaplan-Meier cumulative event curves for target lesion failure in patients with ST-segment elevation myocardial infarction who underwent PCI early (≤12h) vs. late (>12h-48h) vs. very late (>48h) after symptom onset. Legend: CI: confidence interval; HR: hazard ratio

TABLE 1: Patient Characteristics

	All patients	Early presenters 0-12h	Late presenters >12-48h	Very late presenters >48h	p-value late vs. early	p-value very late vs. early	p-value very late vs. late
	N = 6589	N = 4868	N = 1134	N = 587			
Age (years)	63.4 ± 12.9	62.7 ± 12.7	65.3 ± 13.1	66.2 ± 13.2	<0.01	<0.01	0.19
Gender (female)	1469 (22%)	997 (20%)	330 (29%)	142 (24%)	<0.01	0.04	0.03
Body mass index (kg/m²)	26.9 ± 4.4	26.9 ± 4.3	27.1 ± 4.7	26.9 ± 4.7	0.13	0.92	0.33
Current smoker	2663 (41%)	2021 (42%)	437 (39%)	205 (35%)	0.07	<0.01	0.14
Hypertension	3367 (51%)	2397 (49%)	634 (56%)	336 (57%)	<0.01	<0.01	0.68
Diabetes mellitus	971 (15%)	626 (13%)	217 (19%)	128 (22%)	<0.01	<0.01	0.20
Hypercholesterolemia	3449 (53%)	2589 (54%)	589 (52%)	271 (46%)	0.45	<0.01	0.02
Previous myocardial infarction	492 (7%)	383 (8%)	64 (6%)	45 (8%)	0.01	0.94	0.12
Previous PCI	604 (9%)	487 (10%)	74 (7%)	43 (7%)	<0.01	0.04	0.55
Previous CABG	130 (2%)	103 (2%)	16 (1%)	11 (2%)	0.16	0.88	0.54
Family history of coronary artery disease	1484 (23%)	1104 (23%)	251 (22%)	129 (22%)	0.67	0.68	0.95
Peripheral arterial disease	231 (4%)	154 (3%)	54 (5%)	23 (4%)	0.01	0.32	0.46
History of stroke	237 (4%)	147 (3%)	65 (6%)	25 (4%)	<0.01	0.13	0.21
History of gastrointestinal bleeding	76 (1%)	51 (1%)	19 (2%)	6 (1%)	0.09	1.00	0.40
Impaired renal function (eGFR <60ml/min)	816 (13%)	547 (12%)	172 (16%)	97 (17%)	0.01	<0.01	0.48
Left ventricular function (%)	46.8 ± 11.0	47.2 ± 10.8	46.0 ± 11.1	45.0 ± 11.8	0.04	<0.01	0.13
Congestive heart failure					0.39	0.60	0.92
Killip I	5531 (85%)	4102 (85%)	944 (84%)	485 (84%)	0.18	0.32	1.00
Killip II	785 (12%)	564 (12%)	145 (13%)	76 (13%)	0.31	0.34	0.88
Killip III	201 (3%)	144 (3%)	39 (3%)	18 (3%)	0.44	0.90	0.78
eGFR	87.5 ± 26.7	87.8 ± 26.0	88.2 ± 29.1	84.1 ± 27.5	0.65	<0.01	0.01
Max. obtained creatinine kinase (U/L)	1867.0 ± 1844.9	2018.0 ± 1831.2	1665.1 ± 2012.4	982.1 ± 1233.5	<0.01	<0.01	<0.01

Max. obtained cardiac troponin (ng/L)	205529 ± 69000	252056 ± 79000	105315 ± 28000	8222 ± 17794.3	0.55	0.46	0.41
NT-pro BNP (pg/ml)	1022.2 ± 3114.5	556.1 ± 2368.8	1949.0 ± 3543.8	3615.4 ± 5816.5	<0.01	<0.01	<0.01

Depicted are means ± standard deviations and counts (%), p-values from the Chi-square test or Fisher's test in case of counts, otherwise t-tests.
Table legend: CABG: coronary artery bypass graft; eGFR: estimated glomerular filtration rate; NT-pro-BNP: N terminal pro brain natriuretic peptide; PCI: percutaneous coronary intervention

