Version	Version 5, 19 April 2021
Title	STREAM-2 (STrategic Reperfusion in elderly patients Early After Myocardial Infarction)
Phase	IV
Sponsor	Leuven Research & Development (LRD) at University of Leuven, Belgium
Supported by	- Boehringer Ingelheim - Life Sciences Research Partners (LSRP) - Fund for Clinical Cardiovascular Research at LRD
EudraCT	2016-001642-26
Sponsor trial code	LRD.2016.STREAM2

CLINICAL TRIAL SYNOPSIS

Name of sponsor	Leuven Research & Development (LRD) at University of Leuven, Belgium Supported by: - Boehringer Ingelheim - Life Sciences Research Partners (LSRP) - Fund for Clinical Cardiovascular Research at LRD
Planned trial period	September 2016 – June 2022
Protocol version and date	Version 5, 19 April 2021
Title of trial	STREAM-2 (STrategic Reperfusion in elderly patients Early After Myocardial Infarction)
Investigators	Executive Committee and the National Coordinators of the participating countries
Trial sites	Multi-national multi-centre trial
Clinical phase	IV
Objectives	In patients ≥ 60 years with acute ST-elevation myocardial infarction randomised within 3 hours of onset of symptoms the efficacy and safety of a strategy of early fibrinolytic treatment with half-dose tenecteplase and additional antiplatelet therapy with a loading dose of 300 mg clopidogrel, aspirin and coupled with antithrombin therapy followed by catheterisation within 6-24 hours or rescue coronary intervention as required, will be compared to a strategy of primary PCI with a $P2Y_{12}$ antagonist and antithrombin treatment according to local standards.
Methodology	Open-label, prospective, randomised, parallel, comparative international multi-centre trial
No. of patients	Total: Approximately 600 Each treatment: Approximately 400 Pharmaco-invasive (PhI) and 200 Primary PCI (PPCI)
Diagnosis and main criteria for inclusion	Patients (≥ 60 years) with acute ST-segment elevation myocardial infarction (STEMI) randomised within 3 hours of symptom onset in a pre-hospital setting/emergency room (ER) of community hospital that cannot reliably undergo primary PCI (PPCI) within 60 min of ECG diagnosis **Inclusion criteria** 1. Age equal or greater than 60 years 2. Onset of symptoms < 3 hours prior to randomisation 3. 12-lead ECG indicative of an acute STEMI (ST-elevation will be measured from

	the J point; scale: 1 mm per 0.1 mV): ≥ 2 mm ST-elevation across 2 contiguous precordial leads (V1-V6) or leads I and aVL for a minimum combined total of ≥ 4 mm ST-elevation or ≥ 2 mm ST-elevation in 2 contiguous inferior leads (II, III, aVF) for a minimum combined total of ≥ 4 mm ST-elevation 4. Informed consent received **Exclusion criteria** 1. Expected performance of PCI < 60 minutes from diagnosis (qualifying ECG) or inability to arrive at the catheterisation laboratory within 3 hours 2. Previous CABG 3. Left bundle branch block or ventricular pacing 4. Patients with cardiogenic shock - Killip Class 4 5. Patients with a body weight < 55 kg (known or estimated) 6. Uncontrolled hypertension, defined as sustained blood pressure ≥ 180/110 mm Hg (systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg) prior to randomisation 7. Known prior stroke or TIA 8. Recent administration of any i.v. or s.c. anticoagulation within 12 hours, including unfractionated heparin, enoxaparin, and/or bivalirudin or current use of oral anticoagulation (i.e. warfarin or a NOACs) 9. Active bleeding or known bleeding disorder/diathesis 10. Known history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery) or recent trauma to the head or cranium (i.e. < 3 months) 11. Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current myocardial infarction) 12. Clinical diagnosis associated with increased risk of bleeding including known active peptic ulceration and/or neoplasm with increased bleeding risk 13. Known severe renal insufficiency 14. Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks 15. Known acute pericarditis and/or subacute bacterial endocarditis 16. Known acute pancreatitis or known severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis 17. Dementia 18. Previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 7 days

