Timing of coronary angiography in patients with non-ST-elevation acute coronary syndrome: long-term clinical outcomes from the nationwide SWEDEHEART registry

Kai M. Eggers[1]*, MD, PhD; Stefan K. James[1], MD, PhD; Tomas Jernberg[2], MD, PhD; Bertil Lindahl[1], MD, PhD

1. Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; 2. Department of Clinical Sciences, Cardiology, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00982

Abstract

Background: Current guidelines stress the importance of early invasive assessment of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS), in particular those at high risk. However, supporting scientific evidence is limited.

Aims: We aimed to investigate the prognostic impact of the timing of coronary angiography in a large cohort of NSTE-ACS patients.

Methods: We performed a retrospective analysis including 34,666 NSTE-ACS patients registered from 2013 to 2018 in the SWEDEHEART registry. The prognostic implications of the timing of coronary angiography on a continuous scale and within <24 vs 24-72 hours were assessed using Cox regression analyses.

Results: The median time interval from admission to invasive assessment was 32.8 (25th, 75th percentiles 20.4-63.8) hours. There was no apparent time window within 96 hours from admission that provided prognostic benefit. Coronary angiography within 24-72 hours (vs <24 hours) was not associated with worse outcome overall (all-cause mortality: hazard ratio 1.01, 95% confidence interval [CI] 0.92-1.11; major adverse events: hazard ratio 1.04, 95% CI: 0.98-1.12). Interaction analyses indicated a greater relative benefit of coronary angiography <24 hours in some lower-risk groups (women, non-diabetics, patients with minor troponin elevation) but neutral effects in higher-risk groups (defined by age or the GRACE 2.0 score).

Conclusions: These Swedish data do not provide support for an early invasive strategy in NSTE-ACS, especially in high-risk patients. Our results suggest that the timing of invasive assessment should rather be based on individualised decisions integrating symptoms and risk panorama than on strictly defined time intervals.

Corresponding author: Department of Medical Sciences, Cardiology, Uppsala University, Dag Hammarskjölds Väg 38, 751 85 Uppsala, Sweden. E-mail: kai.eggers@ucr.uu.se

Abbreviations

GRACE   Global Registry of Acute Coronary Events
MAE   major adverse event
MI   myocardial infarction
NSTE-ACS   non-ST-elevation acute coronary syndrome
NSTEMI   non-ST-elevation myocardial infarction
SWEDEHEART   Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

Introduction

Current guidelines recommend early invasive assessment in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with the intention to identify and treat critical coronary lesions[1,2]. An invasive approach has consistently been shown to reduce the occurrence of ischaemic outcomes, particularly in patients at high risk[3-5]. Immediate (<2 hours) coronary angiography is recommended in haemodynamically unstable patients, those with cardiogenic shock, and those with other life-threatening complications or refractory/recurrent angina. High-risk patients, defined by dynamic ST-changes, and patients with a high Global Registry of Acute Coronary Events (GRACE) score or cardiac troponin changes should be investigated within <24 hours[1,2]. The 2020 European guidelines have extended this recommendation to all patients with non-ST-elevation myocardial infarction (NSTEMI)[1]. In the remaining NSTE-ACS patients, selective invasive assessment, e.g., within 24-72 hours, is regarded as optimal[1,2].

These recommendations are based on conceptual considerations and the results from the TIMACS and VERDICT studies, which randomised moderately sized NSTE-ACS cohorts to early (within 12-24 hours) or delayed (after ≥36 hours[6]; within 48-72 hours[7]) angiography. Support for these recommendations comes from *post hoc* analyses of clinical trials[8,9] and meta-analyses[10-12]. Prospective studies were, however, underpowered with respect to single, clinically relevant outcomes. TIMACS, moreover, was published more than a decade ago, and real-world patients may differ considerably to NSTE-ACS patients recruited in randomised controlled trials in terms of higher age and higher prevalence of comorbidities.

Previous results from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry demonstrated that percutaneous coronary intervention is associated with prognostic benefit regardless of when it is performed during the first 3 days of hospitalisation[13]. That study was based on NSTEMI patients admitted between 2006 and 2013. In the present investigation, we extend these data to a more contemporary cohort of NSTE-ACS patients, hospitalised from 2013 to 2018, with granular information on the timing of the invasive assessment. Our aims were to investigate the prognostic implications of the time to coronary angiography, both overall, in predefined at-risk cohorts, and with the intention of identifying a time window that provides particular benefits regarding outcome.

Methods

STUDY POPULATION

This study is part of the TOTAL-AMI (Tailoring Of Treatment in All comers with Acute Myocardial Infarction) project. The primary aim of TOTAL-AMI is to investigate the mechanisms and implications of different myocardial infarction (MI) subtypes[14] and of comorbidities (e.g., chronic obstructive pulmonary disease, atrial fibrillation, renal dysfunction) in MI. TOTAL-AMI uses data from SWEDEHEART, which is a registry aggregating information on consecutive patients admitted to Swedish coronary care units or other specialised facilities because of suspected acute coronary syndrome. SWEDEHEART provides nationwide coverage and lifelong follow-up. Upon hospital admission, patients receive information about the registry, have the right to deny participation and have their data erased upon request. Written informed consent is not required according to Swedish law.

For the present analysis, all NSTE-ACS patients hospitalised between January 2013 and May 2018 were considered. Only first-time admissions during the study period were counted. The diagnoses of unstable angina and NSTEMI had been set by the attending clinicians at each respective hospital. Since decisions regarding the performance and timing of coronary angiography might have been affected by the presence of specific comorbidities, patients with dementia, haemoglobin <80 g/L and an estimated glomerular filtration rate (CKD-EPI equation) <20 mL/min/1.73 m^2 were excluded. Moreover, we excluded patients presenting with cardiogenic shock, cardiac arrest or following prehospital resuscitation since immediate invasive assessment may be warranted in these groups. Finally, patients with outlying values for the time to coronary angiography[15] were excluded.

All data were pseudonymised before the statistical analyses. The study was conducted according to the principles of the 1975 Declaration of Helsinki and was approved by the Regional Ethical Review Board in Stockholm (2012/60-31/2).

TIMING OF CORONARY ANGIOGRAPHY

Time to coronary angiography was defined as the time interval from admission to the emergency department or coronary care unit, whichever came first, to arterial puncture at the cath lab. The time interval is given in the dataset in minutes and was considered both on a continuous scale and categorised by time intervals focusing on 24 hours as the threshold[1,2].

PROGNOSTIC EVALUATION

Information on patient outcome was obtained by merging SWEDEHEART with data from the Swedish Population registry (data on the vital status of all Swedish residents) and the mandatory Swedish Patient Registry (hospitalisation dates and discharge diagnoses based on International Classification of Diseases, 10th revision, Clinical Modification [ICD-10-CM] codes), the latter held by the Swedish Board of Health and Welfare. The main outcomes considered for this analysis were all-cause mortality with available data until May 2018, and major adverse events (MAE)

with available data until December 2017. MAE was defined as the composite of all-cause mortality, hospitalisation for MI (ICD-10-CM I21), heart failure (ICD-10-CM I50) or ischaemic stroke (ICD-10-CM I63). During the first 30 days after the index hospitalisation, it is not possible to separate a new MI from the index MI in the patient registry. Therefore, only MI occurring at least 30 days after the index hospitalisation were counted to avoid "contamination" from the index event. Differences in follow-up periods are due to a time lag for the patient registry to process hospitalisation data and make them accessible. As a safety outcome, we also assessed bleeding, defined as major bleeding during the index hospitalisation or readmission with a bleeding-related primary diagnosis **(Supplementary Table 1)** until December 2017.

STATISTICAL ANALYSIS

We used the following approach to investigate the prognostic implications of the time to coronary angiography. First, Cox regressions were conducted, modelling time as a continuous variable and per 24-hour intervals. The intention of this part of the analysis was to use an approach that was strictly data driven. Analyses were adjusted for admission year, hospital, time and date of admission (outside office hours, on weekends or public holidays), age, sex, current smoking, hypertension, diabetes mellitus, hyperlipidaemia, previous MI, previous coronary revascularisation, previous heart failure, previous stroke, ST-segment changes on the admission electrocardiogram (ECG), atrial fibrillation on the admission ECG, estimated glomerular filtration rate, chronic obstructive pulmonary disease, previous or present cancer and peripheral vascular disease. Due to positive skew, time was ln-transformed before being entered into the analyses, when appropriate. The proportional hazard assumptions had been checked by visual inspection of the log-cumulative hazard plots and were found to be satisfied. Risk estimates are described as hazard ratios (HR) with 95% confidence intervals (CI).

