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MORTALITY RISK ESTIMATION OF ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS TREATED WITH PRIMARY PERCUTANEOUS CORONARY INTERVENTION

PhD thesis

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List of abbreviations

ACE: Angiotensin Converting Enzyme

ACS: Acute Coronary Syndrome

ADP: Adenosine Diphosphate

ALPHA (acronym for a risk estimation algorithm): Age, Life support, Pressure, Heart rate, Access site

APEX AMI: “Assessment of Pexelizumab in Acute Myocardial Infarction” study

AR-G: “Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines“ study

ATE: Average Treatment Effect

ATLANTIC: “Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery” study

ATT: Average Treatment Effect for The Treated

AUC: Area Under Curve

BMS: Bare Metal Stent

CABG: Coronary-Artery Bypass Graft

CADILLAC: “Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications” study

CHF: Chronic Heart Failure

CI: Confidence Interval

CIRCUS: "Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction" study

CMR: Cardiac Magnetic Resonance Imaging

COPD: Chronic Obstructive Pulmonary Disease

CRF: Chronic Renal Failure

CVD: Cerebrovascular Disease

CS: Cardiogenic Shock

CYP: Cytochrome P isoenzymes

DAPT: Dual Antiplatelet Therapy

DES: Drug Eluting Stent

EH: EuroHeart (STEMI PCI score)

ECG: Electrocardiogram

et al.: et alii (and others)

etc.: et cetera (and the rest of the things)

Fig.: Figure

g: gram

GRACE: “Global Registry of Acute Coronary Events”

HR: Hazard Ratio

i.e.: id est (in other words)

IABP: Intraaortic Balloon Pump

IDI: Integrated Discrimination Improvement

IMPRESSION: "Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction" study

IPTW: Inverse Probability of Treatment Weighting

IQR: Interquartile Range

IV: Intravenous

kg: kilogram

L: litre

LR: Likelihood Ratio

LV: Left Ventricular

LVEF: Left Ventricular Ejection Fraction

m: metre

MI: Myocardial Infarction

µmol: micromol (10^{-9} mol)

mmol: millimol (10^{-6} mol)

min: minute(s)

mmHg: millimetre of mercury

MO: Morphine

NCDR CathPCI: National Cardiovascular Data Registry for Catheterization Percutaneous Coronary Intervention

ng: nanogram (10^{-9} gram)

non-STEMI: Non-ST-Elevation Myocardial Infaction

NSTE-ACS: Non-ST-Elevation Acute Coronary Syndrome

PAD: Peripheral Artery Disease

PAMI: “Primary Angioplasty In Myocardial Infarction” study

PCI: Percutaneous Coronary Intervention

PSM: Propensity Score Matching

$P2Y_{12}$: a G protein-coupled purinergic receptor for ADP

ROC: Receiver Operating Characteristics

STEMI: ST-Elevation Myocardial Infarction

TIMI: Thrombolysis In Myocardial Infarction

TR Band®: Brand name of a radial compression device

U: Unit(s)

VIF: Variance Inflation Factor

1. Introduction

1.1. Importance of risk estimation algorithms

Risk estimation is an integral part of the daily medical practice. Algorithms offer an especially promising avenue, to reduce the variability in judgments, the potential bias and noise in medical decisions, thereby saving lives and money. The medical profession is likely to rely on algorithms more and more in the future (1).

Risk estimation algorithms may provide objective, reliable and useful information for patients or relatives and help physicians to allocate hospital resources. Moreover, they may contribute to an improved quality of care as they can be used for risk adjustment in inter-organizational comparisons of health care providers with different case mixes. They also enable intra-organizational quality monitoring. Furthermore, risk models may be helpful in clinical trial design identifying patients with the needed risk profile thereby increasing statistical power or reducing sample size and costs (2).

1.2. Primary percutaneous coronary intervention and platelet $P2Y_{12}$ receptor inhibitors

Primary percutaneous coronary intervention (PCI) is defined as an urgent coronary angioplasty (catheter intervention) performed in the context of ST elevation myocardial infarction (STEMI), without previous fibrinolytic treatment (3, 4).

Primary PCI is the preferred therapeutic option when it can be performed expeditiously by an experienced team. Patients undergoing primary PCI should receive a parenteral anticoagulant, and dual antiplatelet therapy (DAPT), a combination of aspirin and $P2Y_{12}$ inhibitor in all cases. Preferred P2Y12 inhibitors are prasugrel or ticagrelor. When neither of these agents is available, or if they are contraindicated, clopidogrel should be given instead (3).

Plain (old) balloon angioplasty has been superseded in the treatment of de novo coronary lesions after demonstration of the superiority of stenting in terms of the requirement for repeat revascularization. Stenting with bare metal stents (BMS) results in approximately 30% lower rate of restenosis in comparison with plain balloon angioplasty. Early generation drug (sirolimus, paclitaxel) eluting stents (DES) reduced restenosis by 50-70% but increased the risk of very late stent thrombosis compared with BMS. With the use of the new-generation DES, the risk of subacute and late stent thrombosis is significantly

lower. New-generation drug eluting stent (DES) should be considered as the default stent type for PCI (5).

The platelet $P2Y_{12}$ receptor is a purinergic, G_i-coupled protein receptor, which mediates a part of the platelet-activating effects of adenosine diphosphate (ADP). ADP is derived from a nearby platelet and play a role in enhancing platelet activation (6).

Clopidogrel and prasugrel (thineopyridines) are prodrugs that need metabolic activation in the liver. Clopidogrel will become active following a two-step oxidation process involving hepatic cytochrome P450 (CYP) isoenzymes, notably CYP2C19 in both steps. The transiently active thiol-metabolite binds specifically and irreversibly to the platelet $P2Y_{12}$ receptor. Following intestinal hydrolysation, prasugrel undergoes a one-step oxidation via mainly CYP3A4 and CYP2B6 to form the active metabolite. For both drugs, a loading dose is generally used since several days are required with the standard dose in order to achieve the steady state for the inhibition of platelet function. After a 600 mg loading dose, the onset of clopidogrel antiplatelet action appears at 2 hours compared to 30 minutes for prasugrel while both drugs have a slow offset of action (5 to 10 days). The active metabolites for both drugs are equipotent. In ACS patients undergoing percutaneous coronary intervention, a reduction of major cardiovascular events (notably nonfatal myocardial infarction and stent thrombosis) was observed with prasugrel compared to clopidogrel with 300 mg as loading dose (7). However, an increased risk of bleeding was also observed with prasugrel compared to clopidogrel, although there was a net clinical benefit with prasugrel. In daily practice, prasugrel is contraindicated in patients with TIA/stroke and dose reduction is recommended over 75 years of age and below 60 kg-s (8).

Unlike thienopyridines, ticagrelor binds to a separate site of the P2Y12 receptor. Moreover, it is not a prodrug: the platelet inhibition is mostly related to the parent drug and for up to 30-40% to its active metabolite via hepatic CYP3A4/5. Ticagrelor has a plasma half-life of 8-12 hours, reaches steady state after 2 to 3 days, and requires a twice-daily administration. The onset of action is fast, with more than 40% of platelets inhibited within 30 minutes post dosing, and a peak effect within 2 hours. The offset of ticagrelor effect is also quicker due to its reversible binding to the $P2Y_{12}$ receptor. (8)

1.3. Mortality prediction for patients treated with primary percutaneous coronary intervention

Our research group previously collected, analysed, and published the mortality risk models that were developed using data of patients with STEMI, and their external validation studies. Only reports with populations involving STEMI and primary PCI as a treatment modality were analysed. In that review article we analysed the risk factors found to be significant for mortality prediction in previous studies.

Some of the models use exclusively predictors that are available at presentation like demographic and historical data, presentation and electrocardiogram (ECG) characteristics (9, 10) ("admission model"), while others also make use of findings/results of the coronary intervention and/or more time consuming imaging/laboratory studies/in-hospital events assessing risk later during the hospital stay (11-18) or only at the time of discharge (19) ("discharge model") (Fig. 1, Table 1). The most common variables used in the models are age, which is a predictor in each of the studied models (9-19), Killip class/presence of cardiogenic shock/haemodynamic instability (9-15, 17-19), heart rate (9-11, 14, 16, 18, 19) and systolic blood pressure at admission (9, 11, 14, 16, 18, 19), ECG localization of the infarction (9, 10, 12, 18, 19), renal function (11, 14, 15, 17, 18), ischaemia time (9, 12, 13, 19), and history of diabetes mellitus (9, 10, 13, 19). Each of the variables presented in Table 1 was independently associated with mortality being parts of one or more models. Yet, researchers have to maintain a balance between including too many predictors and model parsimony. Omitting better treatment options, such as primary PCI (9, 19) and/or under-representation of other important prognostic factors (e.g., cardiogenic shock) (9, 10, 15, 19) may cause biased prediction. On the other hand, using too many variables may result in loss of precision in the estimation of the coefficients and the predictions of new responses (2).

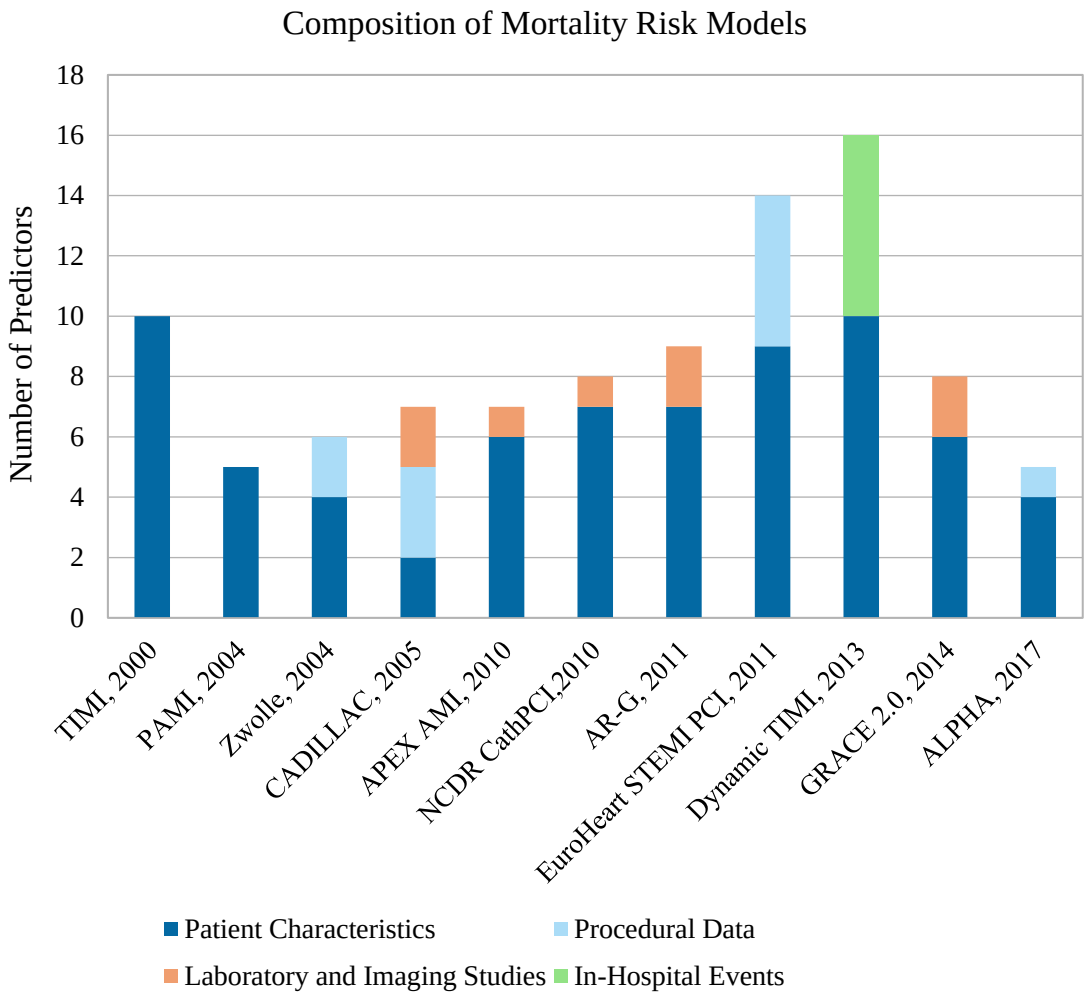

Fig. 1. and Table 1. (see next page) Composition of mortality risk scores (2).[1] Height of the bars shows the number of predictors needed for calculation of the score. Colour of the predictor groups corresponds with the time needed for the availability of predictors: blue: variables that are available at or soon after admission (presentation characteristics and procedural data); orange: laboratory and imaging studies requiring some more time; green: in hospital events that can only be assessed at the time of discharge. True admission models are the TIMI and PAMI scores, whereas dynamic TIMI can only be calculated at the time of discharge. With the exception of the GRACE 2.0 and ALPHA models, there is a trend that newer algorithms became more complex with more predictors. (2) ALPHA, Age, Life support, Pressure, Heart rate, Access site; APEX AMI, Assessment of Pexelizumab in Acute Myocardial Infarction; AR-G, Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines; CADILLAC, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; EH, EuroHeart; GRACE, Global Registry of Acute Coronary Events; NCDR CathPCI, National Cardiovascular Data Registry for Catheterization Percutaneous Coronary Intervention; TIMI, Thrombolysis In Myocardial Infarction.

Table 1: Characteristics and composition of mortality risk models (2)[2]

Acronym	TIMI	PAMI	Zwolle	CADILLAC	APEX AMI	NCDR CathPCI	AR-G	EH STEMI PCI	Dynamic TIMI	GRACE 2.0	ALPHA	← N° of scores
N° of predictors →	10	5	6	7	7	8	9	14	16	8	5	
Patient characteristics												
Age	■	■	■	■	■	■	■	■	■	■	■	11
Gender								■				1
Body Weight or Body Mass Index	■							■	■			3
Heart Rate	■	■			■		■		■	■	■	7
Systolic Blood Pressure	■				■		■		■	■	■	6
Heart Failure on Presentation						■	■					2
Killip Class / Cardiogenic Shock / Hemodynamic Instability	■	■	■	■	■	■	■	■	■	■		10
ECG localization (STEMI)	■	■	■		■				■			5
ST-segment deviation					■		■			■		3
Ischemia time	■		■					■	■			4
Cardiac arrest at or prior to admission										■	■	2
Timing of PCI						■						1
Known Diabetes Mellitus	■	■						■	■			4
Known Hypertension	■								■			2
History of Angina Pectoris	■								■			2
History of Stroke								■				1
History of CABG								■				1
History of Congestive Heart Failure						■						1
Chronic Lung Disease						■						1
Peripheral Artery Disease						■	■					2
Smoking Status								■				1
Procedural data												
Access Site											■	1
Multi / Triple Vessel Disease			■	■				■				3
Pre-Procedural TIMI Flow								■				1
Final TIMI Flow			■	■								2
Culprit Vessel / Infarct Related Artery								■				1
Bifurcation Lesion								■				1
Type-C Lesion								■				1
Laboratory test, echocardiography												
Elevated Necrosis Biomarkers							■			■		2
Renal Function				■	■	■	■			■		5
Anaemia				■								1
Reduced LVEF				■								1
In-Hospital Events												
Recurrent Myocardial Infarction									■			1
Stroke									■			1
Major Bleeding									■			1
Congestive Heart Failure / Shock									■			1
Arrhythmia									■			1
Renal Failure									■			1

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1.4. Additional considerations on haemodynamic parameters in the risk estimation

In many of the risk estimation algorithms for patients with ST-elevation myocardial infarction (STEMI), heart rate and systolic blood pressure are key predictors.