<table>
<tr><td></td><td>19. Known allergic reactions to tenecteplase, clopidogrel, enoxaparin and aspirin
20. Inability to follow the protocol and comply with follow-up requirements or any other reason that the investigator feels would place the patient at increased risk if the investigational therapy is initiated</td></tr>
<tr><td>Test products</td><td>½ dose tenecteplase with concomitant antithrombotic therapy including 300 mg clopidogrel</td></tr>
<tr><td>Dose and mode of administration</td><td><u>Pre-PCI hospital/ER community hospital treatment:</u>
Tenecteplase
50 or 40 mg of drug reconstituted in 10 or 8 ml sterile water for injection given as single weight-adjusted i.v. bolus over 5 - 10 seconds
<table><tr><th><u>Weight (kg)</u></th><th><u>Dose (mg)</u></th><th><u>Dose (ml)</u></th></tr><tr><td>≥55 to <60</td><td>15.0 mg</td><td>3.0 ml</td></tr><tr><td>≥60 to <70</td><td>17.5 mg</td><td>3.5 ml</td></tr><tr><td>≥70 to <80</td><td>20.0 mg</td><td>4.0 ml</td></tr><tr><td>≥80 to <90</td><td>22.5 mg</td><td>4.5 ml</td></tr><tr><td>≥90</td><td>25.0 mg</td><td>5.0 ml</td></tr></table>Clopidogrel
300 mg p.o. initial loading dose
Maintenance dose of 75 mg p.o. once daily
The maintenance dose of Clopidogrel (75 mg p.o. per day) should be continued for 1 year

<u>In-hospital treatment:</u>
Assessment of reperfusion (by ECG and evaluation of clinical symptoms) 90 min after injection of tenecteplase or earlier if clinically indicated
Catheterisation:
- If ST-segment resolution is ≥ 50 % in the qualifying lead (i.e. with maximum initial ST-segment elevation in the baseline ECG), diagnostic coronary angiography (followed by elective PCI +/- stenting, if indicated) should be performed no sooner than 6 hours but within 24 hours after administration of tenecteplase (considered as planned catheterisation according to protocol)
- If ST-segment resolution is < 50 % in the qualifying lead, irrespective of the presence or absence of clinical symptoms, rescue coronary intervention should be performed promptly
- In case of haemodynamic or electrical instability or worsening ischaemia requiring coronary intervention, urgent coronary intervention is indicated at any time (irrespective of previous ST-segment resolution)</td></tr>
</table>

Reference therapy	**Standard primary PCI (PPCI)**
Dose and mode of administration	**Pre-hospital treatment:** In agreement with international guidelines, upfront antithrombin treatment, aspirin and a P2Y12 antagonist according to local standards and at the discretion of the investigator (e.g., unfractionated heparin/ enoxaparin or bivalirudin, clopidogrel or ticagrelor). Prasugrel is not recommended (cfr bleeding risk in elderly patients). **In-hospital treatment**: Maintenance dose of aspirin and a P2Y12 antagonist. Additional GP IIb/IIIa antagonists during PCI are at the investigator's discretion (eg for bail-out).
Criteria for efficacy	**Pharmaco-invasive strategy compared with primary PCI** Number of patients achieving ≥ 50 % ST-segment resolution before and after PCI in lead with maximal ST elevation at baseline; % rescue PCI; TIMI flow grades Clinical events of interest i.e. death, shock, heart failure, recurrent MI, rescue PCI and aborted MI will be recorded and assessed as single or composite endpoints for evaluation.
Criteria for safety	- Total stroke, intracranial haemorrhage (ICH), ischaemic stroke, haemorrhagic conversion up to 30 days - Non-intracranial bleeds (total, major, minor, and blood transfusions) up to 30 days - Serious cardiac events (e.g. death , congestive heart failure, reinfarction, resuscitated ventricular fibrillation, repeat target vessel recanalization, stent thrombosis, total AV block etc) up to 30 days
Statistical methods	The trial is a hypothesis-generating study to examine the medical question whether half-dose tenecteplase plus 300 mg clopidogrel in STEMI patients 60 years of age or older who cannot undergo PPCI within 1 hour after first medical contact is as effective and safe as PPCI according to local practice. A minimum of 100 patients ≥ 70 years will be randomized to the PhI arm. No confirmatory statistical hypothesis is pre-specified. All statistical tests are of exploratory nature based on descriptive statistics for formal statistical hypotheses generation. An intent-to-treat analysis of all patients randomized will be carried out. After 50 % of the planned recruitment a formal interim analysis will be performed by the DSMB to evaluate and advise the Executive Committee on the feasibility and justification of enlarging the sample size with provision to proceed to a confirmatory trial. For this analysis the available data from STREAM 2 and similar data from STREAM 1 will be used. In order to ensure adequate balance between the representation of ambulance and community hospital patients their relative proportions will be monitored and an adjustment in their numbers considered.