Next, we intended to more directly address the recommendations issued by current guidelines[12]. For this purpose, we compared outcomes associated with coronary angiography at <24 vs 24-72 hours. Patients who had died within 72 hours from admission were censored in order to avoid immortal time bias. As a sensitivity analysis, this step was repeated in 1:1 propensity score-matched patients based on the same set of covariates as used for the Cox regressions. Secondary subgroup analyses with interaction testing were conducted in cohorts defined by sex, age tertiles, diabetes, cardiac troponin concentrations (≤99th percentile, and divided by the median ratio to the 99th percentile for those with concentrations >99th percentile), and low, intermediate or high risk according to the GRACE 2.0 score[16,17]. Kaplan-Meier curves were constructed to visualise the cumulative incidence of all-cause mortality and MAE in selected subgroups.

Continuous variables are reported as medians with 25th and 75th percentiles. Categorical variables are expressed as frequencies and percentages. In all tests, a two-sided p-value <0.05 without correction for multiple testing was considered significant. The software

packages SPSS 27.0 (SPSS Inc.) and R version 4.0.5 (R Foundation for Statistical Computing) were used for the analyses.

Results

In total 44,366 NSTE-ACS patients had been registered in SWEDEHEART between January 2013 and May 2018. Information on the time from admission to coronary angiography was available in 39,571 patients. Following exclusions **(Supplementary Figure 1)**, 34,666 patients formed the final study cohort. The median age was 70 (62-77 [25th, 75th percentiles]) years and 23,906 (69.0%) patients were male. The median time interval to angiography was 32.8 (20.4-63.8) hours. In total, 25,579 (73.8%) patients underwent in-hospital coronary revascularisation and 27,688 (79.9%) patients were discharged with a diagnosis of NSTEMI. Further information on clinical characteristics is presented in **Table 1**.

Over a median follow-up of 2.4 (1.2-3.8) years, 3,078 (8.9%) patients died. The median follow-up regarding MAE was 2.0 (0.8-3.3) years. During this time, 3,027 (9.3%) patients died, 1,663 (4.8%) patients suffered an MI, 1,551 (4.5%) patients were readmitted due to heart failure and 569 (1.6%) patients were readmitted due to stroke. In total 5,231 (15.1%) patients had an MAE. A bleeding event occurred in 1,179 (3.4%) patients.

Crude rates of all-cause mortality and MAE increased across greater 24-hour intervals to coronary angiography **(Supplementary Figure 2)**. In a fully adjusted Cox model, a 1-standard deviation increase in the ln-transformed time interval was associated with 4% risk increases regarding both all-cause mortality and MAE at borderline levels of significance **(Table 2)**. The association with MAE was driven by a significant 11% risk increase regarding heart failure hospitalisations. The associations of the time interval with MI, stroke or bleeding were neutral. Using NSTE-ACS patients assessed at <24 hours as reference, delayed coronary angiography exhibited similar associations with all-cause mortality and MAE, unless performed late, i.e., after 96 hours **(Figure 1)**. Patients assessed late were older, more often female, had more cardiovascular comorbidities but also less often had troponin elevation **(Supplementary Table 2)**.

In our next step, we investigated outcomes in 3-day survivors who underwent coronary angiography within <24 vs 24-72 hours (n=27,888). Patients assessed within <24 hours tended to be younger, were more often male, had a lower prevalence of cardiovascular risk factors and comorbidities, and more often had troponin elevation and lower GRACE 2.0 scores. Moreover, crude event rates were lower in this cohort **(Supplementary Table 3)**. However, compared to these patients, those assessed within 24-72 hours had similar risks of all-cause mortality or MAE upon multivariable adjustment **(Table 3, Central illustration)**. We noted a 12% increased risk of MI, albeit at a borderline level of significance (HR 1.12, 95% CI: 1.00-1.26; p=0.052). The adjusted risks for the other assessed outcomes, including bleeding, did not differ statistically between both cohorts (data not shown). The sensitivity analysis based on 1:1 propensity score-matched patients provided similar

Table 1. Clinical characteristics and treatments.

	Total cohort (n=34,666)	Missing values
Risk factors		
Age (years)	70 (62-77)	–
Men	23,906 (69.0%)	–
Current smoking	6,224 (18.0%)	–
Hypertension	19,605 (56.6%)	–
Diabetes	7,928 (22.9%)	–
Hyperlipidaemia	11,530 (33.3%)	30
Body mass index (kg/m^2)	26.9 (24.5-30.1)	858
eGFR (mL/min/1.73m^2)	80.2 (64.3-91.3)	–
Comorbidities		
Previous MI	6,245 (18.0%)	–
Previous PCI/CABG	6,354 (18.3%)	–
Heart failure	1,858 (5.4%)	–
Previous stroke	2,042 (5.9%)	–
Peripheral artery disease	1,687 (4.9%)	–
COPD	2,390 (6.9%)	–
Previous/present cancer	1,001 (2.9%)	–
Angiographic findings		356
Non-conclusive	34 (0.1%)	–
Normal/non-obstructive	3,891 (11.3%)	–
1- or 2-vessel disease	20,657 (60.2%)	–
3-vessel disease/left main	9,728 (28.4%)	–
Clinical findings		
Atrial fibrillation	2,568 (7.4%)	1
ST-depression	9,749 (28.1%)	5
cTn >99th percentile	31,579 (92.2%)	424
GRACE score		
Low risk	12,955 (37.4%)	–
Intermediate risk	13,924 (40.2%)	–
High risk	7,787 (22.5%)	–
Diagnosis		
Unstable angina	6,978 (20.1%)	–
NSTEMI	27,688 (79.9%)	–
Invasive treatment		
No treatment	9,087 (26.2%)	–
PCI	22,805 (65.8%)	–
CABG	2,774 (8.0%)	–
Medications at discharge*		
Aspirin	32,048 (93.1%)	24
P2Y$_{12}$ blockers	28,525 (82.9%)	24
Anticoagulants	2,852 (8.3%)	24
Beta blockers	29,214 (84.9%)	24
RAAS-inhibitors	27,108 (78.8%)	24
Statins	32,512 (94.5%)	24

* Assessed in in-hospital survivors: n=34,442. CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; cTn: cardiac troponin; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RAAS: renin-angiotensin-aldosterone-system

Table 2. Association of the time interval to coronary angiography with adverse outcome.

	n (total)	n (events)	HR (95%CI)	*p*-value
All-cause mortality	34,394	3,046	1.04 (1.00-1.08)	0.069
Major adverse event	32,273	5,181	1.04 (1.00-1.07)	0.031
Myocardial infarction	29,091	1,652	1.01 (0.96-1.07)	0.742
Heart failure	29,830	1,530	1.11 (1.05-1.18)	<0.001
Stroke	29,372	565	1.01 (0.92-1.11)	0.858
Bleeding	29,550	1,163	1.03 (0.97-1.10)	0.356