Acute myocardial infarction (AMI) with subsequent left ventricular (LV) dysfunction is the most common cause of cardiogenic shock (CS) complicating acute coronary syndrome (ACS). It is characterized by hypotension, pulmonary congestion and an impaired tissue and vital organ perfusion. Cardiogenic shock complicating an acute coronary syndrome is observed in up to 10% of patients and is associated with high mortality still approaching 50%. The extent of ischaemic myocardium has a profound impact on the initial, in hospital and post-discharge management and prognosis of the cardiogenic shock patient. Careful risk assessment of each patient, based on clinical criteria, is mandatory, to decide appropriately regarding revascularisation, drug treatment with inotropes and vasopressors, mechanical left ventricular support, additional intensive care treatment, triage among alternative hospital care levels, and allocation of clinical resources. (20) Patients with cardiogenic shock complicating MI have a substantial benefit with PCI compared with no or late in-hospital revascularisation. These patients need to be directly admitted or transferred to tertiary care shock centres with expertise in acute revascularisation and advanced intensive care. (21)

During the emergency management of complicated ST-elevation myocardial infarction (clinical signs of acute pulmonary oedema, low-output cardiogenic shock or arrhythmia) the haemodynamic parameters may be influenced by pharmacologic treatment (morphine, furosemide, fast acting ACE inhibitors, nitroprusside or nitroglycerin, catecholamines [i.e., dobutamine, dopamine, norepinephrine], milrinone etc.), antitachycardia / -bradycardia treatment, or mechanical circulatory support (21). These interventions may act in the direction of normalising blood pressure and heart rate, thereby improving the result of the risk calculation, even though there is no evidence for better survival.

Oxygen transport is dependent on both respiratory and circulatory function. Total O_2 delivery (DO_2) to tissues is the product of arterial O_2 content (Ca_{O2}) and cardiac output (Q_T). [$DO_2 = Ca_{O2} * Q_T$]. Deficiencies in O_2 delivery may be due to a low Pa_{O2}, a low haemoglobin concentration, or an inadequate cardiac output. The body normally consumes only 25% of the O_2 carried on haemoglobin. When O_2 demand exceeds supply, the extraction fraction exceeds 25%. With further reductions in the total oxygen delivery

(D_{O2}), a critical point is reached beyond which the O_2 consumption (V_{O2}) becomes directly proportional to D_{O2}. This state of supply-dependent O_2 is typically associated with progressive lactic acidosis caused by cellular hypoxaemia (22).

In critical illness, an oxygen debt develops when oxygen delivery is inadequate to meet tissue demand and compensatory mechanisms are exhausted. This results in global tissue hypoxia, anaerobic metabolism, and lactate production. High lactate is a prognostic marker in critically ill patients with various forms of shock (23).

The lactate level, as a well-known marker of microcirculatory failure, may have an added prognostic value on top of the conventional variables for predicting mortality of STEMI patients treated with primary PCI.

1.5. Possible hazard of the interaction of morphine and the platelet inhibitors

In the setting of ST-segment elevation myocardial infarction (STEMI), intravenous (IV) morphine (MO) is traditionally employed to relieve pain, reduce pulmonary congestion, and anxiety. Though the efficacy and safety of morphine use were not studied in randomised clinical trials, both European and American guidelines on STEMI recommend its application in these conditions based on expert consensus (24, 25). Nevertheless, according to recent studies, morphine delays and decreases the effects of all currently available oral platelet $P2Y_{12}$ receptor inhibitors (i.e., clopidogrel, prasugrel, and ticagrelor) in vitro (26-32) which may result in poorer myocardial reperfusion (33) and larger infarct size (34). In the light of that, the current European guidelines add a note of caution that the diminished effects of clopidogrel, ticagrelor, and prasugrel may lead to early treatment failure (24). Yet, there are few data available about the impact of this interaction on clinical outcomes and the effect on long-term mortality is barely investigated (35-42).

2. Objectives

2.1. Admission lactate level as a predictor of mortality

In many of the risk estimation algorithms for patients with ST-elevation myocardial infarction (STEMI), heart rate and systolic blood pressure are key predictors. Yet, these parameters may also be altered by the applied medical treatment / circulatory support without concomitant improvement in microcirculation. Therefore, we aimed to investigate whether venous lactate level, a well-known marker of microcirculatory failure, may have an added prognostic value on top of the conventional variables of the "Global Registry of Acute Coronary Events" (GRACE) 2.0 model for predicting 30-day all-cause mortality of STEMI patients treated with primary PCI (43).

2.2. Impact of morphine use on mortality

Morphine decreases the effect of $P2Y_{12}$ receptor inhibitors in vitro and observational reports suggest that its use is associated with larger infarct size. Yet, there are few data available about the impact of this interaction on clinical outcomes. Therefore, we studied the impact of periprocedural morphine application on all-cause mortality in STEMI patients treated with primary percutaneous coronary intervention using a prospective registry (44).

3. Methods

3.1. Venous lactate level

3.1.1. Study design, outcome measures

In a pilot real-world prospective single-centre registry, data of 334 STEMI cases were collected from May 2020 through April 2021. All patients were treated with primary PCI using standard techniques within 12 hours from symptom onset. All but 10 of them underwent venous blood gas analysis at cardiac care unit admission. One patient was lost for follow-up at 30 days and another one at 180 days (Fig. 2). To evaluate the predictive role of venous lactate level, nested logistic regression models were built using the GRACE 2.0 score alone and with the addition of venous lactate with 30-day all-cause mortality as the dependent variable / primary outcome measure. Similarly, in-hospital and 180-day all-cause mortalities were also studied as secondary outcomes of interest by constructing nested logistic and Cox regression models, respectively.

This was an observational study using a single-centre registry. The blood sampling for routine laboratory analysis was performed according to the institutional protocol, in that venous blood gas analysis is included, i.e., no specific study-related intervention was done. (Regional Ethics Committee approval number: SE RKEB: 4/2021.)

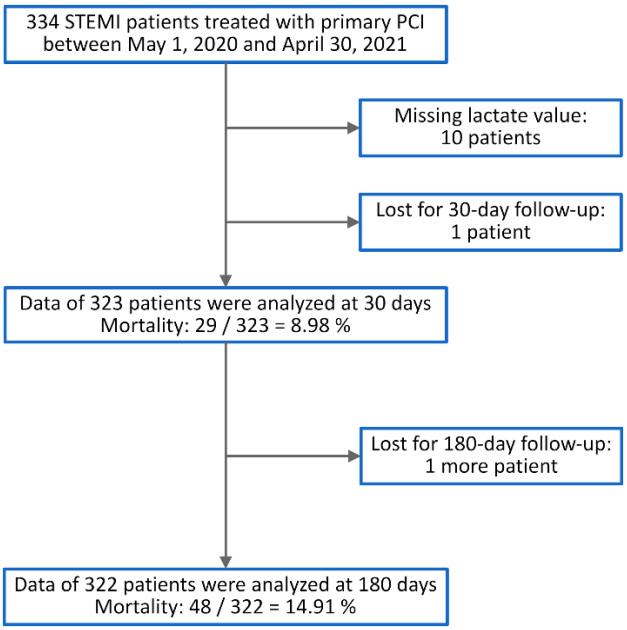

Fig. 2: Patient flow chart (43). For details: see text. PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction[3]

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3.1.2. Statistical analysis

Nested logistic regression models were constructed using the 6-month score value of the GRACE 2.0 algorithm alone (base model, online calculator available at https://www.outcomes-umassmed.org/grace/acs_risk2/index.html) and with the addition of venous lactate (expanded model) with 30-day all-cause mortality as the dependent variable / primary outcome measure.

As secondary outcomes of interest in-hospital and 180-day all-cause mortalities were also assessed by nested logistic and Cox regression models, respectively. Model performance was characterized by receiver operating characteristic curve analysis (ROC, c-statistic). Difference in model performance was primarily analysed by the likelihood ratio (LR) test. Though the application of the integrated discrimination improvement (IDI, i.e. the change in the discrimination slope) and the widely used receiver operating characteristic curve analysis (ROC, c-statistic) for model selection has been criticized, they have also been performed (45-47). The correlated ROC curves were compared by a bootstrap test with 10000 resamples. Independence of the predictors (lack of collinearity) was evaluated by the variance inflation factor (VIF) using a cut-off value of 5.

For better characterisation of the studied population, as a quality control measure the observed and expected 30- and 180-day death rates were compared by the exact binomial test. Expected individual 30- and 180-day absolute mortality risks were calculated using the ALPHA (2, 16, 48) and GRACE 2.0 (14) scores, respectively. All statistical analyses and graphical interpretation of the results were carried out with R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value less than 0.05 was considered statistically significant.

3.2. Impact of morphine use on mortality

3.2.1. Study design, outcome measures

We analysed observational data of 1255 consecutive STEMI patients of a single-centre prospective registry who were treated with primary PCI from September 2007 through December 2011. Of them, 397 (31.6%) received morphine intravenously based on physician's judgment in the periprocedural period. The decision to use morphine during primary PCI was independent of the present research. To control for biased baseline covariates, two distinct propensity score-based methods were performed: 1 to 1 nearest neighbour propensity score matching (PSM) yielding a total of 728 patients and inverse probability of treatment weighting (IPTW) retaining data from all patients. Primary outcome measure of the study was time to all-cause death, whereas predischarge left ventricular ejection fraction (LVEF) assessed by echocardiography was used as secondary end point. All patients were followed-up by means of hospital records, follow-up visits, telephone interviews, and records of the National Health Insurance Fund. No patients were lost to follow-up. Median follow-up time was 7.5 years. All the 1255 cases were complete cases with no missing data.[4]

3.2.2. Procedure

Application of intravenous morphine in the periprocedural period (i.e., from onset of the symptoms to two hours following the PCI) was left to the physician's discretion and was independent of the present analysis. During the study, morphine hydrochloride (molecular weight: 321.8 g/mol) was used exclusively, morphine sulfate (molecular weight: 668.8 g/mol) was not applied. Primary PCI was performed using standard techniques. The arterial sheath was removed immediately after the procedure. Bleeding from the radial artery was stopped using the TR Band® (Terumo Europe, Leuven, Belgium), while the femoral artery was closed by the FemoSeal device (St. Jude Medical, St. Paul, Minnesota). In cases of persistent femoral artery bleeding, manual compression was

[4] A formal approval of data collection by the institutional review board was not required because all Hungarian health care providers are obliged by the above-mentioned laws to provide anonymized data of all patients with myocardial infarction for the prospective National Registry of Myocardial Infarction. The use of these institutional anonymized data for this specific scientific research was approved by the head of the institution.

applied. All patients were treated with acetylsalicylic acid and a loading dose of 600 mg clopidogrel and discharged on dual antiplatelet therapy for at least 12 months. Successful PCI was defined as <50% diameter stenosis with a final TIMI flow grade 2. Interventional cardiologists were high-volume operators (i.e., >200 PCIs/year) skilled in both transfemoral and transradial techniques. Left ventricular ejection fraction was assessed by echocardiography within 48 hours after the index procedure.

3.2.3. Statistical analysis

For descriptive statistics, variables in 2×2 contingency tables were assessed using Fisher's exact test. Categorical data in 2×k tables were analysed using the unordered chi-squared test or, to detect linear trend, the chi-squared test for trend. As none of the continuous variables showed normal distribution, the Wilcoxon rank sum test was applied for their comparisons. A two-tailed p value less than 0.05 was considered statistically significant. To adjust for confounders, two distinct propensity score-based techniques were applied (49). We used 1 to 1 nearest neighbour propensity score matching with a caliper width of 0.2 to estimate the average treatment effect for the treated (ATT) yielding a total of 728 cases (50). In addition, we also assessed the average treatment effect (ATE) by inverse probability of treatment weighting (IPTW) using stabilised weights retaining data from all patients (49, 51). The propensity score model included all measured baseline covariates listed in Table 2 that could affect treatment assignment and/or are known to be associated with the primary end point. Balance on baseline covariates between the treated and control groups was evaluated using absolute standardised differences (52). A value less than 0.1 was considered as an acceptable standardised bias. Absolute risk differences in all-cause mortality were captured by Kaplan-Meier survival curves which were compared using log-rank tests. The relative change in the hazard of death was estimated using univariable Cox models as suggested by Austin (49, 53). As to the secondary outcome measure, distributions of predischarge LVEFs in the treated and control groups were compared by rank tests. All statistical analyses and graphical interpretation of the results were carried out with R version 4.0.2 (R Foundation for Statistical Computiing, Vienna, Austria).