FLOW CHART

Trial Periods	**Screening/ Baseline**	**Randomised period**		**End of trial**	**Follow-up period**
Period **Days**	**Pre-PCI hospital**	**In PCI-Hospital**	**Hospital discharge or Day 30**	**Day 30[j]** **30 (to 37)**	**1-year F[k]** **365 (to 395)**
Informed consent	X				
Demographic data	X				
Medical history/current diseases	X				
Physical assessment[a]	X				
Vital signs	X				
Concomitant therapy	X	X	X		
Haematology[b]	X[b]		X[b]		
Renal function[c]	X[c]				
Troponin I/T (CK/CK-MB)[d]	X[d]	X[d]			
Twelve-lead ECG[e]	X	X[e]	X[e]		
Killip class[f]	X[f]		X[f]		
Inclusion/exclusion criteria	X				
Randomisation	X				
Administration of medication[g]	X[g]	X[g]			
Catheterisation/PCI[h]		X			
TIMI flow grade		X			
Check for rehospitalisation				X	X
Check for clinical events	X				
Check for vital status	X				X
Check for SAEs/serious clinical events[i]	X[i]				

[a] Physical assessments can be performed by paramedics.

[b] According to hospital practice; but it is required to include at least haemoglobin, haematocrit, platelets pre-hospital or, if not possible, on hospital arrival and before hospital discharge.

[c] Renal function: A laboratory test of serum creatinine clearance (as per Cockcroft-Gault formula) should be done at the first occasion to rule out renal insufficiency or, if applicable, to adapt the dose of subcutaneous enoxaparin according to protocol in Group PhI patients with low creatinine clearance.

[d] Cardiac biomarkers : The first available value (pre-hospital or upon arrival at hospital) should be recorded. Additional values should be taken 8-12 hours and 24 hours after randomisation. Cardiac biomarkers should also be taken in case of signs and symptoms suggestive of recurrent myocardial ischaemia or reinfarction until day 30.

[e] Twelve-lead ECG in Group PhI: In the receiving hospital an ECG will be recorded 90 min after injection of tenecteplase or earlier, if clinically indicated, for assessment of ST resolution. If planned catheterization or rescue or

urgent PCI is done, ECGs will be taken immediately before the procedure and 30 min after the end of the procedure, respectively.
Twelve-lead ECG in Group PPCI: In the receiving hospital an ECG will be taken prior to the PCI procedure and 30 min after the end of the procedure.
In all patients, in addition to baseline and possible in-hospital ECGs, an ECG will be recorded before hospital discharge. Serial in-hospital ECGs should be taken in case of symptoms of recurrent ischaemia or reinfarction. ECGs will be centrally adjudicated.

[f] Killip class will be determined prior to randomization (or, if this is not possible, immediately on hospital arrival).

[g] Patients randomized to Group PhI will receive the trial medication in the ambulance/ER community hospital immediately after randomization. Patients randomized to PPCI will receive medication in the ambulance/ER community hospital and/or prior to PPCI according to the local hospital standards.

[h] In Group PhI catheterization and PCI should be delayed for at least 6 hours, but no longer than 24 hours after randomization, if ST resolution is ≥ 50% and no rescue or urgent PCI is indicated (for details refer to section 6.2.2.1); whereas in Group PPCI all patients are expected to receive catheterization and PCI according to local standards. Catheterization and PCI data will be recorded in the eCRF (cf. section 6.2.2.2).

[i] Serious clinical events will be recorded until and including day 30.

[j] Visit at 30 days either at outpatient clinic or via phone.

[k] Visit at 1 year either at outpatient clinic, via phone or from medical records.

TABLE OF CONTENTS

ABBREVIATIONS

ACC	American College of Cardiology
AE	Adverse Event
AHA	American Heart Association
ARO	Academic Research Organisation
AUC	Area Under The Curve
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CCU	Coronary Care Unit
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CK-MB	Creatine Kinase Muscle Band
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CRO	Clinical Research Organisation
CTP	Clinical Trial Protocol
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
ER	Emergency room
ESC	European Society of Cardiology
EU	European Union
EC/IEC	(Independent) Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation Intracranial Haemorrhage
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRA	Infarct-Related Artery
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	Intravenous(ly)
IVRS	Interactive Voice Response System
LMWH	Low Molecular Weight Heparin
LRD	Leuven Research & Development
LSRP	Life Sciences Research Partners