HR refers to 1-SD increase in the ln-transformed time interval (per 60-minute intervals) from admission. Adjusted for admission year, hospital, time and date of admission, age, sex, current smoking, hypertension, diabetes, hyperlipidaemia, previous myocardial infarction, previous coronary revascularisation, congestive heart failure, previous stroke, ST-changes upon admission, atrial fibrillation upon admission, estimated glomerular filtration rate, chronic obstructive pulmonary disease, previous or present cancer and peripheral vascular disease. CI: confidence interval; HR: hazard ratio; SD: standard deviation

results with respect to all-cause mortality and MAE, as indicated by largely overlapping CI compared to the Cox models **(Table 3)**. Secondary subgroup analyses with interaction testing indicated greater all-cause mortality risk associated with coronary angiography within 24-72 hours in some lower-risk cohorts, i.e., patients with minor troponin elevation and non-diabetics **(Central illustration)**. For women, coronary angiography within 24-72 hours was associated with increased risk of MAE. The cumulative incidence of adverse outcome in these cohorts is presented in the **Supplementary Figures 3A-Supplementary Figure 3C**. The interactions within the other subgroups were neutral.
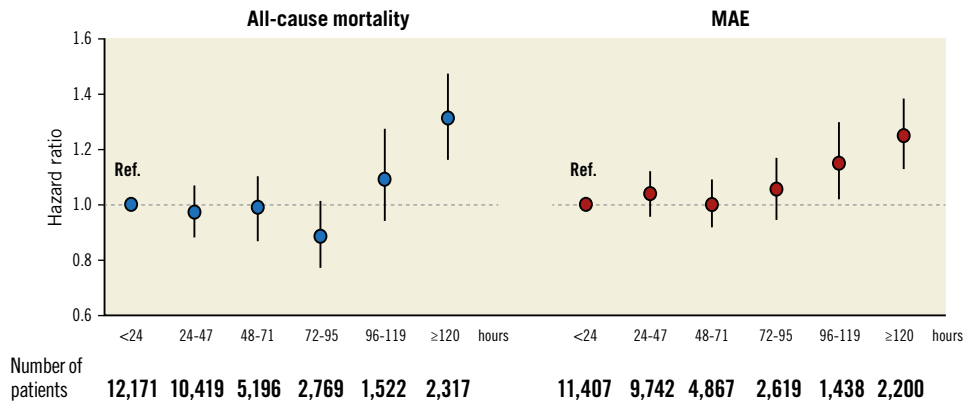
Table 3. Association of coronary angiography within 24-72 hours (vs <24 hours) with adverse outcome in 3-day survivors.

	n	HR (95% CI)	*p*-value
Without PS-matching			
All-cause mortality	27,690	1.01 (0.92-1.11)	0.821
Major adverse event	25,915	1.04 (0.98-1.12)	0.218
With 1:1 PS-matching			
All-cause mortality	19,450	1.11 (1.00-1.23)	0.059
Major adverse event	18,212	1.09 (1.01-1.18)	0.027

Adjusted for admission year, hospital, time and date of admission, age, sex, current smoking, hypertension, diabetes, hyperlipidaemia, previous myocardial infarction, previous coronary revascularisation, congestive heart failure, previous stroke, ST-changes upon admission, atrial fibrillation upon admission, estimated glomerular filtration rate, chronic obstructive pulmonary disease, previous or present cancer and peripheral vascular disease. CI: confidence interval; HR: hazard ratio; PS: propensity score

Discussion

It is well established that early coronary reperfusion improves outcome in ST-elevation MI where the infarct-related artery is usually occluded. However, the optimal timing of coronary angiography

Figure 1. *Association of increasing time intervals to coronary angiography with adverse outcome. Adjusted for admission year, hospital, time and date of admission, age, sex, current smoking, hypertension, diabetes, hyperlipidaemia, previous myocardial infarction, previous coronary revascularisation, congestive heart failure, previous stroke, ST-changes upon admission, atrial fibrillation upon admission, estimated glomerular filtration rate, chronic obstructive pulmonary disease, previous or present cancer and peripheral vascular disease. MAE: major adverse event; Ref: reference.*

EuroIntervention

CENTRAL ILLUSTRATION Association of coronary angiography within 24-72 hours (vs <24 hours) with adverse outcome in 3-day survivors overall and in subgroups.

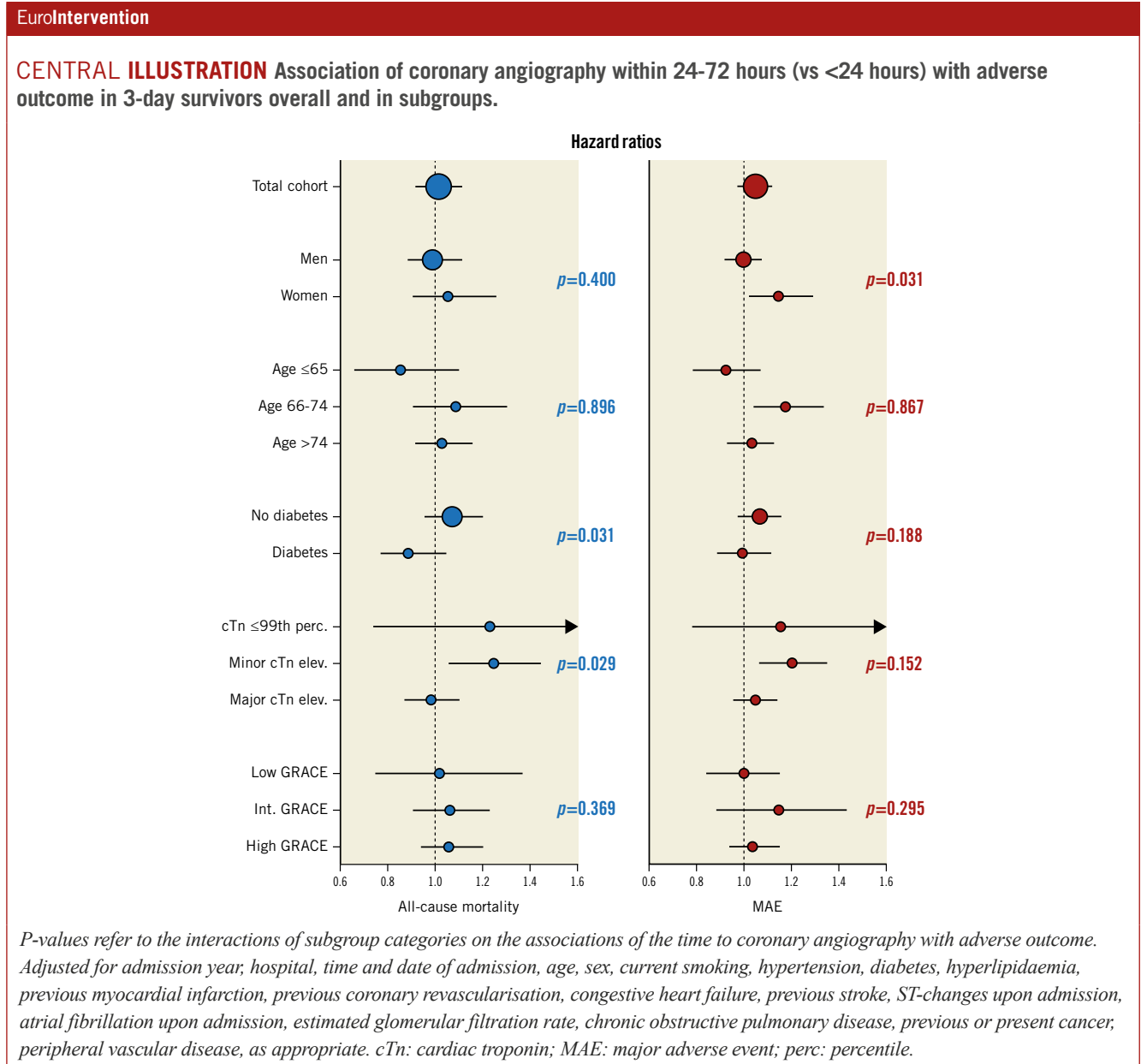*P-values refer to the interactions of subgroup categories on the associations of the time to coronary angiography with adverse outcome. Adjusted for admission year, hospital, time and date of admission, age, sex, current smoking, hypertension, diabetes, hyperlipidaemia, previous myocardial infarction, previous coronary revascularisation, congestive heart failure, previous stroke, ST-changes upon admission, atrial fibrillation upon admission, estimated glomerular filtration rate, chronic obstructive pulmonary disease, previous or present cancer, peripheral vascular disease, as appropriate. cTn: cardiac troponin; MAE: major adverse event; perc: percentile.*

is less clearly defined in NSTE-ACS, a condition characterised by sudden plaque disruption with subocclusive thrombus formation and distal embolisation of thrombotic debris.