4. Results

4.1. Lactate as a predictor of mortality in STEMI patients

4.1.1. Patient characteristics

Demographic, clinical, procedural characteristics of the patients and baseline laboratory data are summarised in Table 2. The real-world nature of the population is reflected by the facts that 12.7% of the cases had cardiac arrest on or prior to admission, whereas 11.8% of them were in cardiogenic shock. Also, the contemporariness of the treatment is shown by the high proportion of transradial interventions (94.4%), the almost exclusive use of drug eluting stents (in one patient with ectatic right coronary artery and huge thrombus burden two 7.0 mm bare metal stents wrapped with a polymer mesh were implanted), and the use of guideline-directed discharge medications. (Table 3)

As a quality control measure, observed and expected 30- and 180-day mortality rates were analysed. Observed mortality at 30 days was 29/323 = 8.98%, whereas the expected rate (sum of the individual risks / number of patients) was 8.44%, i.e., the risk adjusted mortality was 8.98%/8.44% = 1.06, p = 0.6891. As to the 180-day data, the risk adjusted mortality was 14.91%/14.64% = 1.02, p = 0.8748. (Fig. 2)

Table 2/A: Demographic and anamnestic data (43)

Demographic and anamnestic data	**n (%) / median (IQR)**
Age (years)	63.0 (53.0 to 73.0)
Sex (Female)	99 (30.7%)
Weight (kg)	80.0 (70.0 to 92.0)
Height (m)	1.71 (1.65 to 1.77)
BMI (kg/m^2)	27.6 (24.2 to 31.0)
Known Hypertension	191 (59.1%)
Known Diabetes Mellitus	67 (20.7%)
Newly diagnosed Diabetes Mellitus	16 (5.0%)
Current smoker	55 (17.03%)
Previous Myocardial Infarction	46 (14.24%)
Previous Angina	55 (17.0%)
Known Congestive Heart Failure	4 (1.2%)
Known Cerebrovascular Disease	27 (8.4%)
Known Peripheral Artery Disease	15 (4.6%)
Known Chronic Renal Failure	6 (1.9%)
Known Chronic Obstructive Pulmonary Disease	27 (8.4%)
Known Hyperlipidaemia	39 (12.1%)
Active or previous malignancy	22 (6.8%)

Table 2/B: Clinical and procedural data (43)

Clinical and procedural data	**n (%) / median (IQR)**
Onset-to-door time (hours)	3.0 (2.0 to 7.0)
ECG Localisation of the STEMI	
- Anterior / Left Bundle Branch Block	142 (44.0%)
- Inferior	143 (44.3%)
- Other	38 (11.8%)
Cardiac Arrest on or Prior to Admission	41 (12.7%)
- Initial Non-shockable Rhythm	5 (12.2%)
- Initial Shockable Rhythm	36 (87.8%)
Heart rate (1/min)	80.0 (70.0 to 97.0)
Systolic blood pressure (mmHg)	135.0 (114.0 to 153.5)
Killip Class	
- 1	254 (78.6%)
- 2	28 (8.7%)
- 3	3 (0.9%)
- 4	38 (11.8%)
Intra-Aortic Balloon Pump	6 (1.9%)
Venoarterial Extracorporeal Membrane Oxygenation	6 (1.9%)
Mechanical Ventilation	38 (11.8%)
Transradial Primary Percutaneous Coronary Intervention	303 (93.8%)
Access Site conversion	16 (5.0%)
Vessel dilated	
- Left Anterior Descending	128 (39.7%)
- Left Circumflex	28 (8.7%)
- Right Coronary	120 (37.2%)
- Left main / Multivessel	47 (14.6%)
Type of Percutaneous Coronary Intervention	
- Drug Eluting Stent	309 (95.7%)
- Drug Eluting Balloon / Plain Old Balloon Angioplasty	11 (3.4%)
- Bare Metal Stent Wrapped With a Polymer Mesh	1 (0.3%)
- Failed Wire Crossing	2 (0.6%)
Thrombus Aspiration	94 (29.1%)
Glycoprotein IIb/IIIa Receptor Inhibitor	97 (30.0%)
Initial TIMI Flow Grade	
- 0	166 (51.4%)
- 1	95 (29.4%)
- 2	56 (17.3%)
- 3	6 (1.9%)
Final TIMI Flow Grade	
- 0	4 (1.2%)
- 1	0 (0.0%)
- 2	8 (2.5%)
- 3	311 (96.3%)
Total Stent Length (mm)	33.0 (24.0 to 53.0)

Table 2/C: Baseline laboratory data (43)

Baseline laboratory data	**median (IQR)**
Initial Haemoglobin (g/L)	140.0 (127.0 to 151.0)
Initial Haematocrit (L/L)	0.41 (0.38 to 0.44)
C-Reactive Protein (mg/L)	3.14 (1.56 to 8.54)
Creatinine (μmol/L)	83.0 (70.0 to 102.0)
Cholesterol (mmol/L)	4.9 (4.1 to 5.7)
LDL Cholesterol (mmol/L)	3.47 (2.75 to 4.22)
HDL Cholesterol (mmol/L)	1.07 (0.93 to 1.29)
Triglycerides (mmol/L)	0.90 (0.64 to 1.25)
Cardiac Troponin T (ng/L)	567.0 (235.0 to 2306.0)
Creatin Kinase-MB (U/L)	69.0 (31.0 to 158.0)
Lactate (mmol/L)	2.2 (1.6 to 3.3)

Table 3: Discharge medications (43)

Discharge drugs (n of patients=304)	**n (%)**
Acetylsalicylic Acid	302 (99.34%)
Clopidogrel	114 (36.19%)
Prasugrel	171 (54.28%)
Ticagrelor	18 (5.71%)
Direct Oral Anticoagulant	33 (10.48%)
Vitamin K Antagonist	13 (4.13%)
Heparin or Low Molecular Weight Heparins	27 (8.57%)
Beta Blocker	271 (86.03%)
Angiotensin-Converting Enzyme Inhibitor	240 (76.19%)
Angiotensin Receptor Blocker	30 (9.52%)
Brain Aminopeptidase A Inhibitor / Angiotensin-Converting Enzyme Inhibitor[5]	12 (3.81%)
Angiotensin Receptor-Neprilysin Inhibitor	0 (0.00%)
Mineralocorticoid Receptor Antagonist	38 (12.06%)
Ivabradine	1 (0.32%)
Statin	287 (91.1%)
Proton Pump Inhibitor	290 (92.06%)
H2-Receptor Blocker	9 (2.79%)

[5] Quantum Genomics Firibastat or Ramipril after Acute Myocardial Infarction for Prevention of Left Ventricular Dysfunction (QUORUM) Randomized Clinical Trial

4.1.2. Lactate level as a single predictor

In both logistic regression and Cox modelling with in-hospital, 30-day, and 180-day mortalities as dependent variables venous lactate level proved to be a highly significant predictor. ROC analysis of the lactate level as a single predictor revealed good discriminative ability (Fig. 3). According to these analyses, the optimal cut-off point (i.e., the lactate level where the sum of sensitivity and specificity reaches its maximum) for the lactate level was 3.65 mmol/L.

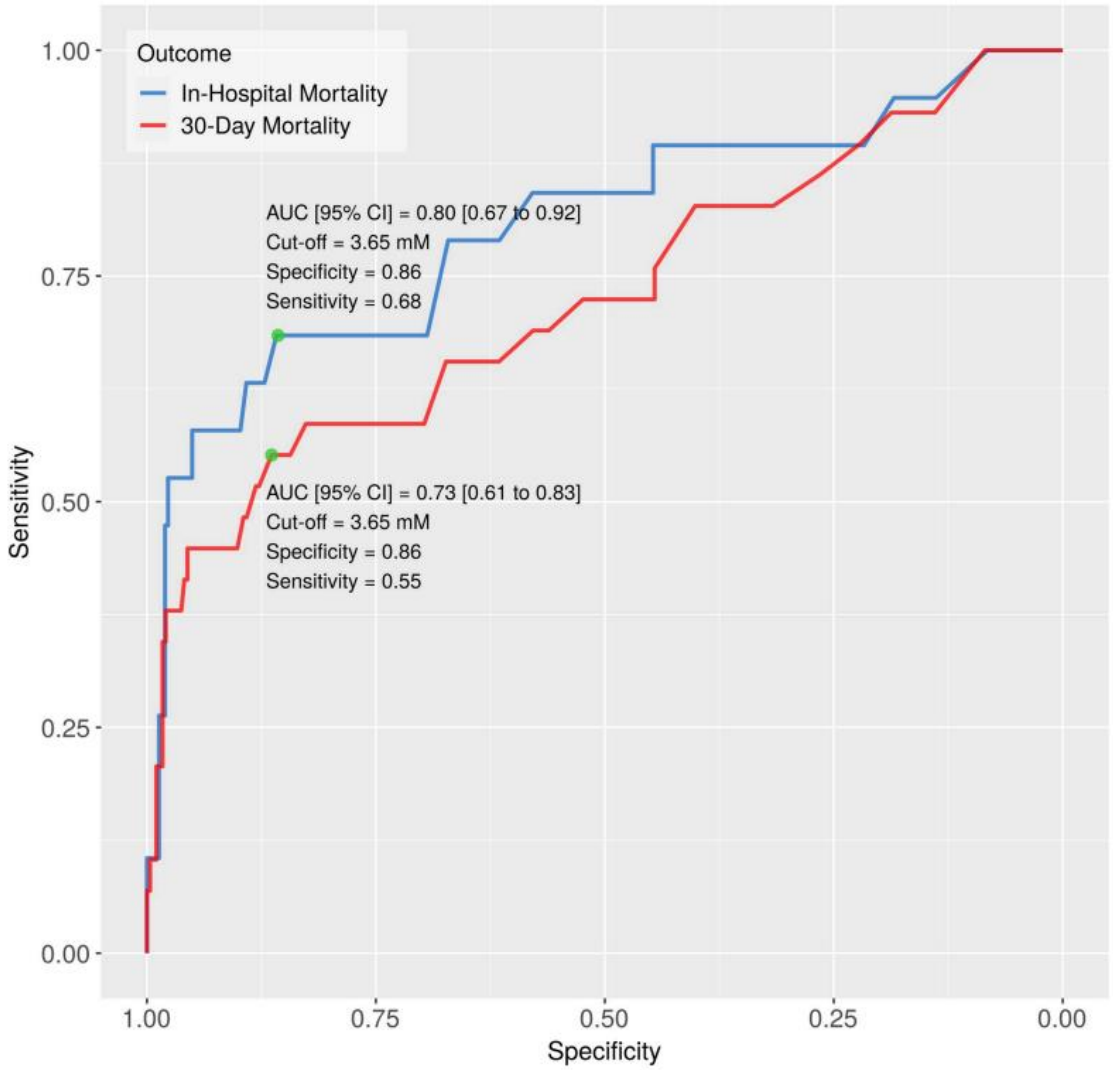

Fig. 3: ROC curves for lactate as predictor. Lactate level alone may have good predictive ability for predicting both in-hospital and 30-day mortality (43). ROC: Receiver Operating Characteristics; AUC: area under curve.[6]

4.1.3. Primary outcome measure

We used 30-day mortality as dependent variable as our primary outcome measure. Compared with the base model, the addition of lactate improved the model's performance as assessed by both likelihood ratio test (LR Chi-square = 8.7967, p = 0.0030) and integrated discrimination improvement (IDI [95% Confidence Interval (CI)]: 0.0685 [0.0031 to 0.1338], p = 0.0402), suggesting that the expanded model may have better predictive ability than the GRACE 2.0 score (Fig. 4 upper panels). The c-statistic was 0.8485 for the base and 0.8458 for the expanded model which were statistically not different (bootstrap test for two correlated ROC curves: p = 0.7506). The variance inflation factor was 1.1203, indicating lack of collinearity, i.e., the measured lactate values were independent of the calculated GRACE 2.0 scores.

4.1.4. Secondary outcome measures

Similarly to the results with 30-day mortality, using the less exact in-hospital mortality as dependent variable, both likelihood ratio test and IDI revealed better model performance (LR test: Chi-square = 11.4213, p=0.0007; IDI [95% CI]: 0.1135 [0.0145 to 0.2124], p=0.0246, Fig. 4 lower panels.). In contrast, the c-statistic did not show a significant change in discrimination being 0.8805 and 0.8892 for the GRACE 2.0 and GRACE 2.0 plus lactate model, respectively, p=0.3956. There was no sign of collinearity as the VIF was 1.0743. For time- to-event analysis of the 180-day data Cox modelling was applied. Again, the likelihood ratio test demonstrated a statistically significant improvement (Chi-square = 5.9146, p=0.0150). Nonetheless, with this relatively small sample size, the change in the discrimination slope at 180 days was not statistically relevant: IDI [95% CI]: 0.0350 [-0.0030 to 0.1090], p=0.0730. Also, comparison of the two correlated ROC curves did not show any increase in discriminatory power with c-statistics of 0.8151 and 0.8111, for the base and expanded models, respectively, p=0.1809. No signal of collinearity could be observed: VIF = 1.1051.

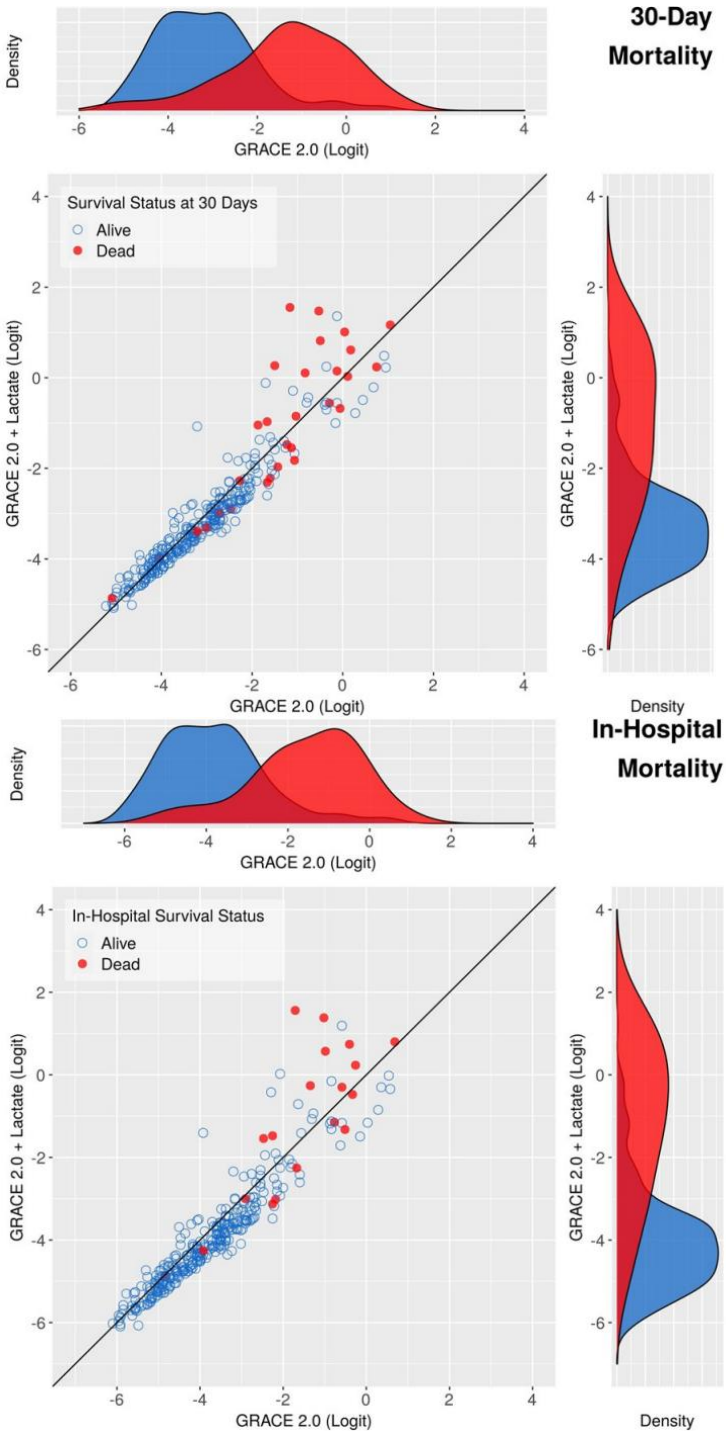

Fig. 4/A: Exploratory analysis: Combined scatter and density plots for 30-day (upper panel) and in-hospital (lower panel) mortality. The diagonal line represents identical predictive ability. With the inclusion of lactate, the probability of dying within 30 days / during hospital stay was shifted downwards in most survivors (blue circles), whereas the majority of non-survivors (red dots) were shifted towards higher risk. The change in density plots suggest an increased discriminatory power of the expanded models (43).[7]