mg	Milligram(s)
min	Minute(s)
ml	Millilitre(s)
No.	Number
PCI	Percutaneous Coronary Intervention
PhI	Pharmaco-invasive
PPCI	Primary Percutaneous Coronary Intervention
p.o.	per os (latin); oral(ly)
PTCA	Percutaneous transluminal coronary angioplasty
SAE	Serious Adverse Event
s.c.	Subcutaneous(ly)
SOP	Standard Operating Procedure
STEMI	ST-Segment Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Trans-ischaemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TNK	Tenecteplase
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The use of timely primary percutaneous coronary intervention (PPCI) in patients with ST-segment elevation myocardial infarction (STEMI) is recommended by guidelines of the European Society of Cardiology (ESC)[1] and American College of Cardiology (ACC)/American Heart Association (AHA)[2] and has steadily increased during recent years. There is strong evidence that PPCI is a very effective therapy for STEMI.[3, 4]
To be efficacious PPCI must be provided in an expert and timely fashion. This capacity is not equally accessible for all STEMI patients; moreover the frequency of PPCI use differs between countries and even between and within hospitals in the same country.
Fibrinolysis is a well-accepted, evidence-based and guideline-supported strategy, especially in patients presenting soon after symptom onset, i.e. within 3 hours.[5-8]
Pre-hospital fibrinolysis has proven to be feasible in various countries and patient's management organisations, to increase the proportion of patients treated early and improve outcome.[5, 6, 9-12]

In contemporary practice patients receiving fibrinolytic therapy may subsequently be treated with PCI either as part of a routine angiographic assessment before hospital discharge, as a rescue strategy based on inadequate pharmacologic reperfusion, or because of spontaneous or provoked recurrent ischaemia. Fibrinolysis combined with subsequent PCI has therefore been investigated in several contexts in recent trials.[7, 10, 13, 14]

The STREAM-1 trial[15, 16] demonstrated that in STEMI patients presenting within 3 hours of symptom onset (who could not undergo PPCI within 60 minutes), a pharmaco-invasive strategy that includes tenecteplase , urgent PCI for failed reperfusion and angiography within 24 hours in the remaining fibrinolytic-treated patients, achieved a comparable 30-day composite endpoint of all-cause death, cardiogenic shock, congestive heart failure (CHF), and re-infarction when compared to timely, contemporary PPCI. Mortality was also similar in both treatment groups at 1 year.[17] Importantly the original trial protocol was amended after 21% (n=379) of the intended enrolment because of an excess of intracranial haemorrhage (ICH) in patients ≥75 years. Thereafter there was a 50% reduction in the dose of tenecteplase in these patients. When concluded, the overall primary composite endpoint of death, cardiogenic shock, CHF and re-MI occurred in 12.4% of the PhI group versus 14.3% of the PPCI patients (relative risk (RR) 0.86; 95% confidence interval (CI) 0.68-1.09; P=0.21) in 1892 patients. Whereas no further ICH occurred in the subsequent 97 patients ≥75 years randomised to the PhI strategy, the relationship between the dose reduction and efficacy remains uncertain. Preliminary data indicates that the extent of ST-segment resolution 60 to 90 minutes after ½ dose tenecteplase was comparable to full dose but this requires confirmation in a larger data set.[18]
Importantly at least one third of PhI- treated patients required urgent coronary intervention because of failed fibrinolysis or early recurrent ischemia after initially successful reperfusion.[19] The role of

platelet aggregation as it relates to this issue is unclear, but has been postulated to be significant and is known to be ameliorated by administration of P2Y12 antagonists. In STREAM-1 no additional loading dose of clopidogrel was given because when designing the study no reliable data were available in patients ≥ 60 years. Hence the role of a more effective dosing of clopidogrel (a loading dose of 300 mg vs 75 mg used in STREAM-1) in patients ≥ 60 years is worthy of further exploration and will be incorporated in STREAM-2. Such a dose has been used safely in the elderly as reported by Larson et al.[20].

Recognizing the continuing challenges in achieving timely expert PPCI, the need to acquire greater confidence in the efficacy and safety of ½ dose tenecteplase in patients ≥ 60 years and the gap in knowledge on both the safety and efficacy of new and adequately-dosed conventional P2Y12 platelet inhibitors, the STREAM-2 study has the following main objectives;

1. Compare the efficacy and safety of a PhI reperfusion strategy with PPCI in STEMI patients ≥ 60 years.
2. Compare the incidence of intracranial and non-ICH major systemic bleeding in STEMI patients ≥ 60 years receiving pre-hospital clopidogrel 300 mg as adjunct to ½ dose tenecteplase.