Our analysis investigating a large cohort of NSTE-ACS patients provides new evidence in this regard. A longer time interval to coronary angiography was associated with a 4% increased risk of all-cause mortality and MAE. These risk gradients were driven by patients assessed late, i.e., after 96 hours, being characterised by a greater burden of comorbidities. Accordingly, clinicians may have been primarily inclined to target these patients for a conservative approach, thus delaying time to angiography. Interestingly, patients investigated after 96 hours less often had elevated troponin concentrations and, for this reason, may not have been considered as being in need of early invasive assessment. Importantly however, we were unable to identify a time window within the first 96 hours from admission that provided a particular prognostic benefit.

The rationale behind early invasive assessment in NSTE-ACS is the intention to identify and treat critical coronary lesions early in the disease course. This may limit infarct size and prevent recurrent ischaemia, thereby promoting clinical stabilisation, improving the well-being of the individual patient and facilitating earlier discharge. Scientific evidence on the prognostic implications of early coronary angiography in NSTE-ACS is, however, conflicting. Some studies reported neutral results regarding hard outcomes[6,7,18,19], whereas others provided evidence supporting early[8,9,13] or delayed[20] assessment. Based on subgroup analyses from randomised trials and meta-analyses[6,7,10-12], and conceptual considerations, current European and US guidelines recommend coronary angiography within <24 hours in all patients with a perceived increased risk (i.e., defined by intercurrent ST-changes or GRACE score >140 using a previous iteration of this tool[1,2]), provided there is an absence of high-risk features such as refractory/recurrent ischaemia or haemodynamic instability. US guidelines also advocate early assessment in patients with dynamic troponin changes[2], whereas recently published ESC guidelines have extended this recommendation to all patients with NSTEMI[1].

Our data provide a differentiated perspective on this important topic. Overall, early coronary angiography was neither associated with improved outcome nor with harm. Risk reductions were noted in some lower-risk cohorts, i.e., patients with minor troponin elevation and also women. Even for non-diabetics, interaction analysis indicated a greater relative benefit with early assessment. However, we found no evidence indicating that angiography within <24 hours might be associated with better outcome in high-risk cohorts. This was not explained by an excess in bleeding risk in the case of delayed assessment.

These data challenge the necessity of early coronary angiography in high-risk patients, for example those with a GRACE score >140[2]. There has been ambiguity on this matter since this recommendation is only based on subgroup analyses from TIMACS and VERDICT[6,7]. Recently published real-world data provided no supporting evidence[19], and the optimal timing in relation to the GRACE 2.0 score remains debated[21,22]. The ongoing RapidNSTEMI trial (ClinicalTrials.gov identifier: NCT03707314) will hopefully provide clarification. The lack of prognostic benefit by earlier coronary angiography in patients with major troponin elevation was unexpected since the magnitude of troponin release is associated with the severity of coronary lesions in NSTE-ACS[23]. Further mechanistic analyses are needed to study the interrelationship of invasive assessment, its timing, troponin concentrations and outcome. There is also a need for further in-depth exploration of the prognostic implications of the timing of coronary angiography in relation to sex.

Strengths and limitations

Our study has several strengths. The investigated cohort was large and had longer follow-up compared to those assessed in previous trials and meta-analyses[6-12,18-20]. SWEDEHEART is a real-world registry covering all hospitalisations in Sweden due to suspected acute coronary syndrome. This offers the advantage of investigating outcomes and subcohorts that may be underrepresented in randomised controlled trials. There are also some limitations that need to be considered. Although all hospitals participating in SWEDEHEART are annually monitored, the data cannot be of the same quality as in a prospective study. However, the accuracy of the data and the registry have been found to be high[24]. Our results may have been affected by unmeasured confounders. For example, SWEDEHEART does not capture all data surrounding the timing of invasive assessment. Decisions towards an earlier approach may have been triggered in some patients by signs of coronary instability, e.g., recurrence of ischaemic symptoms or intercurrent ECG changes not documented in SWEDEHEART. Timing decisions could also have been delayed by logistical problems such as long transportation distances or limitations in available hospital beds, by patient refusal, comorbidities or frailty. This could have contributed to the high event rates in patients assessed very late. We acknowledge that the timing of coronary angiography most likely has different prognostic implications in type 1 and type 2 MI, the latter often characterised by stable coronary lesions. We were not able to consider this issue specifically since data on the MI type is incomplete in SWEDEHEART. MI occurring early (<30 days) after hospital discharge could not be studied since such information is not available in the Swedish Patient Registry. However, previous studies found no evidence of increased MI risk within 15-30 days in NSTE-ACS patients undergoing early coronary angiography[6,7]. We lack information on periprocedural MI and softer endpoints such as recurrent ischaemia after discharge. We did not account for the prognostic effects of methodological improvements during the observation period, e.g., the use of newer-generation drug-eluting stents or different regimes of antiplatelet therapy. Finally, caution is warranted when inferring causality on the observed associations.

Conclusions

Whether or not patients with NSTE-ACS may benefit from early invasive assessment has been a matter of debate for a long time. Our

findings demonstrate that an invasive approach within <24 hours is not associated with improved outcome apart from for some lower-risk groups in whom there were indications of risk reduction. Therefore, the timing of invasive assessment should be based rather on individualised decisions integrating symptoms, risk panorama and available resources than on strictly defined time intervals.

Impact on daily practice

The present study demonstrates that early invasive assessment has limited impact on outcome in patients with NSTE-ACS. Earlier coronary angiography, e.g., within <24 hours, may expedite patient management towards earlier discharge but places logistical demands on the healthcare system. A delayed approach seems to be at least as safe provided there is clinical stability. Our data suggest that invasive assessment should be based on individualised decisions integrating symptoms, risk panorama and available resources rather than on strictly defined time intervals.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42:1289-367.

2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64:e139-228.

3. Mehta SR, Cannon CP, Fox KA, Wallentin L, Boden WE, Spacek R, Widimsky P, McCullough PA, Hunt D, Braunwald E, Yusuf S. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA.* 2005;293:2908-17.

4. Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, Lagerqvist B, Wallentin L; FIR Collaboration. 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. *J Am Coll Cardiol.* 2010;55:2435-445.

5. Fanning JP, Nyong J, Scott IA, Aroney CN, Walters DL. Routine invasive strategies versus selective invasive strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. *Cochrane Database Syst Rev.* 2016;2016:CD004815.

6. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S; TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med.* 2009; 360:2165-75.

7. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, Holmvang L, Helqvist S, Jørgensen E, Galatius S, Pedersen F, Bang L, Saunamaki K, Clemmensen P, Linde JJ, Heitmann M, Wendelboe Nielsen O, Raymond IE, Kristiansen OP, Svendsen IH, Bech J, Dominguez Vall-Lamora MH, Kragelund C, Hansen TF, Dahlgaard Hove J, Jørgensen T, Fornitz GG, Steffensen R, Jurlander B, Abdulla J, Lyngbæk S, Elming H, Therkelsen SK, Abildgaard U, Jensen JS, Gislason G, Køber LV, Engstrøm T. Early Versus Standard Care Invasive Examination and Treatment of Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. *Circulation.* 2018;138:2741-750.

8. Tricoci P, Lokhnygina Y, Berdan LG, Steinhubl SR, Gulba DC, White HD, Kleiman NS, Aylward PE, Langer A, Califf RM, Ferguson JJ, Antman EM, Newby LK, Harrington RA, Goodman SG, Mahaffey KW. Time to coronary angiography and outcomes among patients with high-risk non ST-segment elevation acute coronary syndromes: results from the SYNERGY trial. *Circulation.* 2007;116:2669-77.

9. Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, Stuckey T, Tcheng JE, Mehran R, Lansky AJ, Grines CL, Stone GW. Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage stategY) trial. *J Am Coll Cardiol.* 2010;55:1416-24.

10. Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, Neumann FJ, Kastrati A, Sciahbasi A, Reuter PG, Lapostolle F, Milosevic A, Stankovic G, Milasinovic D, Vonthein R, Desch S, Thiele H. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *Lancet.* 2017;390:737-46.

11. Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Chahine A, Haykal T, Kanugula AK, Bachuwa G, Alkotob ML, Bhatt DL. Meta-analysis of optimal timing of coronary intervention in non-ST-elevation acute coronary syndrome. *Catheter Cardiovasc Interv.* 2020;95:185-93.

12. Awan A, Ogunti R, Fatima U, Gonzalez H, Ganta N, Rizwan M, Mahajan A, Opoku-Asare I. Timing of Percutaneous Coronary Intervention in Non-ST Elevation Acute Coronary Syndrome - Meta-Analysis and Systematic Review of Literature. *Cardiovasc Revasc Med.* 2020;21:1398-404.

13. Lindholm D, Alfredsson J, Angerås O, Böhm F, Calais F, Koul S, Lagerqvist B, Renlund H, Sarno G, Varenhorst C. Timing of percutaneous coronary intervention in patients with non-ST-elevation myocardial infarction: a SWEDEHEART study. *Eur Heart J Qual Care Clin Outcomes.* 2017;3:53-60.

14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J.* 2019;40:237-69.

15. Exploratory data analysis. 1st edition. Reading, PA, USA: Addison-Wesley; 1977.

16. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, Coste P, Monsegu J, Gabriel Steg P, Danchin N, Anderson F. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open.* 2014;4: e004425.

17. GRACE. GRACE risk table. Available at https://www.outcomes-umassmed.org/grace/grace_risk_table.aspx (accessed 5 July, 2021).

18. Damman P, van Geloven N, Wallentin L, Lagerqvist B, Fox KA, Clayton T, Pocock SJ, Hirsch A, Windhausen F, Tijssen JG, de Winter RJ. Timing of angiography with a routine invasive strategy and long-term outcomes in non-ST-segment elevation acute coronary syndrome: a collaborative analysis of individual patient data from the FRISC II (Fragmin and Fast Revascularization During Instability in Coronary Artery Disease), ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes), and RITA-3 (Intervention Versus Conservative Treatment Strategy in Patients With Unstable Angina or Non-ST Elevation Myocardial Infarction) Trials. *JACC Cardiovasc Interv.* 2012;5:191-9.

19. Mahendiran T, Nanchen D, Meier D, Gencer B, Klingenberg R, Räber L, Carballo D, Matter CM, Lüscher TF, Windecker S, Mach F, Rodondi N, Muller O, Fournier S. Optimal Timing of Invasive Coronary Angiography following NSTEMI. *J Interv Cardiol.* 2020;2020:8513257.

20. Montalescot G, Dabbous OH, Lim MJ, Flather MD, Mehta RH; Global Registry of Acute Coronary Events Investigators. Relation of timing of cardiac catheterization to outcomes in patients with non-ST-segment elevation myocardial infarction or unstable angina pectoris enrolled in the multinational global registry of acute coronary events. *Am J Cardiol.* 2005;95:1397-403.

21. Kite TA, Gershlick AH. High-risk NSTE-ACS: high time for robust data. *Eur Heart J.* 2021;42:352.

22. Jobs A, Collet JP, Thiele H. Optimal timing of invasive angiography in non-ST-segment elevation acute coronary syndromes-do we need more data? *Eur Heart J.* 2021;42:353-4.

23. Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L; FRISC II (Fast Revascularization during InStability in CAD) Investigators. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II sub-study. *J Am Coll Cardiol.* 2001;38:979-86.

24. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart.* 2010;96:1617-21.

Supplementary data

Supplementary Table 1. Discharge diagnosis codes (ICD-10-CM) considered for bleeding events.

Supplementary Table 2. Clinical characteristics, treatments and adverse outcome in relation to coronary angiography <96 hours vs ≥96 hours.

Supplementary Table 3. Clinical characteristics, treatments and adverse outcome in relation to coronary angiography <24 hours vs 24-72 hours in 3-day survivors.

Supplementary Figure 1. Study flowchart.

Supplementary Figure 2. Crude event rates in relation to time intervals to coronary angiography.

Supplementary Figure 3. Cumulative incidence of adverse outcome in relation to coronary angiography <24 hours vs 24-72 hours in 3-day survivors.

The supplementary data are published online at:
https://eurointervention.pcronline.com/
doi/10.4244/EIJ-D-21-00982

Supplementary data

Supplementary Table 1. Discharge diagnosis codes (ICD-10-CM) considered for bleeding events.

ICD-10 CM code	Diagnosis
D62	Acute post-haemorrhagic anaemia
D68.3	Haemorrhagic disorder due to circulating anticoagulants
H31.3	Choroidal haemorrhage and rupture
H35.6	Retinal haemorrhage
H43.1	Vitreous haemorrhage
H45.0	
I31.2	Haemopericardium, not elsewhere classified
I60	Non-traumatic subarachnoid haemorrhage
I61	Non-traumatic intracerebral haemorrhage
I62	Other and unspecified non-traumatic intracranial haemorrhage
I85.0	Oesophageal varices with bleeding
K22.1	Oesophageal ulcer
K22.6	Mallory-Weiss syndrome
K25	Gastric ulcer
K26	Duodenal ulcer
K27	Peptic ulcer, site unspecified
K28	Gastrojejunal ulcer
K62.5	Haemorrhage of anus and rectum
K66.1	Haemoperitoneum
K92.0	Haematemesis
K92.1	Melena
K92.2	Gastrointestinal haemorrhage, unspecified
M25.0	Haemarthrosis
N95.0	Post-menopausal bleeding
R04	Haemorrhage from respiratory passages
R31	Haematuria
R58	Haemorrhage, not elsewhere classified
S06.4	Epidural haemorrhage
S06.5	Traumatic subdural haemorrhage
S06.6	Traumatic subarachnoid haemorrhage
S06.8	Other specified intracranial injuries
T81.0	Complications of procedures, not elsewhere classified (if recorded as bleeding)