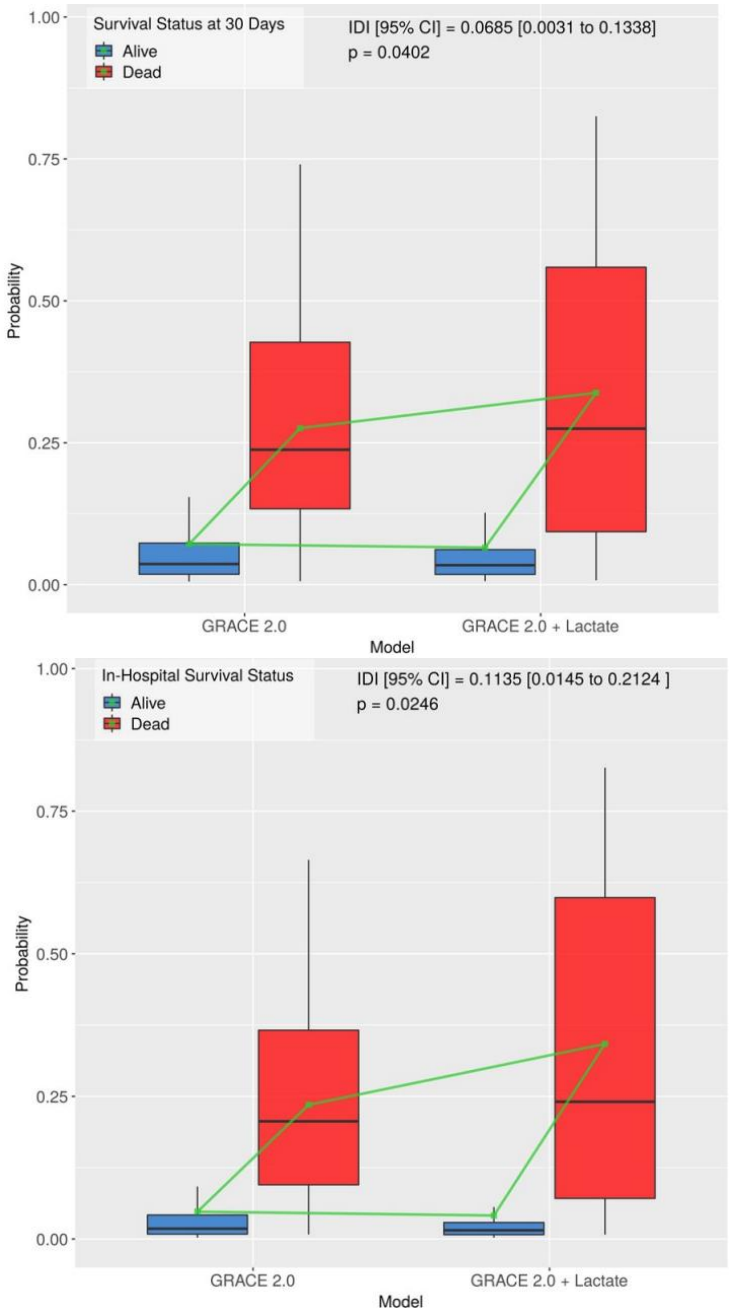

Fig. 4/B: Exploratory analysis: Box-and-whisker plots for 30-day (upper panel) and in-hospital (lower panel) mortality. The boxes represent the median and interquartile range (IQR), whereas the whiskers extend to the most extreme data point which is no more than 1.5 times the IQR from the box. The difference of mean probabilities (green squares) between non-survivors and survivors is known as discrimination slope, whereas the difference of discrimination slopes is defined as the integrated discrimination improvement (IDI). The results suggest that the expanded model may have better predictive ability than the GRACE 2.0 score (43).[8]

4.2. Impact of morphine use on mortality

4.2.1. Patient characteristics, propensity score model, morphine dose

Baseline demographic, clinical, and procedural characteristics of treated and control patients in the original, matched, and weighted samples are summarised in Table 4. Systematic differences between treated and untreated patients in the original cohort have been eliminated in both matched and weighted samples. Adequate balance on baseline covariates has been achieved in both matched and weighted sets since potentially prognostically important covariates have been balanced between the treated and control groups (Table 4, Fig. 5). Importance of each of the baseline variables included in the propensity score model is shown in Fig. 6. It is of note, that symptom-onset-to-door time as a non-linear parameter was by far the most important predictor of allocation of treatment with intravenous morphine (Figs. 6 and 7), followed by the Killip class, current smoking status, prehospital heparin and clopidogrel application, and use of aspiration thrombectomy. Patients were more likely to be treated with morphine when presenting 2 hours after symptom onset (Fig. 6), being in Killip class 2 or 3, being active smokers, having received heparin and clopidogrel as well, and when aspiration thrombectomy was also performed. Median amounts of morphine hydrochloride applied in the treatment arms were 4.0 mg (IQR: 2.0 to 7.0 mg), 4.0 mg (IQR: 2.0 to 7.0 mg), and 4.0 mg (IQR: 2.0 to 6.2 mg) in the original, matched, and weighted data sets, respectively.

Table 4/A: Baseline demographic and anamnestic data (44)

	Original Sample				Matched Sample			Weighted Sample		
Variable	**No Morphine (n=858)**	**Morphine (n=397)**	**Absolute Standardized Difference**	**p Value**	**No Morphine (n=364)**	**Morphine (n=364)**	**Absolute Standardized Difference**	**No Morphine (n=860)**	**Morphine (n=394)**	**Absolute Standardized Difference**
Age Median (IQR) (years)	63.0 (54.0-73.0)	62.0 (54.0-72.0)	0.005	0.38	63.0 (54.0-73.0)	62.0 (54.0-72.0)	0.018	63.0 (54.0-72.0)	62.7 (54.0-72.0)	0.001
BMI Median (IQR) (kg/m^2)	27.2 (24.2-30.4)	27.0 (24.3-30.5)	0.029	0.86	27.0 (24.4-30.4)	26.8 (24.2-30.5)	0.066	27.0 (24.2-30.3)	26.7 (24.2-30.1)	0.052
Female	303 (35.3%)	141 (35.5%)	0.004	0.95	132 (36.3%)	129 (35.4%)	0.017	304 (35.3%)	146 (37.1%)	0.036
Hypertension	594 (69.2%)	275 (69.3%)	0.001	1.00	253 (69.5%)	250 (68.7%)	0.018	596 (69.3%)	271 (68.8%)	0.010
Diabetes mellitus	219 (25.5%)	90 (22.7%)	0.067	0.29	90 (24.7%)	84 (23.1%)	0.039	217 (25.2%)	102 (25.8%)	0.012
Verified dyslipidaemia	345 (40.2%)	154 (38.8%)	0.029	0.66	140 (38.5%)	141 (38.7%)	0.006	342 (39.7%)	151 (38.2%)	0.031
Current smokers	306 (35.7%)	178 (44.8%)	0.188	0.0022	147 (40.4%)	162 (44.3%)	0.084	335 (38.9%)	159 (40.4%)	0.031
Peripheral artery disease	63 (7.3%)	26 (6.5%)	0.031	0.64	24 (6.6%)	25 (6.9%)	0.011	63 (7.3%)	33 (8.4%)	0.041
Cerebrovascular disease	72 (8.4%)	27 (6.8%)	0.060	0.37	24 (6.6%)	26 (7.1%)	0.021	66 (7.7%)	27 (6.9%)	0.030
Congestive heart failure	46 (5.4%)	10 (2.5%)	0.146	0.03	12 (3.3%)	10 (2.7%)	0.028	38 (4.4%)	13 (3.2%)	0.062
Previous myocardial infarction	106 (12.4%)	42 (10.6%)	0.056	0.40	30 (8.2%)	41 (11.3%)	0.095	101 (11.8%)	47 (11.9%)	0.003
Previous percutaneous coronary intervention	63 (7.3%)	26 (6.5%)	0.031	0.64	19 (5.2%)	25 (6.9%)	0.065	63 (7.3%)	25 (6.3%)	0.042
Previous coronary artery bypass graft surgery	16 (1.9%)	10 (2.5%)	0.045	0.52	7 (1.9%)	9 (2.5%)	0.038	18 (2.1%)	8 (2.0%)	0.007
Chronic renal failure	33 (3.8%)	10 (2.5%)	0.076	0.25	11 (3.0%)	10 (2.7%)	0.016	29 (3.4%)	10 (2.7%)	0.043
Baseline Creatinine Median (IQR) (µmol/L)	79.0 (67.0-98.0)	79.0 (65.0-94.0)	0.026	0.50	78.0 (66.0-96.0)	79.0 (65.0-93.3)	0.022	78.0 (67.0-97.0)	50.0 (41.0-55.0)	0.044
Chronic obstructive pulmonary disease	64 (7.5%)	28 (7.1%)	0.016	0.91	21 (5.8%)	27 (7.4%)	0.064	64 (7.4%)	26 (6.5%)	0.033

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Table 4/B: Clinical characteristics (44)

	Original Sample				Matched Sample			Weighted Sample		
Variable	**No Morphine (n=858)**	**Morphine (n=397)**	**Absolute Standardized Difference**	**p Value**	**No Morphine (n=364)**	**Morphine (n=364)**	**Absolute Standardized Difference**	**No Morphine (n=860)**	**Morphine (n=394)**	**Absolute Standardized Difference**
Prehospital heparin	481 (56.1%)	296 (74.6%)	0.396	<0.0001	260 (71.4%)	266 (73.1%)	0.035	534 (62.0%)	248 (63.0%)	0.020
Prehospital clopidogrel	577 (67.2%)	331 (83.4%)	0.380	<0.0001	297 (81.6%)	298 (81.9%)	0.007	624 (72.5%)	291 (73.8%)	0.030
Onset-to-door time Median (IQR) (hours)	3.6 (2.0-6.0)	2.5 (2.0-4.0)	0.399	<0.0001	3.0 (2.0-4.5)	2.68 (2.0-4.0)	0.025	3.0 (2.0-5.5)	3.5 (2.0-5.0)	0.009
Door-to-balloon time Median (IQR) (min.)	47.0 (32.0-75.0)	45.0 (30.0-68.0)	0.174	0.0069	45.0 (30.0-68.0)	45.0 (29.8-67.0)	0.024	46.0 (30.0-71.0)	49.6 (30.0-70-0)	0.048
ECG localization										
- anterior	347 (40.4%)	181 (45.6%)	0.104	0.20	160 (44.0%)	164 (45.1%)	0.022	362 (42.1%)	159 (40.3%)	0.037
- inferior	455 (53.0%)	195 (49.1%)	0.078		186 (51.1%)	183 (50.3%)	0.017	445 (51.7%)	215 (54.5%)	0.056
- posterior / lateral	56 (6.5%)	21 (5.3%)	0.052		18 (4.9%)	17 (4.7%)	0.012	54 (6.2%)	21 (5.2%)	0.041
Cardiac arrest on or prior to admission	81 (9.4%)	22 (5.5%)	0.148	0.02	23 (6.3%)	21 (5.8%)	0.021	70 (8.1%)	33 (8.3%)	0.007
Heart rate Median (IQR) (1/min)	80.0 (69.0-90.0)	78.0 (67.0-90.0)	0.041	0.55	80.0 (68.0-90.0)	79.0 (67.0-90.0)	0.011	80.0 (69.0-90.0)	78.0 (67.0-90.0)	0.012
Systolic blood pressure Median (IQR) (mmHg)	130.0 (110.0-148.0)	130.0 (110.0-145.0)	0.026	0.66	130.0 (111.5-141.2)	130.0 (110.0-140.5)	0.049	130.0 (110.0-145.6)	130.0 (110.0-145-0)	0.005
Killip class										
1	721 (84.0%)	317 (79.8%)	0.109	0.95	300 (82.4%)	294 (80.8%)	0.043	708 (82.3%)	330 (83.8%)	0.038
2	54 (6.3%)	48 (12.1%)	0.202		34 (9.3%)	39 (10.7%)	0.048	70 (8.1%)	32 (8.2%)	0.002
3	13 (1.5%)	11 (2.8%)	0.087		12 (3.3%)	11 (3.0%)	0.019	21 (2.4%)	9 (2.2%)	0.015
4	70 (8.2%)	21 (5.3%)	0.115		18 (4.9%)	20 (5.5%)	0.022	61 (7.1%)	23 (5.8%)	0.053
Cardiogenic shock	64 (7.5%)	21 (5.3%)	0.089	0.18	19 (5.2%)	19 (5.2%)	0.000	57 (6.6%)	22 (5.6%)	0.043
Intra-aortic balloon pump	52 (6.1%)	17 (4.3%)	0.080	0.23	16 (4.4%)	16 (4.4%)	0.000	46 (5.4%)	17 (4.4%)	0.044
Mechanical ventilation	120 (14.0%)	32 (8.1%)	0.190	0.0028	32 (8.8%)	32 (8.8%)	0.000	107 (12.4%)	48 (12.1%)	0.009

Table 4/C: Procedural characteristics (44)