1.2 PHARMACOLOGIC THERAPY

Tenecteplase

Tenecteplase is a derivative of the wild-type tissue type plasminogen activator, tPA (identical to the recombinant marketed agent, rtPA, alteplase) with three amino acid site substitutions: a threonine (T) replaced by an asparagine, which adds a glycosylation site to position 103; an asparagine (N) replaced by a glutamine, thereby removing a glycosylation site from position 117; and four amino acids, lysine (K), histidine (H), arginine (R), and arginine (R), replaced by four alanines at the third site.

These substitutions prolong half-life, increase fibrin specificity, and increase resistance to inhibition by plasminogen activator inhibitor-1 (PAI-1).[21] In pharmacokinetic studies in patients with acute myocardial infarction, tenecteplase was shown to exhibit biphasic disposition kinetics with an initial half-life of 17-24 min and a terminal half-life of 65-132 min. The initial half-life accounted for approximately 70 % of the AUC (area under the curve).[22]

ASSENT-3, a large international phase III study with 6095 patients, compared the efficacy and safety of various treatment regimens combining tenecteplase with different antithrombin agents: unfractionated heparin (UFH) or enoxaparin or UFH plus abciximab.[23] Tenecteplase combined with body weight-adjusted UFH showed the same 30-day mortality as in ASSENT-2 (6.0 % and 6.2 %, respectively), whereas major bleeds (other than ICH) were reduced by half compared to ASSENT-2 (2.2 % and 4.7 %, respectively).[23, 24] The reduced bleeding rate, without reducing efficacy was probably related to the use of a lower body weight-adjusted dose of UFH in ASSENT-

3 in accordance with the ACC/AHA and ESC guidelines of that time. Although there was no difference in mortality between the three treatment groups in ASSENT-3, adjunctive therapy with abciximab or enoxaparin with half-dose tenecteplase reduced ischaemic complications (in-hospital reinfarction or ischaemia) as compared to adjunctive treatment with UFH. Particularly for abciximab and to a lesser extent for enoxaparin, these benefits were obtained at the cost of an increased rate of extracranial and intracranial bleeding complications particularly in female and the elderly patients.[23]

As noted above the STREAM-1 trial used a pharmaco-invasive strategy of tenecteplase, ASA, enoxaparin followed by an invasive strategy urgent PCI for failed reperfusion and angiography within 24 hours in the remaining fibrinolytic-treated patients. This strategy achieved a comparable 30-day composite endpoint of all-cause death, cardiogenic shock, congestive heart failure (CHF), and re-infarction when compared to timely, contemporary PPCI. In the patients ≥ 75 years a change from full to half dose tenecteplase proved to be safer without evidence of reduced efficacy based on the extent of ST resolution and rate of rescue PCI.[16] Based on these results the new ESC guidelines for the treatment of STEMI patients recommend administration of half-dose tenecteplase to patients ≥ 75 years of age.[1] This recommendation is based on the data from 97 patients ≥ 75 years from the STREAM-1 study randomized to half-dose tenecteplase after the amendment. They had a favourable clinical outcome and, importantly, no ICH was observed.[18]

Enoxaparin

Addition of unfractionated or low molecular weight heparin (LMWH) to fibrinolytic therapy has been shown to reduce mortality and the rate of recurrent myocardial infarction.[23, 25] Enoxaparin is a low molecular weight heparin used for anticoagulation that – in contrast to heparin which requires intravenous use – can be administered subcutaneously.

In the ExTRACT-TIMI 25 trial enoxaparin and UFH were compared as adjunctive therapies to fibrinolytic treatment in 20506 patients with STEMI.[25] This trial used reduced enoxaparin doses in the elderly and the renal insufficiency patient as compared to ASSENT-3 and ASSENT-3 PLUS[26]. In the enoxaparin group the primary end point, death or nonfatal myocardial infarction within 30 days, was significantly reduced by 2.1 percentage points (17% relative change) as compared to unfractionated heparin. However, the rate of major bleedings was significantly increased in the enoxaparin group (2.1% vs. 1.4%), whereas the rate of intracranial haemorrhage did not differ significantly at 30 days.[25, 27] The magnitude of excess of bleeding tended to lower in the elderly assigned to reduced-dose enoxaparin, however.