TABLE 2: Clinical Outcomes

	Early presenters	Late presenters	Very late presenters	Late vs. early				Very late vs. early				Very late vs. late			
	0-12h	>12-48h	>48h	HR (95% CI)	p	Adjusted HR (95% CI)	p	Hazard Ratio (95% CI)	p	Adjusted HR (95% CI)	p	Hazard Ratio (95% CI)	p	Adjusted HR (95% CI)	p
Co-primary endpoints															
All-cause mortality	202 (4.4)	63 (5.8)	38 (6.8)	1.34 (1.01-1.78)	0.04	0.95 (0.71-1.27)	0.73	1.59 (1.12-2.25)	<0.01	1.14 (0.80-1.62)	0.46	1.18 (0.79-1.77)	0.42	1.20 (0.80-1.80)	0.38
Target lesion failure	298 (6.5)	89 (8.3)	52 (9.4)	1.29 (1.02-1.63)	0.04	1.03 (0.81-1.32)	0.80	1.47 (1.09-1.97)	0.01	1.15 (0.85-1.55)	0.36	1.14 (0.81-1.60)	0.46	1.11 (0.79-1.57)	0.54
Secondary endpoints															
Cardiac death, MI or stroke	330 (7.1)	85 (7.9)	49 (8.8)	1.11 (0.87-1.41)	0.40	0.87 (0.68-1.11)	0.25	1.25 (0.92-1.68)	0.15	0.93 (0.69-1.27)	0.66	1.12 (0.79-1.60)	0.51	1.08 (0.76-1.53)	0.68
Cardiac death, MI, stroke or BARC 3 or 5 bleeding	492 (10.6)	132 (12.2)	72 (12.9)	1.15 (0.95-1.40)	0.15	0.92 (0.76-1.12)	0.39	1.23 (0.96-1.57)	0.11	0.96 (0.75-1.23)	0.73	1.06 (0.80-1.42)	0.68	1.04 (0.78-1.39)	0.78
Cardiac death	150 (3.2)	48 (4.5)	33 (5.9)	1.38 (1.00-1.91)	0.05			1.85 (1.27-2.70)	<0.01			1.34 (0.86-2.09)	0.19		
Myocardial infarction	132 (2.9)	32 (3.1)	16 (3.0)	1.04 (0.71-1.53)	0.83			1.02 (0.61-1.71)	0.94			0.98 (0.54-1.79)	0.95		
Recurrent TV-MI	78 (1.7)	20 (1.9)	9 (1.7)	1.10 (0.67-1.80)	0.70			0.97 (0.49-1.93)	0.93			0.88 (0.40-1.93)	0.75		
Any revascularisation	292 (6.5)	79 (7.6)	31 (5.9)	1.17 (0.91-1.50)	0.22			0.89 (0.61-1.29)	0.54			0.76 (0.50-1.15)	0.20		
TLR	136	39	18 (3.4)	1.24	0.2			1.12 (0.68-	0.66			0.90 (0.52-	0.72		

	(3.0)	(3.8)		(0.87-1.77)	4			1.83)				1.58)			
TVR	185 (4.1)	54 (5.2)	21 (4.0)	1.26 (0.93-1.71)	0.13			0.96 (0.61-1.50)	0.85			0.76 (0.46-1.26)	0.28		
Non-target vessel revascularisation	148 (3.3)	37 (3.6)	16 (3.1)	1.08 (0.75-1.55)	0.68			0.91 (0.54-1.52)	0.72			0.84 (0.47-1.52)	0.57		
Stent thrombosis (definite)	63 (1.3)	13 (1.2)	8 (1.5)	0.89 (0.49-1.61)	0.69			1.07 (0.51-2.22)	0.87			1.20 (0.50-2.90)	0.68		
early (≤30 days)	52 (1.1)	6 (0.6)	7 (1.3)	0.50 (0.21-1.15)	0.10			1.12 (0.51-2.47)	0.77			2.27 (0.76-6.74)	0.14		
late (31 - 365 days)	11 (0.2)	7 (0.7)	1 (0.2)	2.74 (1.06-7.07)	0.04			0.78 (0.10-6.01)	0.81			0.28 (0.03-2.30)	0.24		
Stroke	72 (1.6)	11 (1.0)	5 (0.9)	0.66 (0.35-1.24)	0.20			0.58 (0.24-1.45)	0.25			0.89 (0.31-2.56)	0.83		
BARC 3 or 5 bleeding	171 (3.6)	51 (4.8)	26 (4.6)	1.28 (0.94-1.75)	0.12			1.28 (0.84-1.93)	0.25			1.00 (0.62-1.60)	0.99		

Table legend: BARC: bleeding academic research consortium; MI: myocardial infarction; TV-MI: target vessel myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation.