	Original Sample				Matched Sample			Weighted Sample		
Variable	**No Morphine (n=858)**	**Morphine (n=397)**	**Absolute Standardized Difference**	**p Value**	**No Morphine (n=364)**	**Morphine (n=364)**	**Absolute Standardized Difference**	**No Morphine (n=860)**	**Morphine (n=394)**	**Absolute Standardized Difference**
Glycoprotein IIb/IIIa receptor inhibitor	686 (80.0%)	351 (88.4%)	0.233	0.0002	313 (86.0%)	320 (87.9%)	0.053	709 (82.4%)	320 (81.2%)	0.033
Transradial primary percutaneous coronary intervention	742 (86.5%)	363 (91.4%)	0.159	0.01	334 (91.8%)	332 (91.2%)	0.018	756 (87.9%)	342 (86.8%)	0.036
Access site conversion	31 (3.6%)	17 (4.3%)	0.034	0.64	16 (4.4%)	15 (4.1%)	0.014	34 (4.0%)	15 (3.7%)	0.016
Vessel dilated										
- Left anterior descending	303 (35.3%)	157 (39.5%)	0.087		147 (40.4%)	145 (39.8%)	0.011	317 (36.8%)	140 (35.4%)	0.029
- Diagonal / Intermediate	10 (1.2%)	9 (2.3%)	0.085		7 (1.9%)	5 (1.4%)	0.042	14 (1.6%)	6 (1.5%)	0.005
- Left circumflex	100 (11.7%)	37 (9.3%)	0.076	0.23	36 (9.9%)	35 (9.6%)	0.009	94 (10.9%)	42 (10.7%)	0.008
- Right coronary	353 (41.1%)	146 (36.8%)	0.090		135 (37.4%)	138 (37.9%)	0.017	340 (39.5%)	161 (40.9%)	0.030
- Left main / Multivessel	88 (10.3%)	45 (11.3%)	0.035		37 (10.2%)	39 (10.7%)	0.018	92 (10.7%)	43 (11.0%)	0.007
- Bypass graft	4 (0.5%)	3 (0.8%)	0.037		2 (0.5%)	2 (0.5%)	0.000	4 (0.5%)	2 (0.4%)	0.004
Number of diseased vessels										
- 1	361 (42.1%)	166 (41.8%)	0.005	0.94	150 (41.2%)	152 (41.8%)	0.011	362 (42.1%)	176 (44.6%)	0.051
- 2	232 (27.0%)	108 (27.2%)	0.004		103 (28.3%)	97 (26.6%)	0.037	231 (26.8%)	99 (25.2%)	0.037
- 3 / Left main	265 (30.9%)	123 (31.0%)	0.002		111 (30.5%)	115 (31.6%)	0.024	268 (31.1%)	119 (30.2%)	0.019
Thrombus aspiration	331 (38.6%)	204 (51.4%)	0.259	<0.0001	163 (44.8%)	179 (49.2%)	0.089	363 (42.2%)	158 (40.1%)	0.043
Initial TIMI flow										
- 0	514 (59.9%)	254 (64.0%)	0.084		230 (63.2%)	232 (63.7%)	0.011	529 (61.5%)	249 (63.2%)	0.036
- 1	147 (17.1%)	76 (19.1%)	0.052	0.02	73 (20.1%)	68 (18.7%)	0.035	153 (17.8%)	74 (18.7%)	0.023
- 2	109 (12.7%)	42 (10.6%)	0.066		33 (9.1%)	39 (10.7%)	0.055	102 (11.8%)	36 (9.1%)	0.087
- 3	88 (10.3%)	25 (6.3%)	0.144		28 (7.7%)	25 (6.9%)	0.032	77 (8.9%)	35 (9.0%)	0.001
Final TIMI flow										
- 0	8 (0.9%)	4 (1.0%)	0.008		4 (1.1%)	3 (0.8%)	0.028	9 (1.1%)	4 (1.0%)	0.010
- 1	6 (0.7%)	3 (0.8%)	0.007	0.96	2 (0.5%)	3 (0.8%)	0.033	6 (0.7%)	2 (0.6%)	0.008
- 2	43 (5.0%)	19 (4.8%)	0.010		15 (4.1%)	17 (4.7%)	0.027	40 (4.6%)	16 (3.9%)	0.035
- 3	801 (93.4%)	371 (93.5%)	0.004		343 (94.2%)	341 (93.7%)	0.023	805 (93.6%)	372 (94.5%)	0.037
Failed PCI	26 (3.0%)	11 (2.8%)	0.86	0.016	12 (3.3%)	10 (2.7%)	0.033	26 (3.1%)	14 (3.6%)	0.031

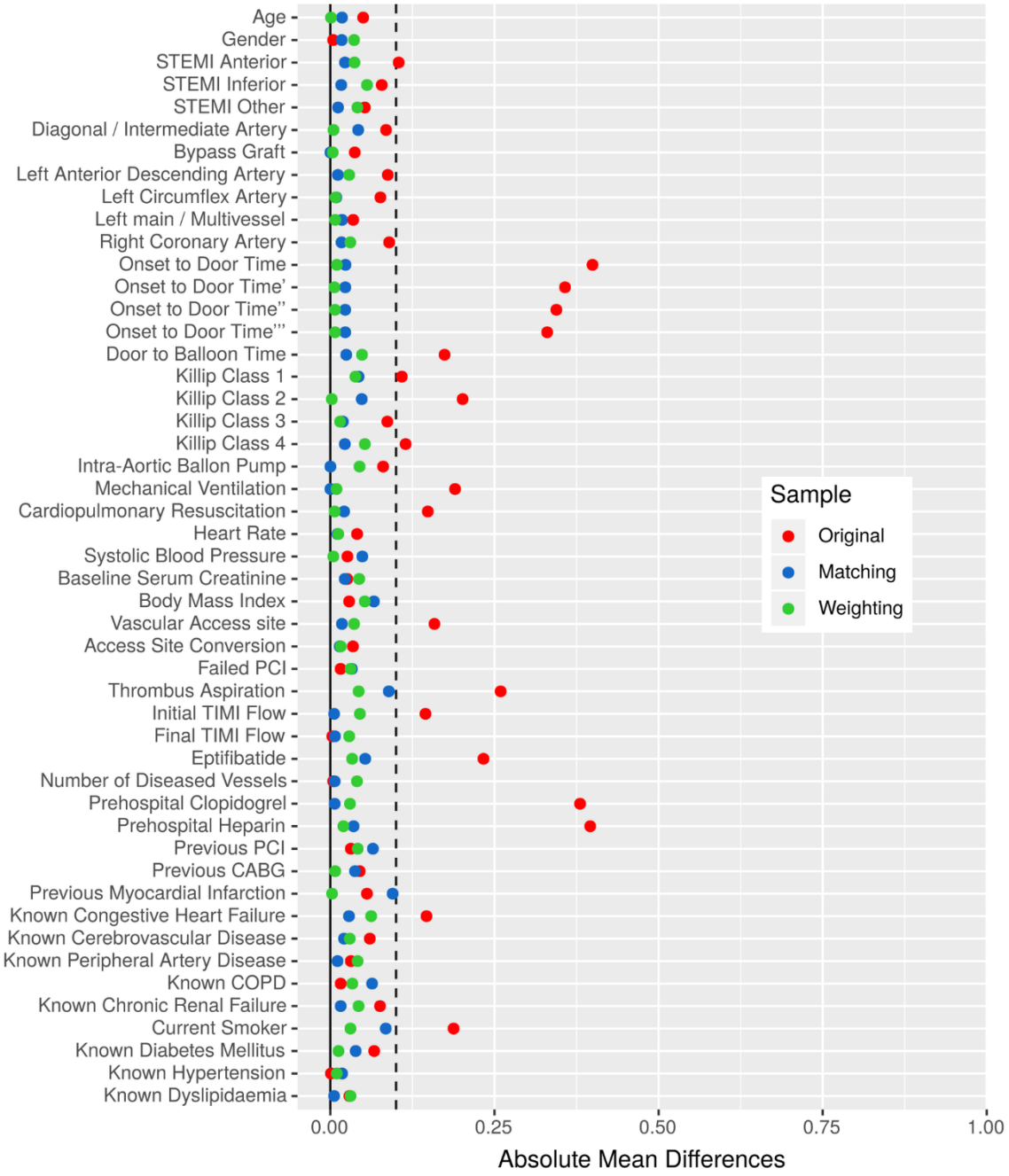

Fig. 5: Covariate balance. The dot chart shows absolute standardized differences between control and treated groups across all measured baseline covariates. A value less than 0.1 was considered as an acceptable standardized bias. Systematic differences between treated and untreated patients in the original cohort have been eliminated in both matched and weighted samples. Adequate balance on baseline variables has been achieved in both matched and weighted sets since potentially prognostically important covariates have been balanced between the treated and control groups (44). CABG: Coronary Artery Bypass Graft, COPD: Chronic Obstructive Pulmonary Disease, PCI: Percutaneous Coronary Intervention, STEMI: ST-Elevation Myocardial Infarction. [9]

[9] This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. https://creativecommons.org/licenses/by-nc-nd/4.0/

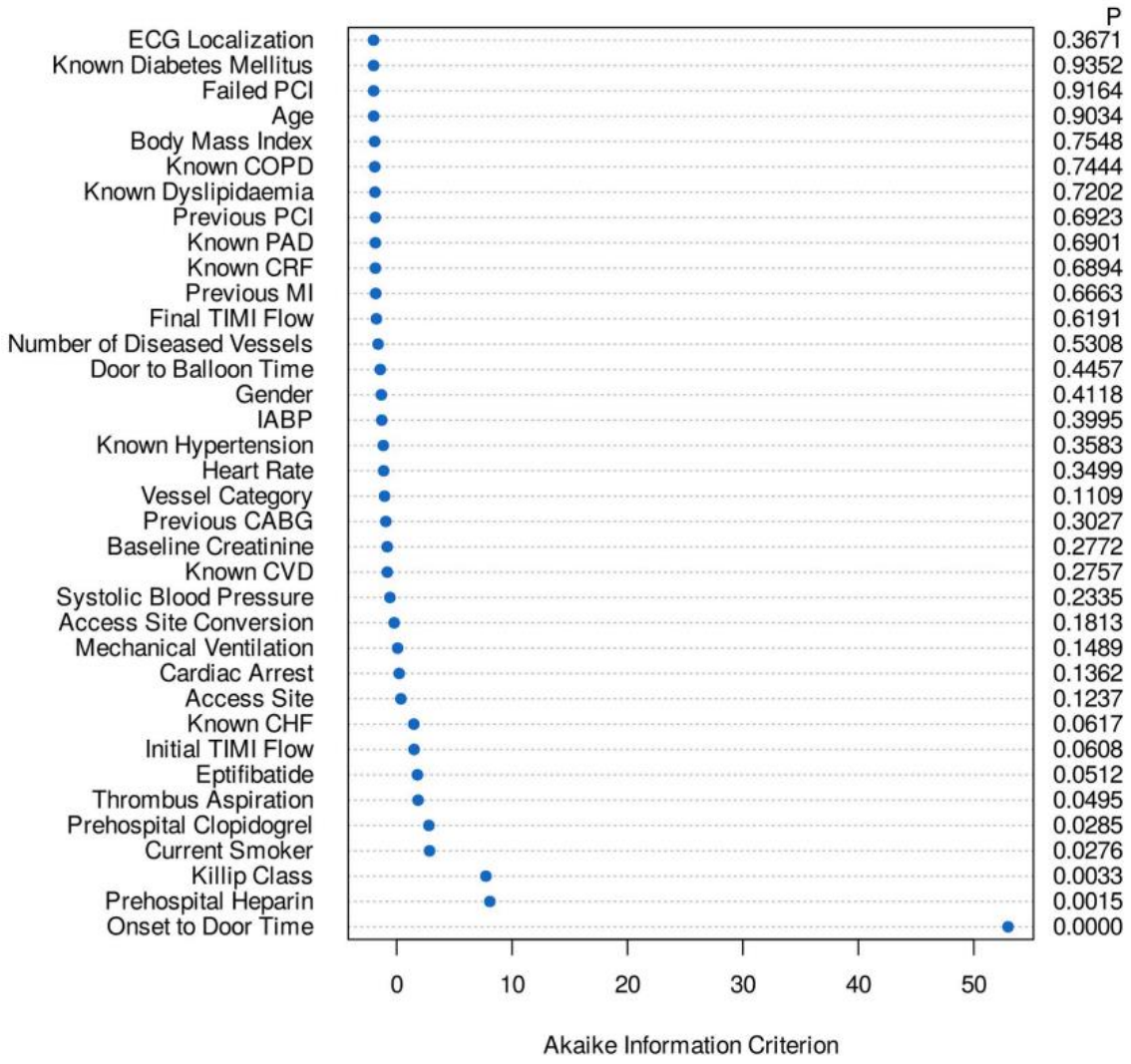

Fig. 6: Importance of variables in the propensity score models. Dot chart depicts the importance of each variable as measured by the Akaike information criterion. The p value denotes statistical significance. The most important predictors of treatment allocation (morphine administration) were onset-to-door time as a non-linear parameter, Killip class, current smoking status, prehospital heparin and clopidogrel application, and use aspiration thrombectomy (44). ECG: Electrocardiogram, PCI: Percutaneous Coronary Intervention, COPD: Chronic Obstructive Pulmonary Disease, PAD: Peripheral Artery Disease, CRF: Chronic Renal Failure, MI: Myocardial Infarction, TIMI: Thrombolysis In Myocardial Infarction, IABP: Intrarterial Balloon Pump, CABG: Coronary-Artery Bypass Graft, CVD: Cerebrovascular Disease, CHF: Chronic Heart Failure. [10]