Clopidogrel

Addition of clopidogrel, a thienopyridine acting as adenosine diphosphate receptor antagonist, to a regimen of fibrinolytic agent, heparin (if indicated), and acetylsalicylic acid lead to a highly significant reduction (15.0 % vs. 21.7 % as compared to placebo) in the composite endpoint (TIMI flow 0-1 on angiogram, death and recurrent myocardial infarction prior to angiography) in the

CLARITY study with 3491 patients presenting with STEMI within 12 hours from symptom onset. Although mortality was not reduced by addition of clopidogrel as compared to placebo, consistent effects of clopidogrel in improving angiographic outcomes and reduction of ischaemic events as well as a near-significant (p = 0.052) reduction of the stroke risk were observed.[28] In addition, the dose used (300 mg loading dose, followed by 75 mg daily) did not increase the risk of bleeding and was therefore considered safe for patients up to 75 years. Additional observational data from Larson et al supports the safety and efficacy of 300 mg clopidogrel in elderly patients receiving half dose fibrinolysis.[20]

These results are supported by the COMMIT trial, a large study with 45852 patients admitted within 24 hours of symptom onset of myocardial infarction, which showed a highly significant proportional reduction of the composite of death, reinfarction, or stroke.[29] Although, in contrast to CLARITY, no loading dose was given, the mortality rate was reduced significantly as compared to placebo. Furthermore, the daily dose of 75 mg neither led to increased bleeding rates in elderly patients (> 70 years of age) nor in patients who received additional fibrinolytic treatment (approximately 54 %).[29]

1.3 RATIONALE FOR PERFORMING A NEW TRIAL COMPARING A PHARMACO-INVASIVE THERAPY WITH PRIMARY PCI

Substantial data indicate that the patient baseline characteristics[30] and the 'PCI-related delay[30, 31, 32] are key factors for the selection of optimal treatment for STEMI patients , i.e. whether a PhI strategy or PPCI is the more favourable treatment for the patient. Local and logistic factors, such as the availability and distance to catheterisation laboratories, have a major impact on the PCI-related delay[33] and also modulate selection of reperfusion strategies. A flexible approach, which retains the ability to employ either strategy, is therefore desirable and is supported by current ACC/AHA/ESC guidelines.[1, 2]

As compared to PPCI, fibrinolytic treatment is a therapy that is immediately available and requires much less technical effort and equipment. It has been shown to be beneficial and most effective, when it is administered early after onset of symptoms.[5, 6, 30, 34] Initiation of fibrinolytic treatment within the first three hours after onset of symptoms was shown to result in a lower or at least equivalent mortality rate for patients receiving fibrinolytic therapy as compared to PPCI.[5, 6, 17, 30, 34] The use of early fibrinolytic treatment in the pre-hospital setting led to reduced mortality as demonstrated in different national registries.[6, 8, 11] Further combination with subsequent routine or rescue coronary intervention as required has also been supported by recent studies.[7, 10, 13, 14, 35]

In the French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) 1492 STEMI patients with a first call ≤ 12 hours from onset, 447 (30%) received fibrinolysis (66% prehospital; 97% with subsequent angiography, 84% with subsequent PCI).[36] 583 (39%) had PPCI, and 462 (31%) received no reperfusion. Crude 5-year survival was 88% for the fibrinolytic based strategy, 83% for PPCI, and 59% for no reperfusion. Adjusted hazard ratios for 5-year death were 0.73 (95% confidence interval, 0.50–1.06) for fibrinolysis versus PPCI, 0.57 (95%

confidence interval, 0.36–0.88) for prehospital fibrinolysis versus PPCI, and 0.63 (95% confidence interval, 0.34–0.91) for fibrinolysis versus PPCI beyond 90 minutes of call in patients having called ≤180 minutes from onset. In propensity score–matched populations, however, survival rates were not significantly different for fibrinolysis and PPCI, both in the whole population (88% lysis, 85% PPCI) and in the population seen early (87% fibrinolysis, 85% PPCI beyond 90 minutes from call). The authors concluded that in a real-world setting, on a nationwide scale, a pharmaco-invasive strategy constitutes a valid alternative to PPCI, with 5-year survival at least equivalent to PPCI.[36] Recent registry data from Belgium and the US similarly supports this supposition.[37, 38]