FIGURE 1

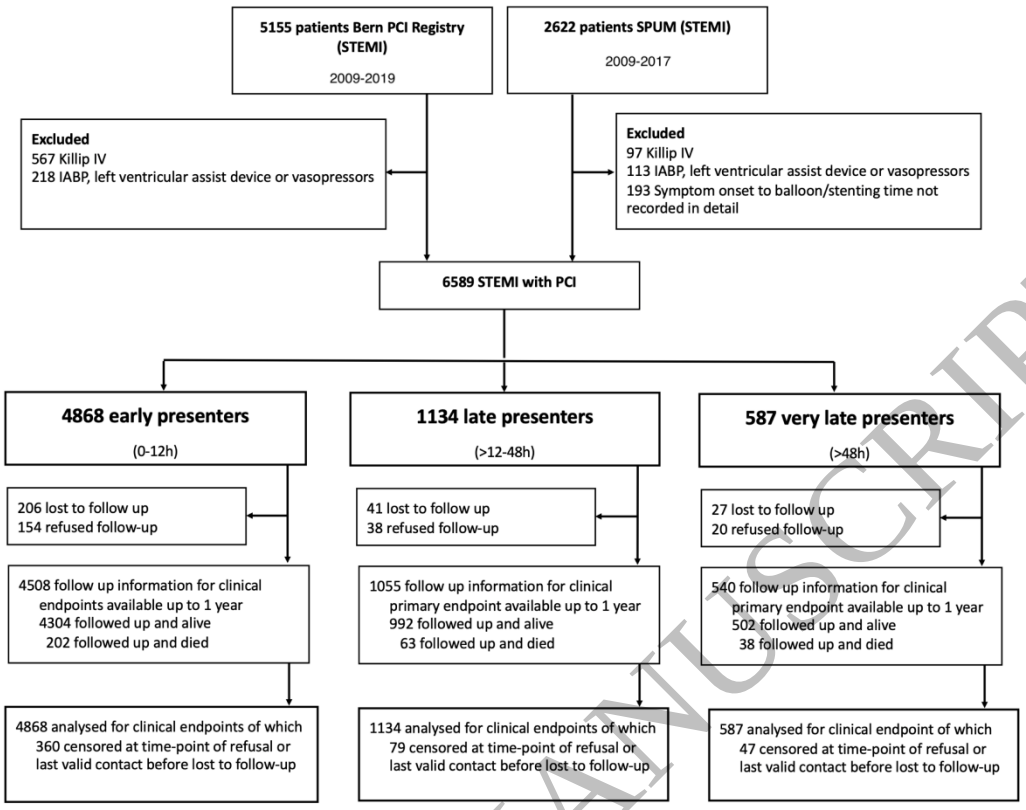


FIGURE 2