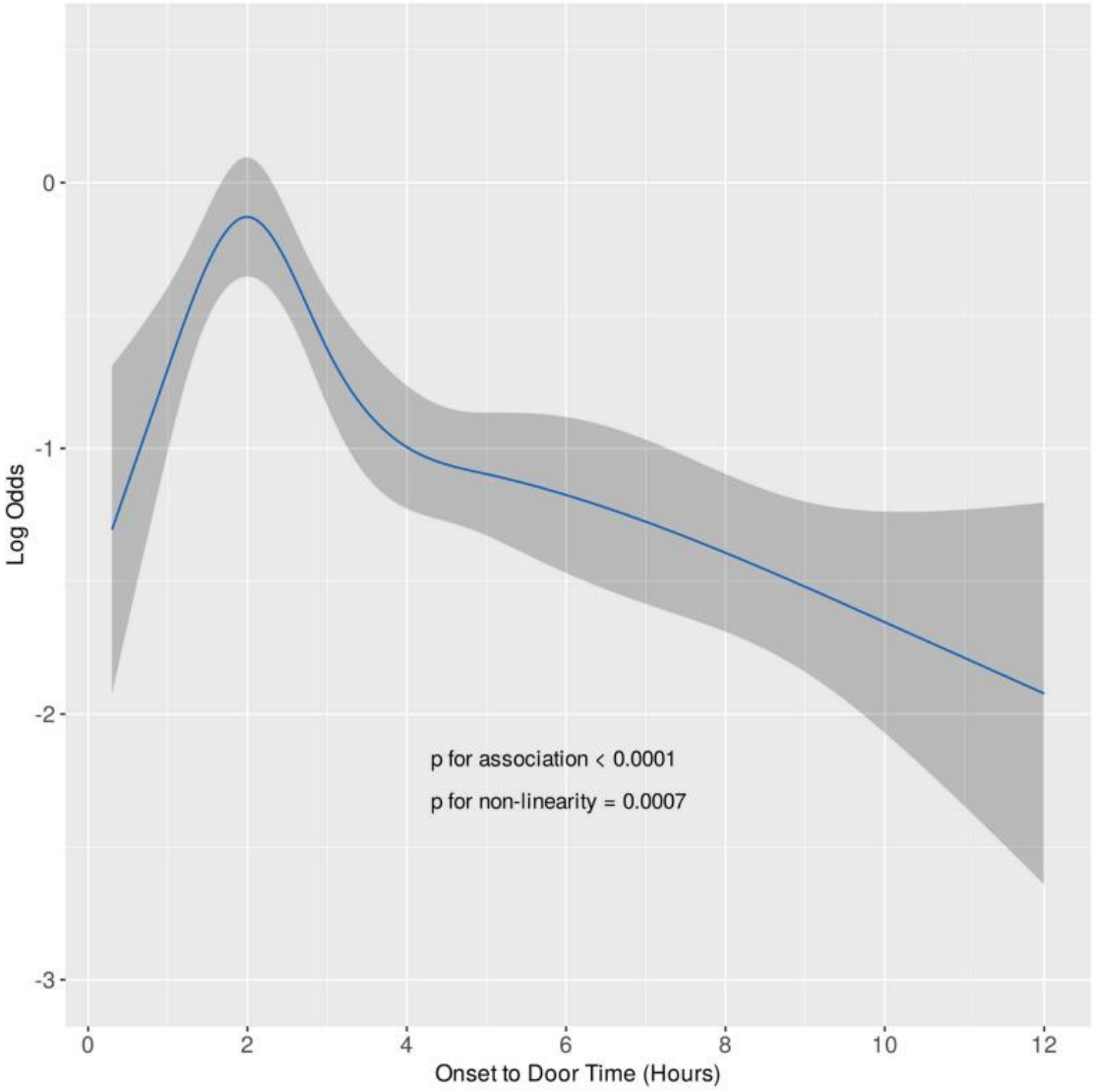

Fig. 7: Unadjusted association of onset-to-door time with intravenous morphine use. The relationship was explored using a restricted cubic spline with five knots placed at 1, 2, 3, 5, and 10 hours (corresponding to percentiles 5, 27.5, 50, 72.5, and 95). With these settings, the curve is allowed to be flexible between 1 and 10 hours, representing 90% of the sample. The gray ribbon shows 95% confidence intervals. The association is highly significant ($p<0.0001$). Wald testing for linearity suggests a strong non-linear relationship ($p = 0.0007$) (44).[11]

4.2.2. Primary endpoint

Original sample, crude analysis. Comparison of the Kaplan-Meier survival curves using the log-rank test revealed a statistically significant absolute all-cause mortality risk difference between the control and treated cohorts favouring treatment with morphine (p=0.0229, Fig. 8/A). Similarly, analysis of the relative effect size using a naïve, univariable Cox model, the hazard ratio (HR) was 0.79, 95% CI: 0.64 to 0.97, p=0.0233, (Fig. 9, upper panel). Estimation of the average treatment effect for the treated (ATT) using propensity score matching. After adjusting for confounding with 1:1 propensity score matching, there was no absolute risk difference detectable between the Kaplan-Meier survival curves of the control and treated groups (p = 0.3046, log-rank test stratified on matched pairs, Fig. 8/B). Likewise, the relative change in the hazard of death was not statistically significant when analyzed by Cox regression (HR: 0.98, 95% CI: 0.76 to 1.26, p=0.8574, Fig. 9, middle panel). Assessing the average treatment effect (ATE) by inverse probability of treatment weighting with stabilised weights. As to absolute mortality risk difference, the Kaplan- Meier curves of the treated and untreated arms were almost identical (p = 0.8518, design-based log-rank test, Fig. 8/C). In addition, the hazard ratio was 1.01, 95% CI: 0.80 to 1.28, p=0.9010 (Fig. 9, lower panel).

4.2.3. Secondary outcome measure

There was no difference in predischarge left ventricular ejection fraction between the control and treated groups–in both statistical and clinical senses–in any of the analysed samples. The results are summarised in Table 5.

Table 5: Secondary outcome measure: Predischarge left ventricular ejection fraction (44)

	Original Sample			Matched Sample			Weighted Sample		
Variable	**No Morphine (n=858)**	**Morphine (n=397)**	**p Value**	**No Morphine (n=364)**	**Morphine (n=364)**	**p Value**	**No Morphine (n=860)**	**Morphine (n=394)**	**p Value**
Predischarge Left Ventricular Ejection Fraction Median (IQR)	50.0 (43.0-56.0)	50.0 (42.0-55.0)	0.4580	50.0 (43.0-55.25)	50.0 (42.0-55.0)	0.7621	50.0 (42.5-55.0)	50.0 (41.0-55.0)	0.8612

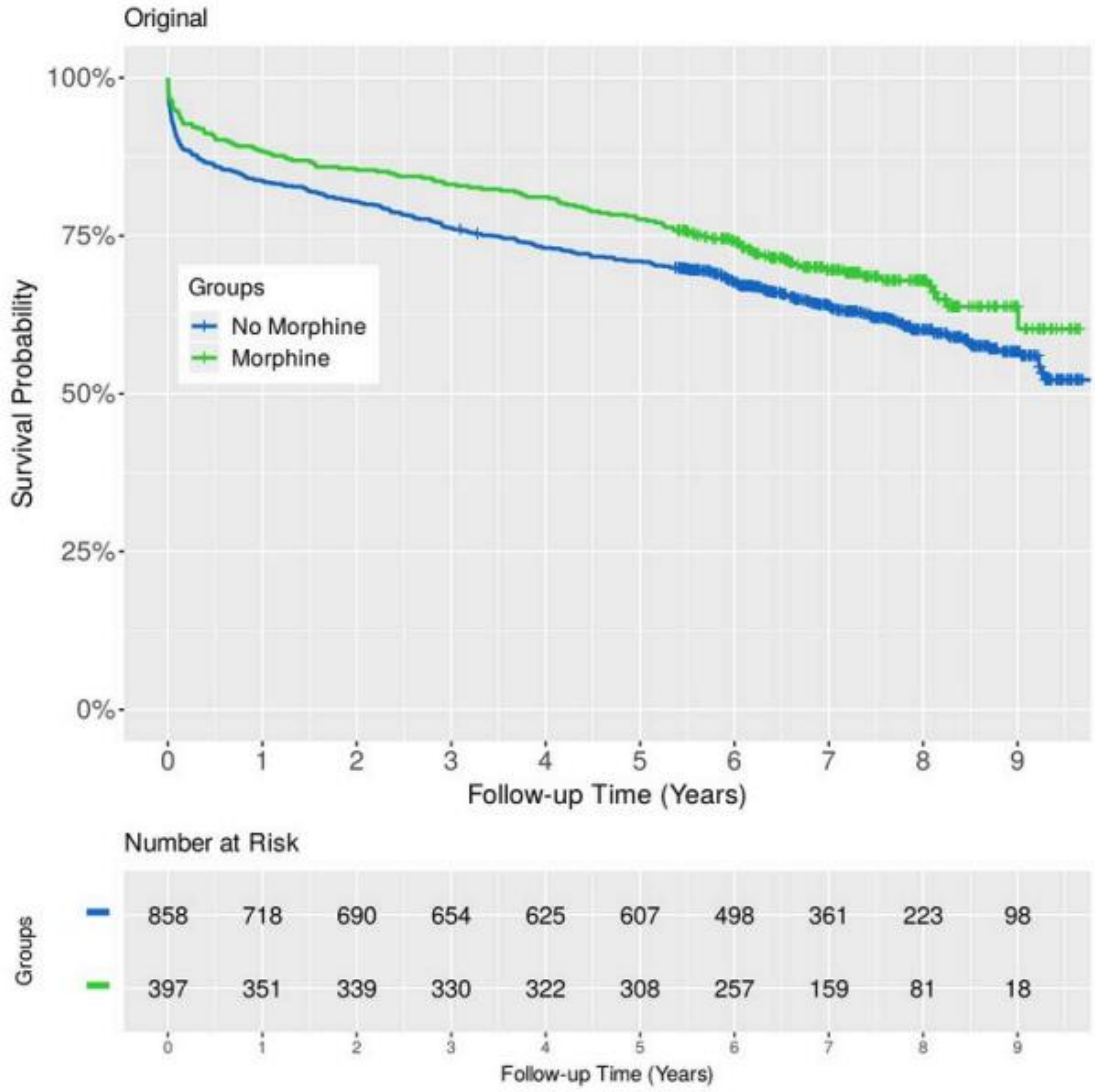

Fig. 8/A: Comparison of Kaplan-Meier survival curves – The original dataset. Analysis of the crude data revealed a statistically significant absolute mortality risk difference between the control and treated groups (p = 0.0229, log-rank test) (44).[12]

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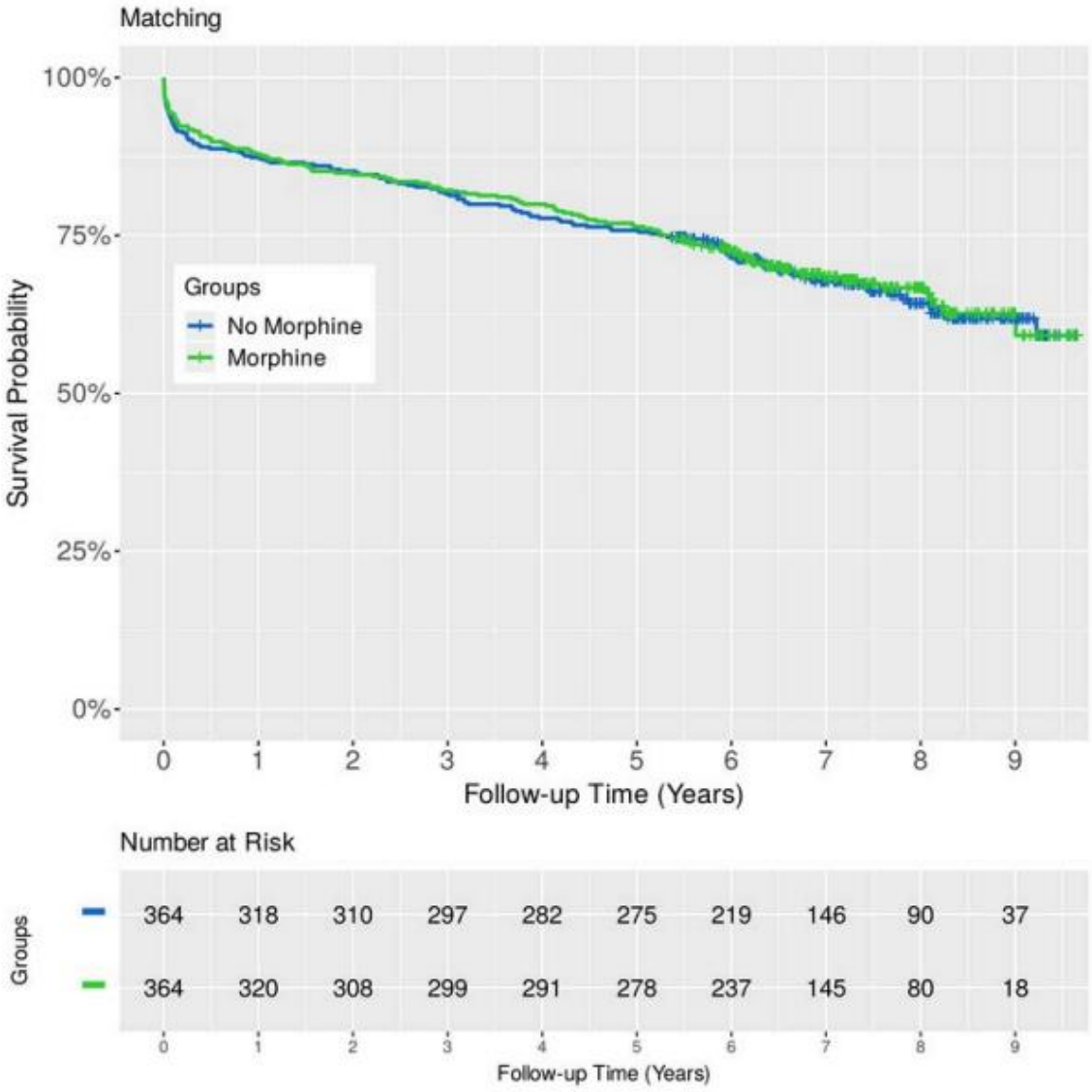

Fig. 8/B: Comparison of Kaplan-Meier survival curves – after propensity score matching. The difference observed in the original dataset is not detectable after adjusting for confounding using propensity score matching (p = 0.3046, log-rank test stratified on matched pairs). Censored data are indicated with small vertical tick-marks (44).[13]

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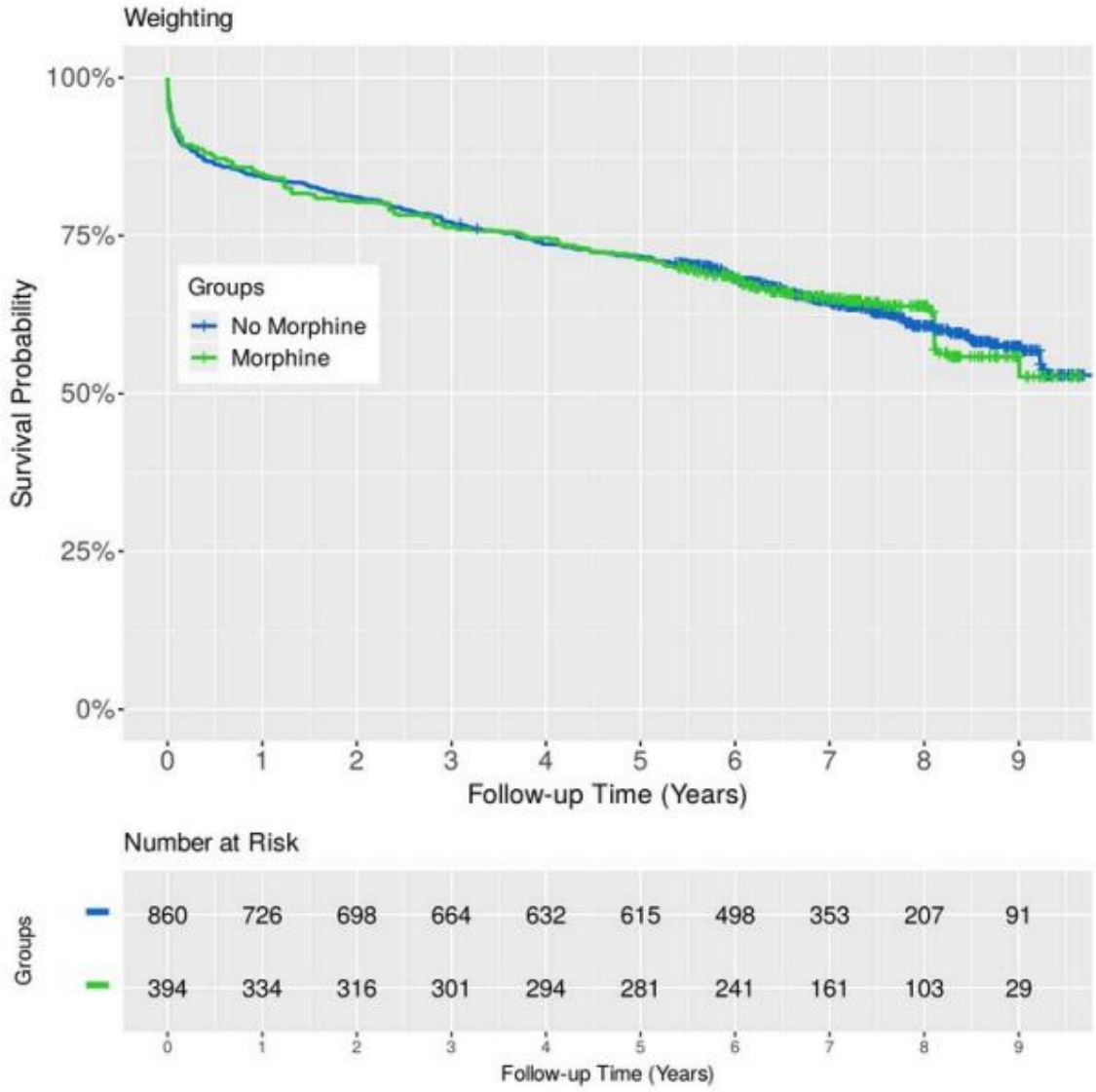