Supplementary Table 2. Clinical characteristics, treatments and adverse outcome in relation to coronary angiography <96 hours vs ≥96 hours.
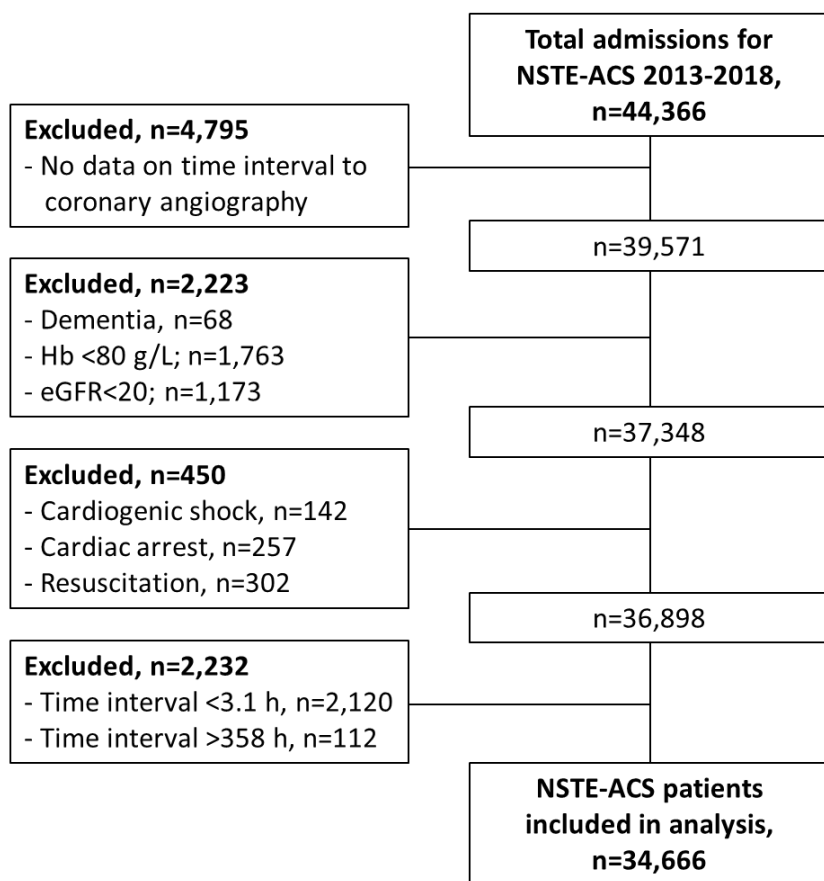
	<96 hours (n=30,784)	≥96 hours (n=3,882)	Total cohort (n=34,666)	Missing values
Risk factors				
Age (years)	69 (61-76)	73 (65-80)	70 (62-77)	-
Men	21,366 (69.4%)	2,540 (65.4%)	23,906 (69.0%)	-
Current smoking	5,660 (18.4%)	564 (14.5%)	6,224 (18.0%)	-
Hypertension	17,229 (56.0%)	2,376 (61.2%)	19,605 (56.6%)	-
Diabetes	6,854 (22.3%)	1,075 (27.7%)	7,928 (22.9%)	-
Hyperlipidaemia	10,027 (32.6%)	1,503 (38.7%)	11,530 (33.3%)	30
Body mass index (kg/m^2)	27.0 (24.5-30.1)	26.7 (24.1-30.0)	26.9 (24.5-30.1)	858
eGFR (mL/min/1.73m^2)	80.8 (65.3-91.7)	74.0 (56.5-87.7)	80.2 (64.3-91.3)	-
Comorbidities				
Previous MI	5,325 (17.3%)	920 (23.7%)	6,245 (18.0%)	-
Previous PCI/CABG	5,485 (17.8%)	869 (22.4%)	6,354 (18.3%)	-
Heart failure	1,508 (4.9%)	350 (9.0%)	1,858 (5.4%)	-
Previous stroke	1,696 (5.5%)	346 (8.9%)	2,042 (5.9%)	-
Peripheral artery disease	1,398 (4.5%)	289 (7.4%)	1,687 (4.9%)	-
COPD	1,987 (6.5%)	403 (10.4%)	2,390 (6.9%)	-
Previous/present cancer	817 (2.7%)	184 (4.7%)	1,001 (2.9%)	-
Angiographic findings				267
Non-conclusive	30 (0.1%)	4 (0.1%)	34 (0.1%)	
Normal/non-obstructive	3,365 (11.0%)	526 (13.8%)	3,891 (11.3%)	
1- or 2-vessel disease	18,697 (61.3%)	1,960 (51.2%)	20,657 (60.2%)	
3-vessel disease/left main	8,393 (27.5%)	1,335 (34.9%)	9,728 (28.4%)	
Clinical findings				
Atrial fibrillation	2,101 (6.8%)	467 (12.0%)	2,568 (7.4%)	1
ST-depression	8,776 (28.5%)	973 (25.1%)	9,749 (28.1%)	5
cTn >99th percentile	28,141 (92.6%)	3,438 (89.3%)	31,579 (92.2%)	424
GRACE score				
· Low-risk	11,937 (38.8%)	1,018 (26.2%)	12,955 (37.4%)	-
· Intermediate-risk	12,415 (40.3%)	1,509 (38.9%)	13,924 (40.2%)	-
· High-risk	6,432 (20.9%)	1,355 (34.9%)	7,787 (22.5%)	-
Diagnosis				
Unstable angina	5,920 (19.2%)	1,058 (27.3%)	6,978 (20.1%)	-
NSTEMI	24,864 (80.8%)	2,824 (72.7%)	27,688 (79.9%)	-
Invasive treatment				
No treatment	7,786 (25.3%)	1,301 (33.5%)	9,087 (26.2%)	-
PCI	20,571 (66.8%)	2,234 (57.5%)	22,805 (65.8%)	-
CABG	2,427 (7.9%)	347 (8.9%)	2,774 (8.0%)	-
Medications at discharge*				
Aspirin	28,603 (93.5%)	3,445 (89.7%)	32,048 (93.1%)	24
P2Y$_{12}$ blockers	25,537 (83.5%)	2,988 (77.8%)	28,525 (82.9%)	24
Anticoagulants	2,299 (7.5%)	553 (14.4%)	2,852 (8.3%)	24
Beta blockers	25,896 (84.7%)	3,318 (86.4%)	29,214 (84.9%)	24
RAAS-inhibitors	24,164 (79.0%)	2,944 (76.6%)	27,108 (78.8%)	24
Statins	28,965 (94.7%)	3,547 (92.3%)	32,512 (94.5%)	24
Adverse outcome				
All-cause mortality	2,468 (8.0%)	610 (15.7%)	3,078 (8.9%)	-
MAE†	4,317 (15.0%)	914 (24.8%)	5,231 (15.1%)	-
Myocardial infarction†	1,436 (5.0%)	227 (6.2%)	1,663 (5.1%)	-
Heart failure†	1,217 (4.2%)	334 (9.1%)	1,551 (4.8%)	-
Stroke†	486 (1.7%)	83 (2.3%)	569 (1.7%)	-
Bleeding†	1,007 (3.5%)	172 (4.7%)	1,179 (3.4%)	-

* Assessed in in-hospital survivors: n=34,442. † n=32,535. CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; cTn: cardiac troponin; eGFR: estimated glomerular filtration rate; MAE: major adverse event; MI: myocardial infarction; PCI: percutaneous coronary intervention; NSTEMI: non-ST-elevation myocardial infarction; RAAS: renin-angiotensin-aldosterone-system

Supplementary Table 3. Clinical characteristics, treatments and adverse outcome in relation to coronary angiography <24 hours vs 24-72 hours in 3-day survivors.

	<24 hours (n=12,179)	24-72 hours (n=15,709)	Total cohort (n=27,888)	Missing values
Risk factors				
Age (years)	68 (59-75)	70 (62-77)	69 (61-76)	-
Men	8,630 (70.9%)	10,820 (68.9%)	19,450 (69.7%)	-
Current smoking	2,461 (20.2%)	2,743 (17.5%)	5,204 (18.7%)	-
Hypertension	6,465 (53.1%)	9,029 (58.3%)	15,494 (55.6%)	-
Diabetes	2,458 (20.2%)	3,654 (24.3%)	6,112 (21.9%)	-
Hyperlipidaemia	3,526 (29.0%)	5,367 (34.2%)	8,893 (31.9%)	23
Body mass index (kg/m^2)	27.0 (24.6-30.0)	27.0 (24.5-30.1)	27.0 (24.5-30.1)	702
eGFR (mL/min/1.73m^2)	82.3 (67.9-92.7)	80.3 (64.6-91.3)	81.3 (66.0-92.0)	-
Comorbidities				
Previous MI	1,760 (14.5%)	2,928 (18.6%)	4,688 (16.8%)	-
Previous PCI/CABG	1,833 (15.1%)	3,012 (19.2%)	4,845 (17.4%)	-
Heart failure	443 (3.6%)	837 (5.3%)	1,280 (4.6%)	-
Previous stroke	557 (4.6%)	908 (5.8%)	1,465 (5.3%)	-
Peripheral artery disease	440 (3.6%)	745 (4.7%)	1,185 (4.2%)	-
COPD	635 (5.2%)	1,100 (7.0%)	1,735 (6.2%)	-
Previous/present cancer	253 (2.1%)	454 (2.9%)	707 (2.5%)	-
Angiographic findings				267
Non-conclusive	11 (0.1%)	13 (0.1%)	24 (0.1%)	
Normal/non-obstructive	1,140 (9.4%)	1,844 (11.9%)	2,984 (10.8%)	
1- or 2-vessel disease	7,678 (63.6%)	9,459 (55.2%)	17,137 (62.0%)	
3-vessel disease/left main	3,246 (26.9%)	4,230 (27.2%)	7,476 (27.1%)	
Clinical findings				
Atrial fibrillation	612 (5.0%)	1,177 (7.5%)	1,789 (6.4%)	1
ST-depression	3,864 (31.7%)	4,138 (26.3%)	8,002 (28.7%)	5
cTn >99th percentile	11,416 (94.6%)	14,134 (91.4%)	25,550 (92.8%)	355
GRACE score				
· Low-risk	5,105 (41.9%)	5,969 (38.0%)	11,074 (39.7%)	-
· Intermediate-risk	4,915 (40.4%)	6,314 (40.2%)	11,229 (40.3%)	-
· High-risk	2,159 (17.7%)	3,426 (21.8%)	5,585 (20.0%)	-
Diagnosis				
Unstable angina	1,774 (14.6%)	3,423 (21.8%)	5,197 (18.6%)	-
NSTEMI	10,405 (85.4%)	12,286 (78.2%)	22,691 (81.4%)	-
Invasive treatment				
No treatment	2,653 (21.8%)	4,220 (26.9%)	6,873 (24.6%)	-
PCI	8,493 (69.7%)	10,335 (65.8%)	18,828 (67.5%)	-
CABG	1,033 (8.5%)	1,154 (7.3%)	2,187 (7.8%)	-
Medications at discharge*				
Aspirin	11,473 (94.6%)	14,596 (93.2%)	26,069 (93.8%)	11
P2Y$_{12}$ blockers	10,296 (84.9%)	13,045 (83.3%)	23,341 (84.0%)	11
Anticoagulants	704 (5.8%)	1,282 (8.2%)	1,986 (7.1%)	11
Beta blockers	10,248 (84.5%)	13,279 (84.8%)	23,527 (84.7%)	11
RAAS-inhibitors	9,751 (80.4%)	12,232 (78.1%)	21,983 (79.1%)	11
Statins	11,558 (95.3%)	14,793 (94.5%)	26,351 (94.8%)	11
Adverse outcome				
All-cause mortality	777 (6.4%)	1,304 (8.3%)	2,081 (7.5%)	-
MAE†	1,394 (12.2%)	2,296 (15.6%)	3,690 (14.1%)	-
Myocardial infarction†	474 (4.2%)	785 (5.3%)	1,259 (4.8%)	-
Heart failure†	386 (3.4%)	646 (4.4%)	1,032 (4.0%)	-
Stroke†	165 (1.4%)	262 (1.8%)	427 (1.6%)	-
Bleeding†	340 (3.0%)	533 (3.8%)	893 (3.4%)	-