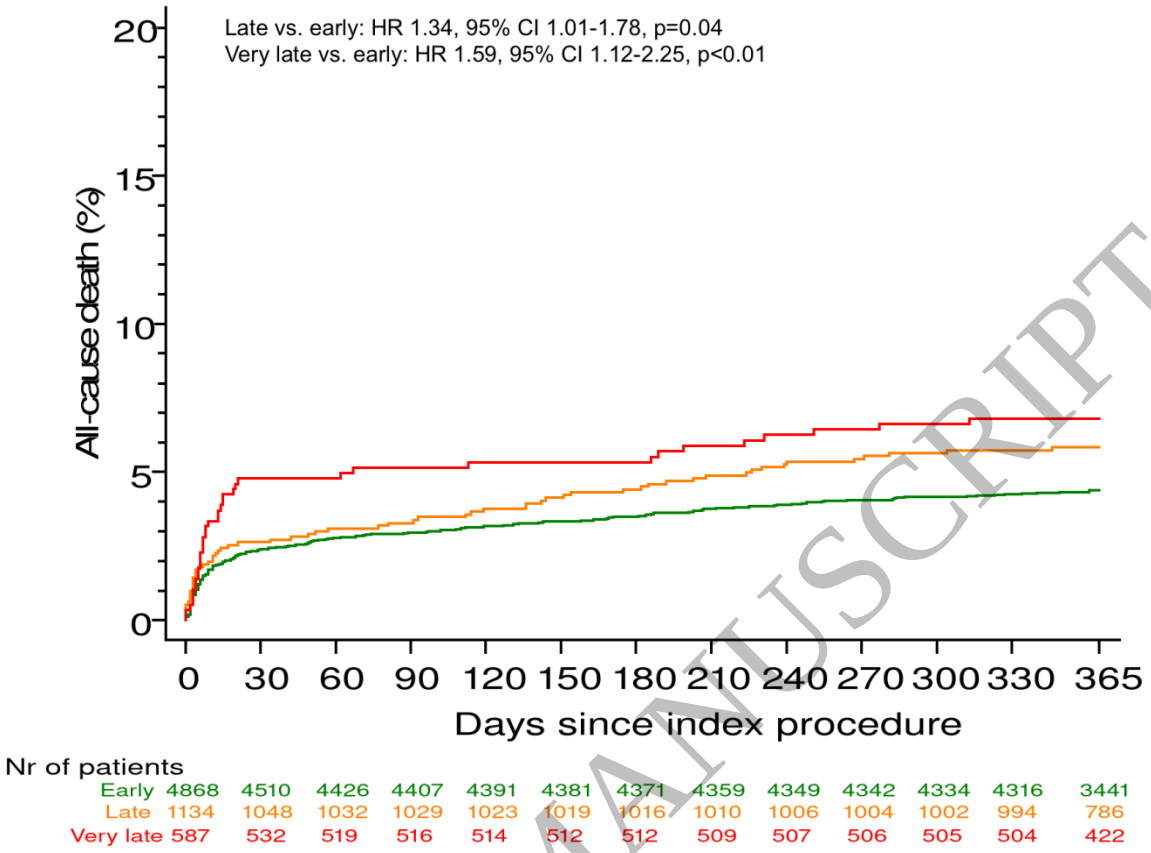
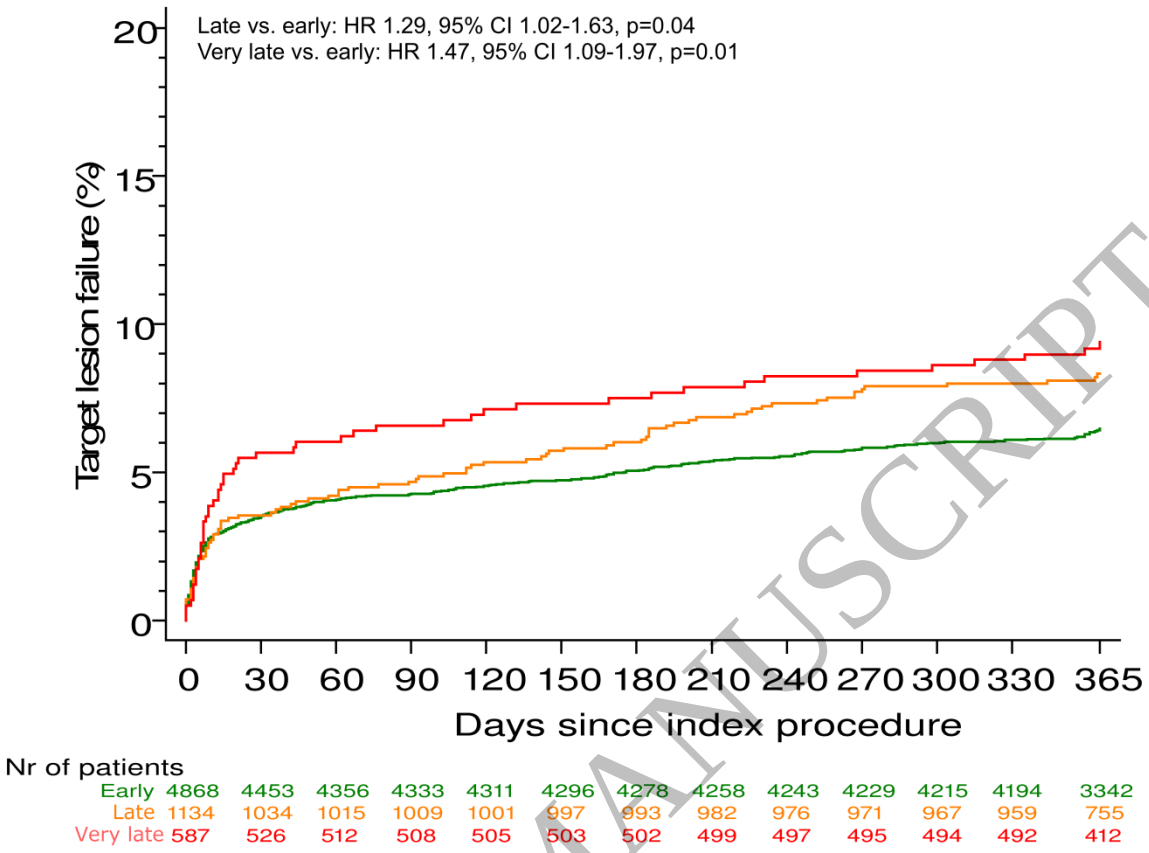