Fig. 8/C: Comparison of Kaplan-Meier survival curves – after inverse probability of treatment weighting. The difference observed in the original dataset is not detectable after adjusting for confounding using inverse probability of treatment weighting (p = 0.8518, design-based log-rank test). Censored data are indicated with small vertical tick-marks (44).[14]

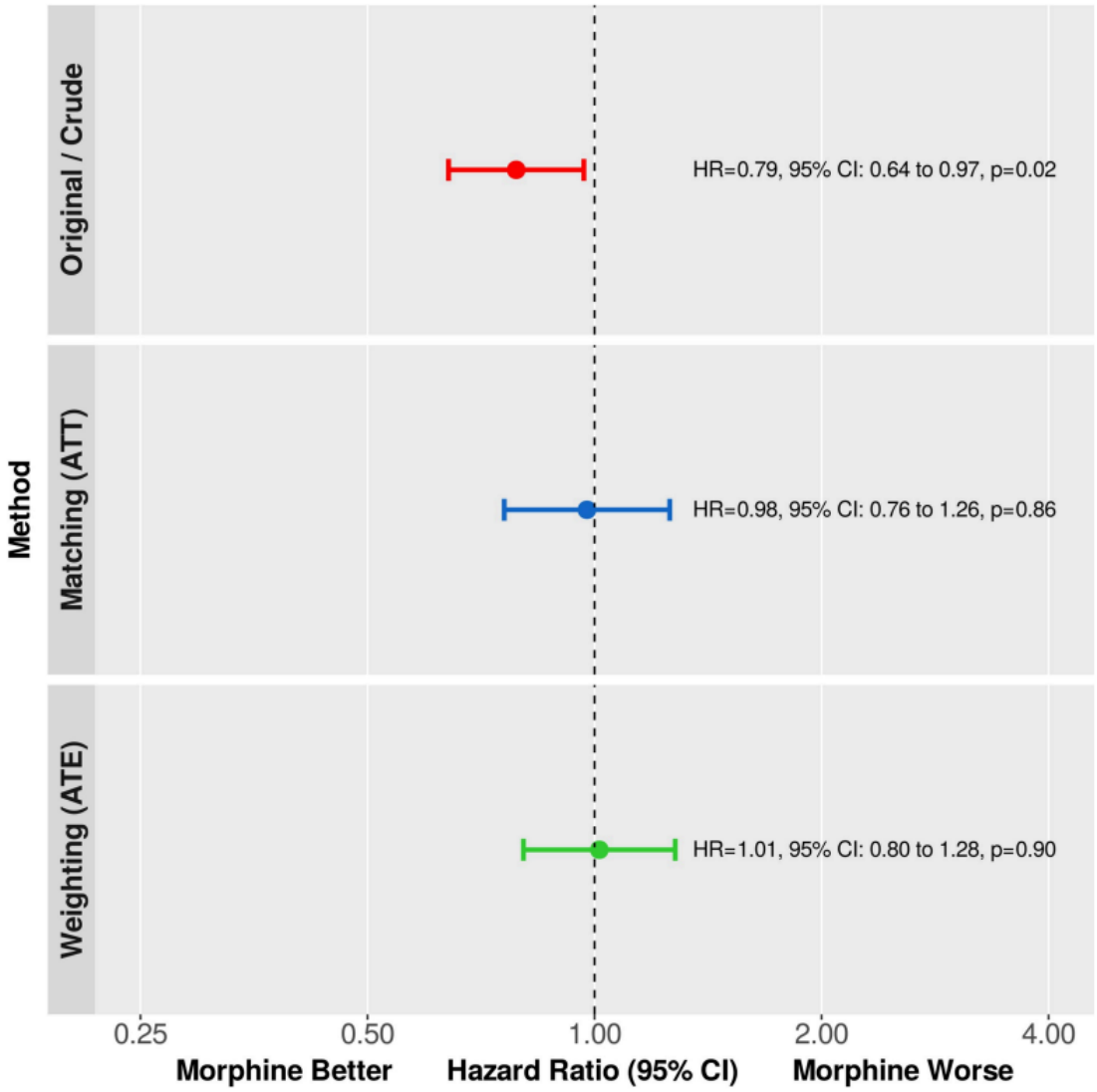

Fig. 9: Primary end point. The relative change in the hazard of death was estimated using univariable Cox regression in the original, matched, and weighted samples. Hazard ratios (HR) are shown as point estimates and 95% confidence intervals. Analysis of the crude data showed a statistically significant relative mortality difference favouring treatment with morphine. However, after reducing the bias with propensity score matching or inverse probability of treatment weighting, there is no significant difference detectable—in both statistical and clinical senses (44). ATE: Average Treatment Effect, ATT: Average Treatment effect of the Treated, CI: Confidence Interval.[15]

5. Discussion

5.1. Venous lactate level as a predictor

5.1.1. Principal findings, general considerations

According to the current guidelines of the European Society of Cardiology, all STEMI patients' short-term risk should be assessed early for which the GRACE 2.0 risk score is recommended (24). As in many of the risk estimation algorithms constructed for STEMI patients, heart rate and systolic blood pressure are key predictors in this model as well (2). Though these vital parameters may be influenced by the applied medical therapy or mechanical circulatory support, there is no evidence, that this is also accompanied by an improvement in microcirculation / prognosis of the patient. Therefore, we investigated whether the admission lactate level, a known marker of microcirculatory failure, may have an added prognostic value on top of the well validated GRACE 2.0 model. We found, that admission venous lactate level and the GRACE 2.0 score may be independent and additive predictors of 30-day all-cause mortality of STEMI patients treated with primary PCI (43).

In our study, we used a set of statistical metrics for new biomarkers following current recommendations (46). The widely used c-statistic, which is known to be a relatively insensitive measure for model selection, failed to show any improvement in the expanded model using any of the investigated dependent variables (45-47, 54). Nevertheless, its use is still recommended – even though not as primary metric – when testing new biomarkers (46).

5.1.2. Context with previous reports

In 2010, Vermeulen et al. drew attention to the early prognostic value of lactate as an indicator for the severity of decreased systemic blood flow with correspondingly poor outcomes in STEMI patients treated with primary PCI. Half of the non-survivors with admission lactate levels above 1.8 mmol/L died within 24 hours after presentation. Nevertheless, this cut-off value was based on tertiles, rather than formal analysis. Also, patients who were on mechanical ventilation at admission following cardiopulmonary resuscitation were excluded from the analysis (55). Meanwhile, several other studies have been published about the prognostic importance of lactate level on survival in acute coronary syndrome patients. Yet, in most of these works, lactate level was neither treated

as a continuous measure, nor was potential non-linearity investigated. Instead, it was used as a binary variable (with arbitrarily set cut-off values), which implies information loss (56-58). Attana´ et al. described the role of lower lactate clearance in higher mortality of patients with STEMI complicated by cardiogenic shock (59). Recently, these initial results from 51 patients were confirmed by Park et al. analysing a large, multi-centre registry with 628 cardiogenic shock patients (60). Gjesdal et al. found that blood lactate is a predictor of short-term mortality in PCI-treated patients with myocardial infarction complicated by mild to moderate heart failure even in the absence of cardiogenic shock (61). Unlike these previous works, we analysed an unselected cohort of STEMI patients undergoing primary PCI and lactate level was treated as a continuous variable, thereby preserving prognostic information. Moreover, we studied lactate level not as a stand-alone variable, but rather on top of the extensively validated GRACE 2.0 score with 8 well-established predictors (43).

Venous sampling may be considered as a limitation of the present work. Yet, for our pilot observational study, we used data that were readily available not requiring any intervention, as venous blood gas analysis – including the measurement of lactate – is routinely performed in all newly admitted acute patients in our cardiac intensive care unit. Moreover, it has been shown that there is a correlation between arterial and central venous (sampled from the right atrium, superior vena cava, or from the pulmonary artery) lactate levels and that the concentrations are essentially equivalent (62). Furthermore, Younger et al. even found a strong association between arterial and peripheral venous lactate levels (63). In a systematic review, Kruse et al. published that the correlation between lactate levels in arterial and venous blood was acceptable and venous sampling should therefore be encouraged thereby minimizing the risk and inconvenience for the patient (64). Despite the strong correlation, the agreement is not perfect, therefore caution should be used in the routine substitution of venous for arterial blood sampling as recommended by Gallagher et al. (65). Nevertheless, the probability of arterial hyperlactataemia may be substantially reduced, if the lactate level is normal in the venous sample (65). For the above reasons, to completely rule out this potential bias, we are planning to repeat the study with arterial blood sampling at the time of coronary angiography.

5.1.3. Potential clinical applications

Though our preliminary findings should be confirmed by larger, preferably multi-centre studies before introducing it into daily practice, they may have several potential clinical implications. For example, an elevated admission lactate level in a patient with a low-to-moderate risk profile based on the GRACE 2.0 score may signal a higher risk of death and may necessitate closer patient monitoring and the search for the underlying causes. The more accurate risk prediction may provide more useful information for patients or relatives and help physicians to allocate hospital resources. It may improve intra-organizational quality monitoring. It may allow a more precise risk adjustment in inter-organizational comparisons of health care providers with different case mixes. Furthermore, it may be helpful in a more exact clinical trial design identifying patients with the needed risk profile thereby increasing statistical power or reducing sample size and costs.

5.1.4. Strengths and limitations

Our results are based on a prospective registry of a single high-volume institution. We analysed data of a real-world, relatively high-risk population treated in a contemporary fashion (i.e., high rate of transradial access site, almost exclusive use of drug eluting stents, guideline-directed discharge medications).

Yet, the single-centre nature of the data does not allow generalization of the findings to populations / centres of other geographic regions. Moreover, we exclusively used venous blood samples. Furthermore, the potential effect of different $P2Y_{12}$ receptor inhibitors on mortality was not investigated. Finally, we did not study data of non-ST-segment elevation acute coronary syndrome cases. Thus, our data are not applicable in this setting.

5.2. Impact of morphine use on mortality

5.2.1. Principal findings, general considerations

Morphine is traditionally used in STEMI patients to relieve pain, decrease pulmonary congestion, and anxiety. However, according to in vitro measurements, intravenous morphine delays and diminishes the effects of all currently used oral platelet $P2Y_{12}$ receptor antagonists (i.e., clopidogrel, prasugrel, and ticagrelor) (26-32). Consequently, the European Society of Cardiology published a warning note in its current guidelines on

STEMI that this phenomenon may lead to early treatment failure (24). Nevertheless, there are limited data available about the impact of this interaction on clinical outcomes. Therefore, we investigated the effect of periprocedural morphine application on all-cause mortality in real-world STEMI patients who underwent primary PCI. We intentionally choose all-cause rather than cardiovascular mortality as an objective, unbiased primary end point (66). Also, though periprocedural use of MO is single time-point intervention, we deliberately investigated long-term rather than short-term mortality, since initial observational reports suggested that application of MO may be associated with poorer myocardial reperfusion (33) and larger infarct size (34) whose deleterious effects on mortality may better be detected later. To adjust for confounding, two distinct propensity score-based procedures were performed to assess both average treatment effect (ATE) and average treatment effect for the treated (ATT). Among the most important predictors of treatment allocation were symptom-onset-to-door time and Killip class suggesting that the application of morphine was not based simply on default preferences of the treating physicians but rather driven by the actual clinical presentation of the patient. Our results indicate that intravenous morphine may have no impact on both absolute and relative measures of mortality in patients treated with primary PCI (44).

5.2.2. Context with previous reports

The importance of the interaction between IV morphine administration and oral platelet $P2Y_{12}$ receptor inhibitors on clinical outcomes is poorly elucidated. There was only one randomised controlled trial conducted in this field, the "Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction" (IMPRESSION) study (29). Beyond the in vitro finding that morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction (both STEMI and non-STEMI), the low number of in-hospital clinical events did not allow statistical analysis whereas longer-term outcomes were not recorded at all. All other available data are observational (two post-hoc analyses of randomised controlled trials (36, 40) and eight cohort studies (31, 33, 34, 37-39, 41, 42) with mainly small to moderate sample sizes). Iakobishvili et al. published data of 249 propensity score-matched pairs showing that IV morphine use was associated with improved 30-day survival of STEMI patients (2.4% vs. 6.2%, $p = 0.04$ in the MO and no MO groups,

respectively) (39). In 2015, de Waha et al. reported data of 276 patients that IV morphine use is related to larger infarct size, greater extent of microvascular obstruction, and lower myocardial salvage index as found by cardiac magnetic resonance imaging (CMR). Yet, similarly to our results (Table 5), these differences could not be observed at the level of left ventricular ejection fraction. Also, in concert with our findings, survival curves were not different during the median follow-up of 16 months (34). In the publication of Parodi et al. the small sample size (300 cases) did not allow to evaluate a potential detrimental consequence of IV morphine on in-hospital clinical end points. Yet, the published data do not imply such an effect (31). According to the data of Puymirat et al. from 388 propensity score-matched pairs, prehospital morphine use in STEMI was not associated with worse in-hospital complications and 1-year mortality (42). Likewise, in the small study by Bellandi et al. (182 cases) no change in complications could be observed during the hospital course that could be related to treatment with IV morphine (33). Similarly, in the study by Gwag et al. with a sample size of 299 patients, there was no significant difference detectable in the clinical end point (a composite of cardiac death, recurrent myocardial infarction, ischaemic stroke, and repeated coronary revascularisation) according to IV morphine use with or without propensity score-matched analysis (38). In addition, McCarthy et al. presented their results from a single-centre observational study indicating that, after propensity score matching (107 pairs), morphine use do not affect in-hospital outcomes in STEMI patients (41). Bonin et al. used the database of the "Does Cyclosporine Improve Outcome in ST Elevation Myocardial Infarction Patients" (CIRCUS) trial with 969 anterior STEMI patients (36, 67). They found no differences in a series of clinical end points including all-cause mortality rate during 1 year of follow-up (36). Similarly, Lapostolle et al. performed a spin-off analysis of the "Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery" (ATLANTIC) study data (40, 68). There was no evidence that IV morphine application had an influence on any of the investigated clinical end points (all-cause death, myocardial infarction, stroke, urgent revascularisation, and definitive acute stent thrombosis) (40). Also, Farag et al. did not detect any statistically significant changes in clinical event rates including death during hospital stay in their 2018 report with 300 patients (37).