* Assessed in in-hospital survivors: n=27,798. † n=26,119. CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; cTn: cardiac troponin; eGFR: estimated glomerular filtration rate; MAE: major adverse event; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RAAS: renin-angiotensin-aldosterone-system

```
                              ┌─────────────────────┐
                              │  Total admissions for│
                              │  NSTE-ACS 2013-2018, │
                              │      n=44,366        │
                              └─────────────────────┘
┌──────────────────────────┐              │
│ Excluded, n=4,795        │              │
│ - No data on time interval to │         │
│   coronary angiography   │              │
└──────────────────────────┘   ┌─────────────────────┐
                              │      n=39,571        │
                              └─────────────────────┘
┌──────────────────────────┐              │
│ Excluded, n=2,223        │              │
│ - Dementia, n=68         │              │
│ - Hb <80 g/L; n=1,763    │              │
│ - eGFR<20; n=1,173       │              │
└──────────────────────────┘   ┌─────────────────────┐
                              │      n=37,348        │
                              └─────────────────────┘
┌──────────────────────────┐              │
│ Excluded, n=450          │              │
│ - Cardiogenic shock, n=142│             │
│ - Cardiac arrest, n=257  │              │
│ - Resuscitation, n=302   │              │
└──────────────────────────┘   ┌─────────────────────┐
                              │      n=36,898        │
                              └─────────────────────┘
┌──────────────────────────┐              │
│ Excluded, n=2,232        │              │
│ - Time interval <3.1 h, n=2,120│        │
│ - Time interval >358 h, n=112 │         │
└──────────────────────────┘   ┌─────────────────────┐
                              │  NSTE-ACS patients   │
                              │ included in analysis,│
                              │      n=34,666        │
                              └─────────────────────┘
```

Supplementary Figure 1. Study flowchart.
eGFR: estimated glomerular filtration rate (given as mL/min/1.73 m^2); Hb: haemoglobin; NSTE-ACS: non-ST-elevation acute coronary syndrome
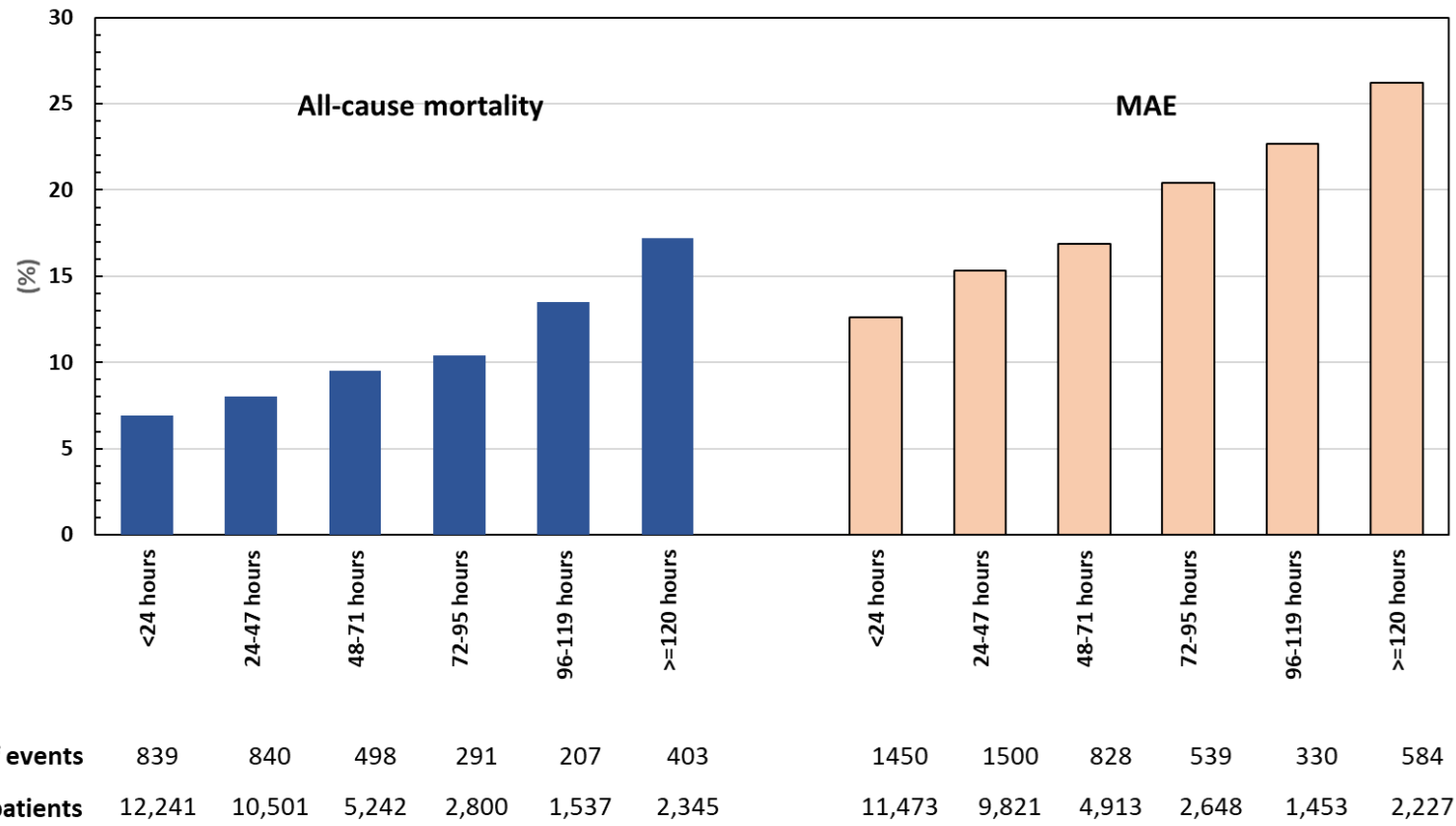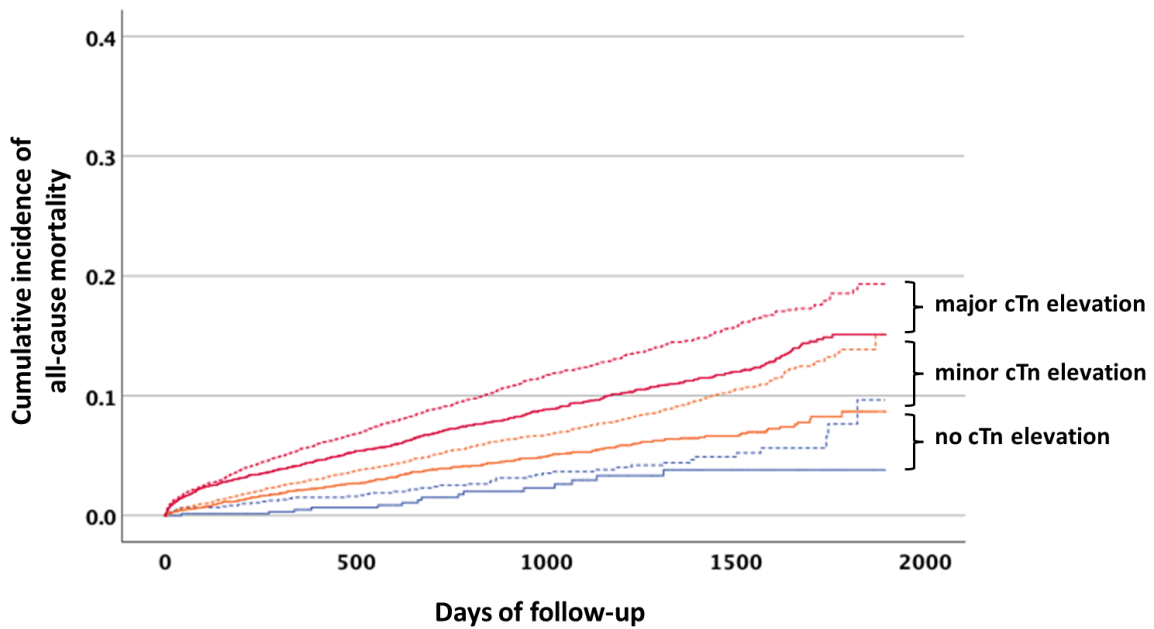
Supplementary Figure 2. Crude event rates in relation to time intervals to coronary angiography.
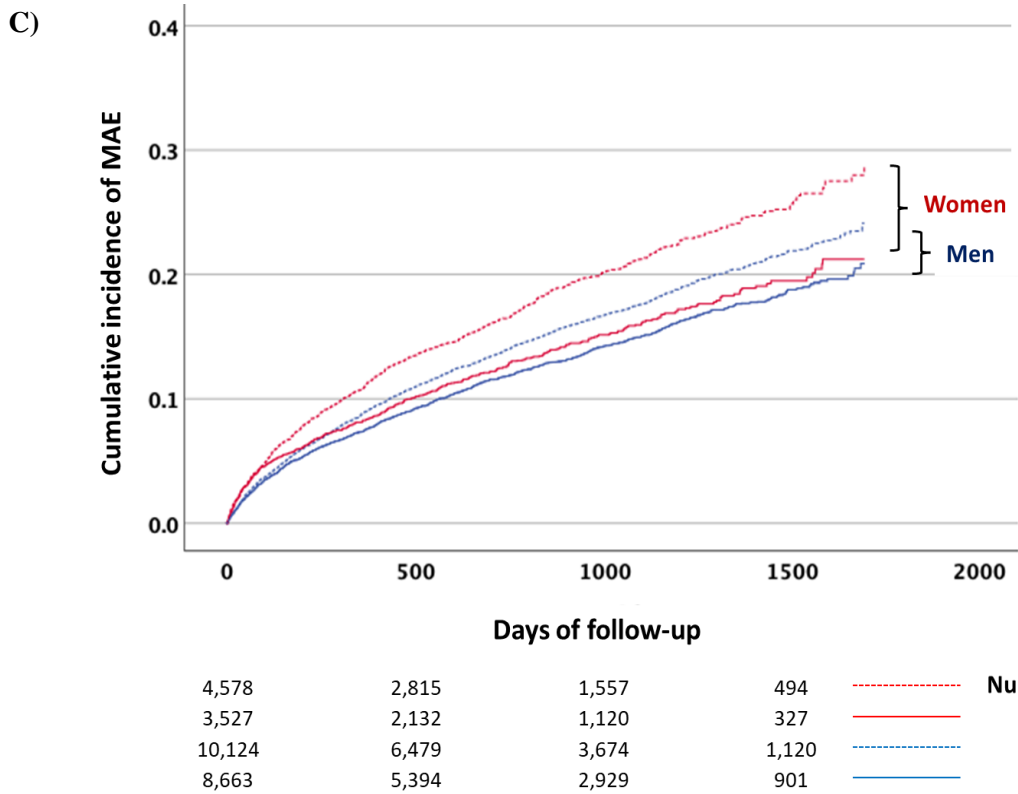MAE: major adverse event.