More recent publications provide additional support for PhI strategy in STEMI. A randomized clinical trial [Circulation 2017] showed that in 171 patients < 76 years half-dose alteplase given as a PhI strategy when there was an expected PCI delay of > 1 hour was safe (no ICH) and associated with more complete epicardial and myocardial reperfusion (tissue reperfusion) compared with standard PPCI.[39] The accompanying editorial highlights the role of a PhI strategy in a broad range of settings and references the STREAM2 study.[40] Another registry study of over 12000 STEMI patients from Germany [European Heart Journal 2018] re-emphasizes the importance of timely PCI (reperfusion) when this is the sole reperfusion strategy.[41] In patients *with or without* hemodynamic instability who had their first balloon inflation within 1 to 3 hours after first medical contact (exactly the same time window for PCI as in STREAM there was a nearly linear relationship between PCI delay and mortality. In cardiogenic shock patients, every 10 min delay resulted in an excess of 3.3 deaths per 100 PCI-treated patients. It is likely that earlier reperfusion with pre-hospital administration of a fibrinolytic agent would have prevented a significant amount of cardiogenic shock and death in this population. The 1.5 % absolute reduction in the incidence of shock observed in the STREAM-1 study supports this conjecture.

Against this background the bleeding risk of full dose tenecteplase was evaluated according to age by using all the data from studies using the current recommended full weight-adjusted dose of tenecteplase. These data are drawn from the following trials: Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-2, ASSENT-3, ASSENT-3 Plus, ASSENT- 4 PCI and STREAM-1.[9, 16, 23, 24, 42] Major bleeding complications and ICH were assessed from almost 24 000 patients treated with full weight-adjusted dose tenecteplase. The results are compelling and are shown in the 3 figures below.