More recently, Batchelor et al. published a meta-analysis of the above studies indicating that periprocedural intravenous morphine administration is not associated with adverse short term clinical outcomes (in-hospital or 30-day myocardial reinfarction/mortality) in patients who undergo primary PCI (35). Nevertheless, as described above, of the 11 investigated studies 10 were observational with predominantly small to moderate sample sizes and considerable methodological heterogeneity, whereas the remaining randomized controlled trial, because of the low sample size and short follow-up, was lacking any mortality events to be analysed (29) making the interpretation of this meta-analysis equivocal. Also, the limited amount of data that are available about long-term outcomes were not sufficient for performing a meta-analysis. In summary, our findings are consistent with all of the above reports suggesting that morphine administration does not increase the mortality in STEMI patients treated with primary PCI. Also, similarly to the results of de Waha et al. assessing the left ventricular ejection fraction with CMR (34), we could not detect any deterioration of the LVEF using echocardiography that could be attributable to IV morphine use (44).

5.2.3. Strengths and limitations

To our knowledge, among the published papers investigating the impact of the interaction between intravenous morphine application and oral platelet $P2Y_{12}$ receptor inhibitors on all-cause mortality in patients treated with primary PCI, this study has the longest follow-up time (median 7.5 years, IQR: 6.5 to 8.6 years) and the highest number of events (457 deaths).

Despite the observational nature of the present work, the long follow-up of a real-world population with an adequate number of events together with the applied complex statistical methods may allow an unbiased estimation of the treatment effect (53).

Our results are based on a prospective registry of a single institution. Also, we exclusively used a clopidogrel throughout the study period (from September 2007 through December 2011). Therefore, our findings may not be generalizable to populations/centres of other geographic regions and to other $P2Y_{12}$ receptor inhibitors.

To overcome this limitation, a pilot validation test was performed on the database of the lactate study population (see details in the previous chapter), who were predominantly treated with the novel $P2Y_{12}$ inhibitors prasugrel or ticagrelor, according to the current

guidelines. Kaplan-Meier analysis showed no statistically significant difference in all-cause mortality of the treatment groups neither in the original nor in the propensity score-matched population. In the matched population we found no difference in survival. Our preliminary data suggest that morphine may have no impact on mortality in STEMI patients treated with primary PCI and medical therapy according to the current guidelines including novel $P2Y_{12}$ antagonists (69) (see also the Appendix).

Lacking comprehensive long-term data on non-fatal ischemic events, we could not assess a possible effect of periprocedural intravenous morphine on them. Finally, we did not study (and discuss) data of non ST-segment elevation acute coronary syndrome (NSTE-ACS) cases because the inherent differences in the time frames of morphine/ $P2Y_{12}$ inhibitor administration and the invasive procedure might have introduced substantial bias into the results. Thus, our data are not applicable for the setting of NSTE-ACS.

6. Conclusions

Our results suggest that admission venous lactate level and the GRACE 2.0 score may be independent and additive predictors of 30-day all-cause mortality of STEMI patients treated with primary PCI. Because of the aforementioned limitations, further, preferably multi-centre randomized trials with arterial blood sampling are warranted to confirm the findings of the present study.

Despite previous findings indicating that periprocedural intravenous morphine administration may delay and reduce the effect of oral platelet $P2Y_{12}$ receptor inhibitors in vitro which may be associated with larger infarct size, our data suggest that intravenous morphine may have no impact on predischarge left ventricular ejection fraction and–more importantly–on all-cause mortality in STEMI patients treated with primary PCI. Thus, it may safely be used for pain relief, pulmonary congestion, and anxiety even in the era of primary percutaneous coronary intervention, when reliable platelet $P2Y_{12}$ receptor inhibition is of crucial importance.

7. Summary

Background & Aims: Risk estimation is an integral part of the daily medical practice. Our research group previously collected and analysed the mortality risk models and their external validation studies used for patients with STEMI. In many of the algorithms, heart rate and systolic blood pressure are key predictors. We aimed to investigate whether venous lactate level, a marker of microcirculatory failure, may have a prognostic value. Morphine (MO) is used for symptom relief in STEMI, however it decreases and delays the effect of $P2Y_{12}$ receptor inhibitors in vitro and its use may be associated with larger infarct size. We studied the impact of periprocedural MO application on all-cause mortality. **Methods:** We used two distinct prospective real-world registries, with the data of STEMI patients treated with primary PCI within 12 hours from symptom onset. In the 'Lactate' study we collected 323 patients who underwent venous blood gas analysis at cardiac care unit admission. Nested logistic regression models were built using the GRACE 2.0 score alone and with the addition of venous lactate with 30-day all-cause mortality. ROC analysis, likelihood ratio test, integrated discrimination improvement and variance inflation factor were used for statistical analysis. In the 'MO' study we collected 1255 cases. Primary outcome measure was time to all-cause death, median follow-up time was 7.5 years. In this work, to adjust for confounders, two distinct propensity score-based techniques were applied. Both absolute and relative change in mortality risk were also estimated. **Results:** The addition of lactate improved the model's performance: the expanded model may have better predictive ability than the GRACE 2.0 score alone. The variance inflation factor indicated lack of collinearity. The results based on the original dataset, suggested a statistically significant absolute and relative mortality risk difference between the MO-treated and control cohorts favouring treatment with MO. However, reducing the bias in treatment allocation using propensity score matching or inverse probability of treatment weighting, there was no significant difference detectable in the outcomes of the two treatment groups.

Conclusion: Admission venous lactate level, a biomarker of microcirculatory failure and the extensively validated GRACE 2.0 score may be independent and additive predictor of mortality in STEMI patients treated with primary PCI. Intravenous MO administration during the periprocedural care may have no impact on long-term all-cause mortality in STEMI patients treated with primary PCI.

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9. Bibliography of the candidate's publications[16]

9.1. Publications related to the present thesis (Σ IF: 10.399)

1. Hizoh I, Domokos D, Banhegyi G, Becker D, Merkely B, Ruzsa Z. Mortality prediction algorithms for patients undergoing primary percutaneous coronary intervention. J Thorac Dis. 2020;12(4):1706-20.

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2. Domokos D, Szabo A, Banhegyi G, Major L, Kiss RG, Becker D, et al. Impact of periprocedural morphine use on mortality in STEMI patients treated with primary PCI. PLoS One. 2021;16(1):e0245433.

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IF: 3.752

9.2. Publications not related to the present thesis (Σ IF: 29.607)

1. Pólos M*, Domokos D*, Şulea CM, Benke K, Csikós G, Nagy A, et al. Needle in the heart: a rare case of cardiac tamponade caused by a migrated foreign body and mimicking ST segment elevation myocardial infarction. BMC Cardiovasc Disord. 2021;21(1):143.

**contributed equally to the preparation of the manuscript*

IF: 2.174

2. Szabó A, Tóth K, Nagy Á, Domokos D, Czobor N, Eke C, et al. The effect of cognitive dysfunction on mid- and long-term mortality after vascular surgery. BMC Geriatr. 2021;21(1):46.

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In 2020, we organized and managed a prospective registry to investigate whether venous lactate level, a well-known marker of microcirculatory failure, might have additional prognostic value in predicting 30-day all-cause mortality in STEMI patients treated with primary PCI, in addition to the conventional variables of the GRACE 2.0 model. This investigation required daily in-person attendance and data collection, which would not have been possible without the assistance of my colleagues: A special thank you to Szilvia Kugler, Anita Pintér, Levente Magyar, Vencel Juhász, Mihály Ruppert and Attila Oláh. I would also like to thank the scientific support of Drs. Zoltán Ruzsa, István Ferenc Édes, Professor Béla Merkely and Professor Dávid Becker. During this research, I was able to acquire a more complex methodology and attitude from István Hizoh.

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Appendix: additional preliminary results to the impact of morphine use on mortality

Our results (see the chapter 4.2.) are based on a prospective registry of a single institution. Also, we exclusively used a clopidogrel and bare metal stents throughout the study period (from September 2007 through December 2011). Therefore, our findings may not be generalizable to populations/centres of other geographic regions, to other P2Y12 receptor inhibitors and the modern drug eluting stents, they are used in today's clinical practice.

To overcome this limitation, a pilot validation test was performed on the database of the lactate study population, who were predominantly treated with the novel P2Y12 inhibitors prasugrel or ticagrelor, according to the current guidelines.

Of the 297 consecutive STEMI cases who were treated with primary PCI, 126 patients (42.4%) received IV morphine during the periprocedural period. Outcome measure was time to all-cause mortality. The median follow-up time was 147 days (IQR 71 to 242 days), with 39 events. To adjust for confounding, a 1:1 propensity score matching analysis (PSM) was performed using 186 cases. Absolute difference in survival was analysed using Kaplan-Meier survival curves and the log-rank test, whereas the relative change was assessed by univariable Cox regression.

An adequate balance on baseline covariates was achieved by the propensity score-matching. Kaplan-Meier analysis showed no statistically significant difference in all-cause mortality of the treatment groups neither in the original nor in the propensity score-matched population (p=0.220 and 0.762 respectively). In the matched population we found no difference in survival as the HR (Morphine/No Morphine) was 0.88 (95% confidence interval [CI]: 0.39–2.00), p=0.76. (Fig. 10.)

Our preliminary data suggest that morphine may have no impact on mortality in STEMI patients treated with primary PCI and medical therapy according to the current guidelines including novel P2Y12 antagonists (69).

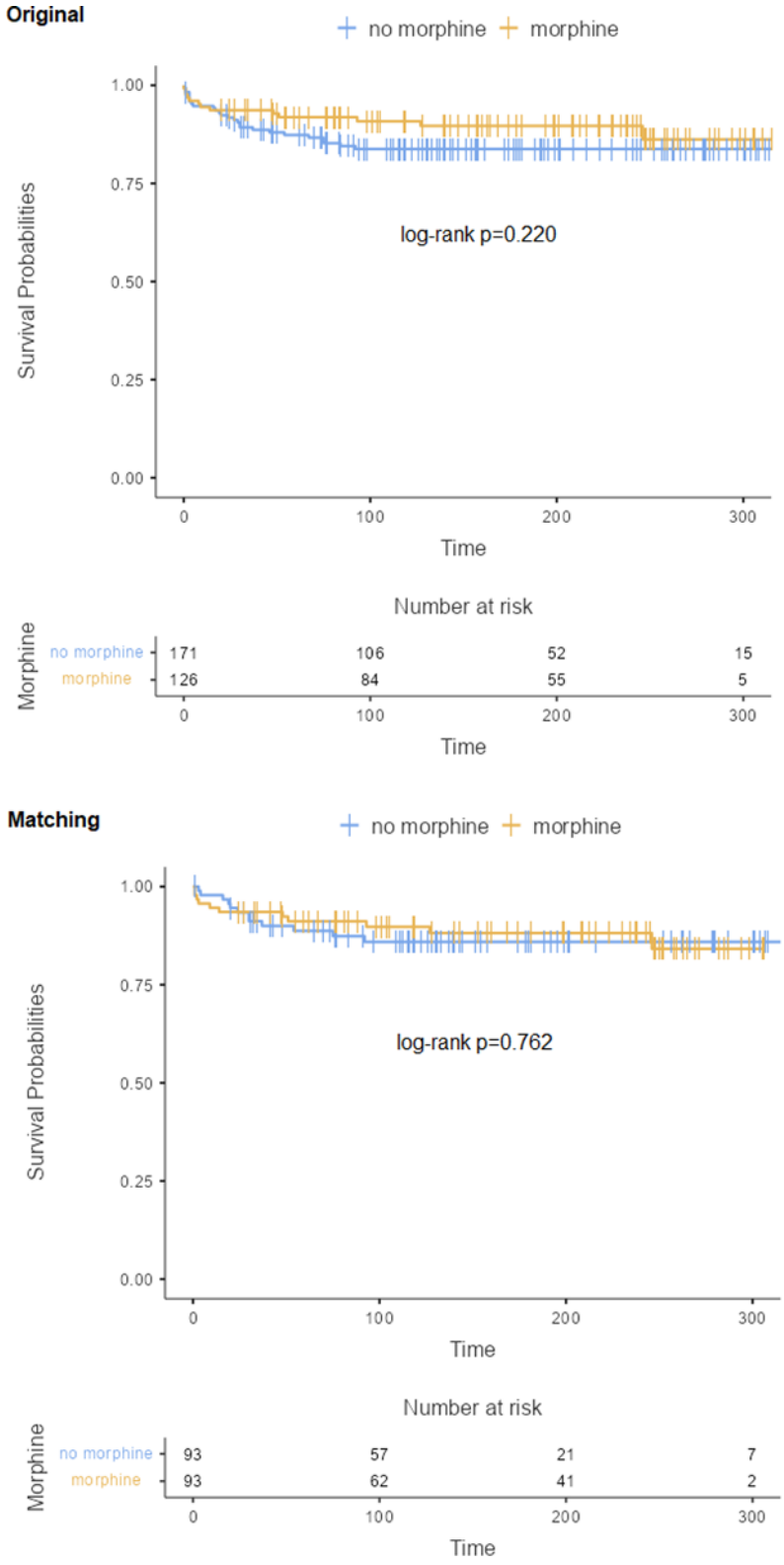

Fig. 10: Preliminary results of an external validation study. Preliminary results suggest that morphine may have no impact on mortality in STEMI patients treated with primary PCI and medical therapy according to the current guidelines including novel P2Y12 antagonists (69).