A)

Cumulative incidence of all-cause mortality

Days of follow-up
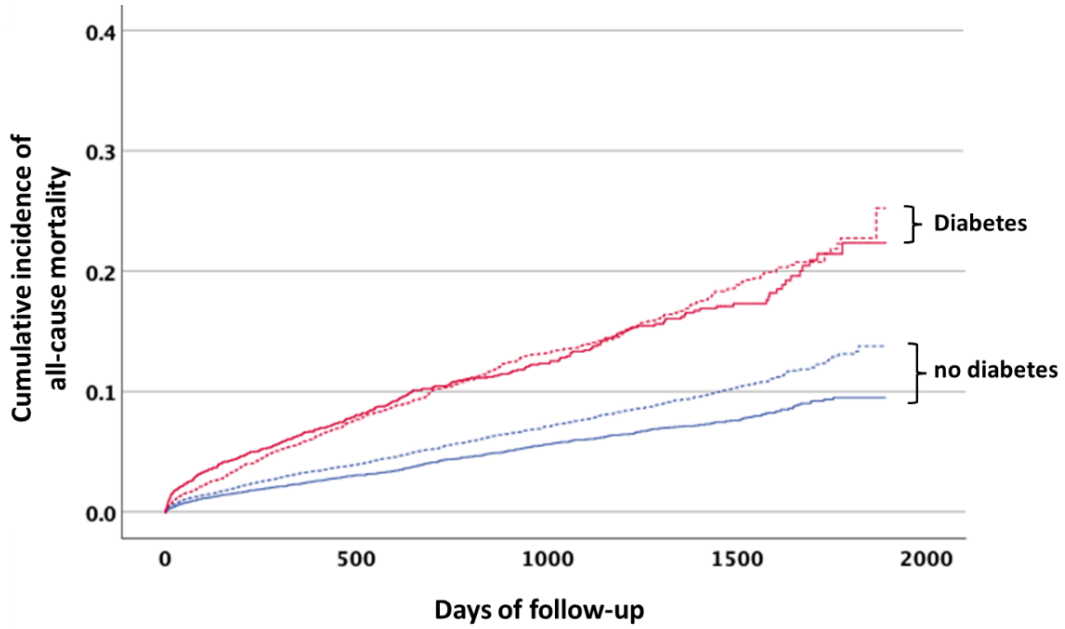
3,654	2,496	1,503	610	- - - - -	Numbers at risk
2,615	1,690	940	375	———	
12,055	8,752	5,468	2,392	- - - - -	
10,398	7,341	4,385	1,892	———	

B)

Cumulative incidence of all-cause mortality

Days of follow-up

6,460	4,554	2,759	1,197	- - - - -	Numbers at risk
7,023	4,776	2,776	1,201	———	
7,674	5,471	3,382	1,435	- - - - -	
5,191	3,640	2,160	886	———	
1,336	1,035	698	294	- - - - -	
675	514	309	126	———	

C) Cumulative incidence of MAE vs Days of follow-up

Numbers at risk			
4,578	2,815	1,557	494
3,527	2,132	1,120	327
10,124	6,479	3,674	1,120
8,663	5,394	2,929	901

Supplementary Figure 3. Cumulative incidence of adverse outcome in relation to coronary angiography <24 hours vs 24-72 hours in 3-day survivors.
A. Diabetes (all-cause mortality);
B. cTn elevation (all-cause mortality);
C. Sex (major adverse events).
Straight lines refer to coronary angiography within <24 hours. Dotted lines refer to coronary angiography within 24-72 hours.

cTn: cardiac troponin.