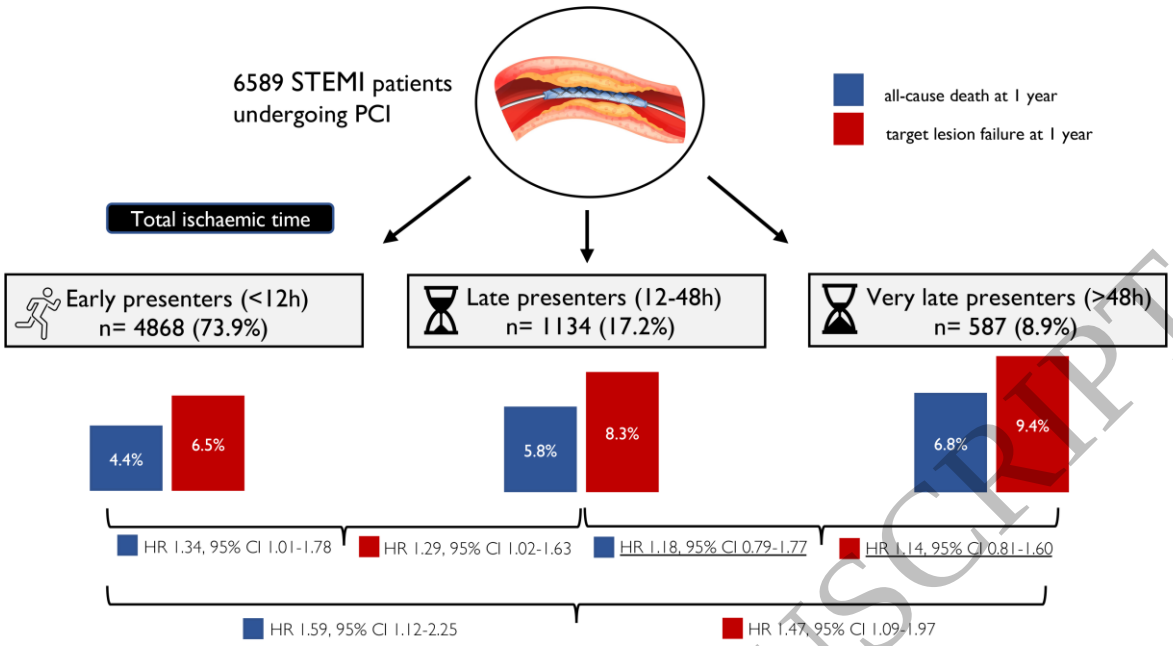


FIGURE 3





Graphical Abstratc
160x111 mm (1.8 x DPI)