Figure 1: ICH

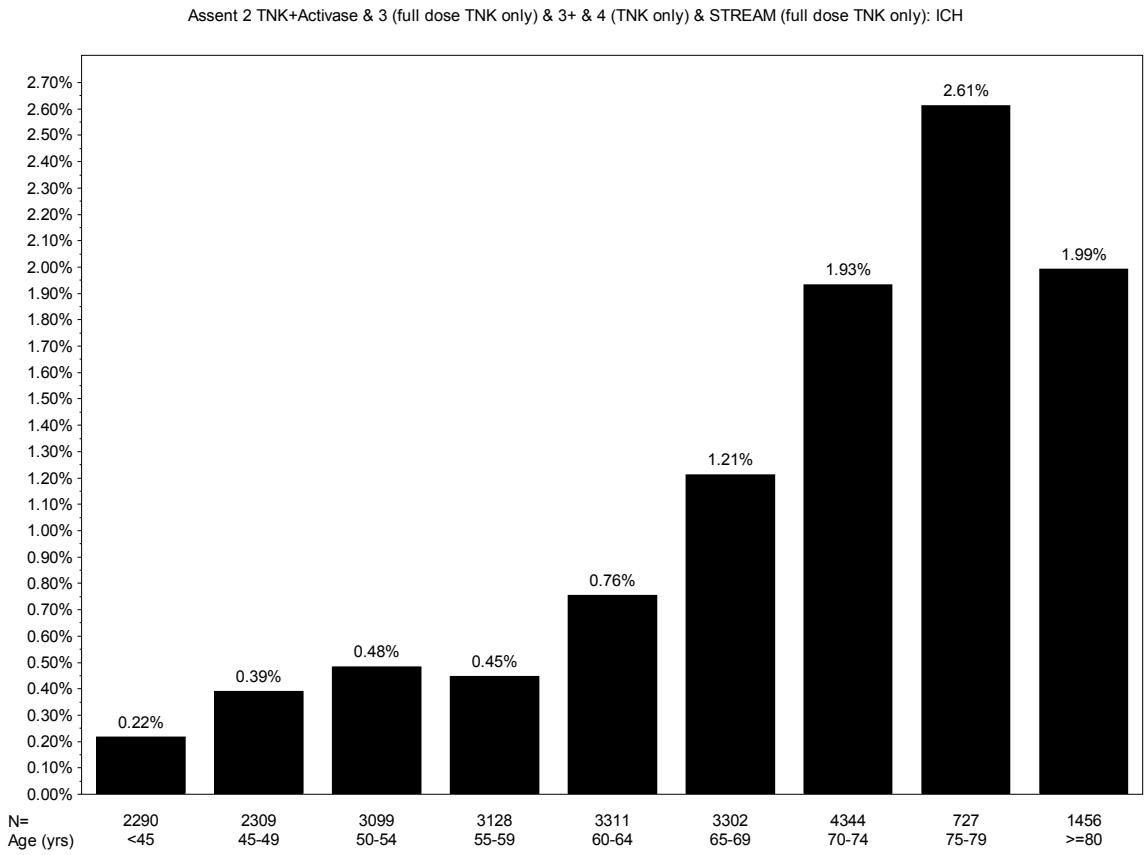

Assent 2 TNK+Activase & 3 (full dose TNK only) & 3+ & 4 (TNK only) & STREAM (full dose TNK only): ICH
2.70%
2.60%
2.50%
2.40%
2.30%
2.20%
2.10%
2.00%
1.90%
1.80%
1.70%
1.60%
1.50%
1.40%
1.30%
1.20%
1.10%
1.00%
0.90%
0.80%
0.70%
0.60%
0.50%
0.40%
0.30%
0.20%
0.10%
0.00%
0.22%
0.39%
0.48%
0.45%
0.76%
1.21%
1.93%
2.61%
1.99%
N=
Age (yrs)
2290 <45
2309 45-49
3099 50-54
3128 55-59
3311 60-64
3302 65-69
4344 70-74
727 75-79
1456 >=80

Figure 2: Major non-intracranial bleeding

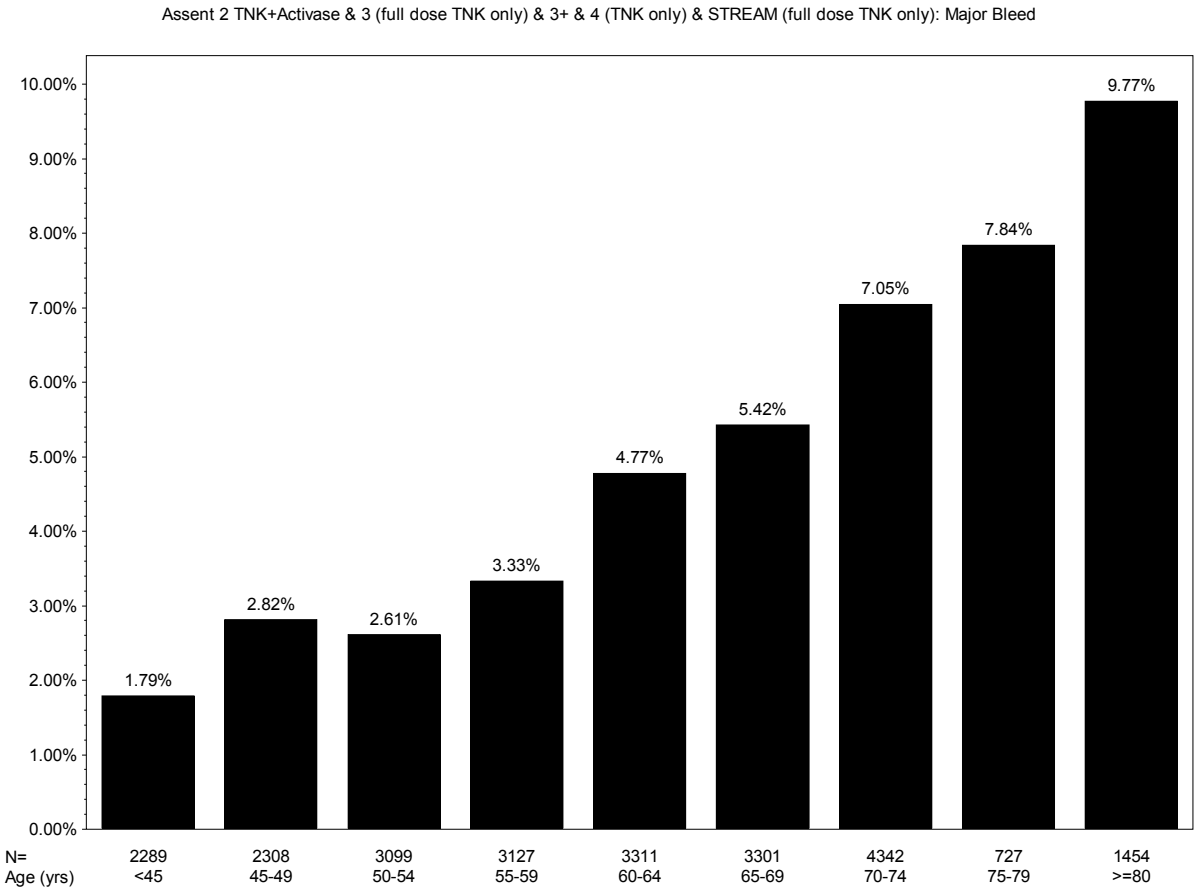
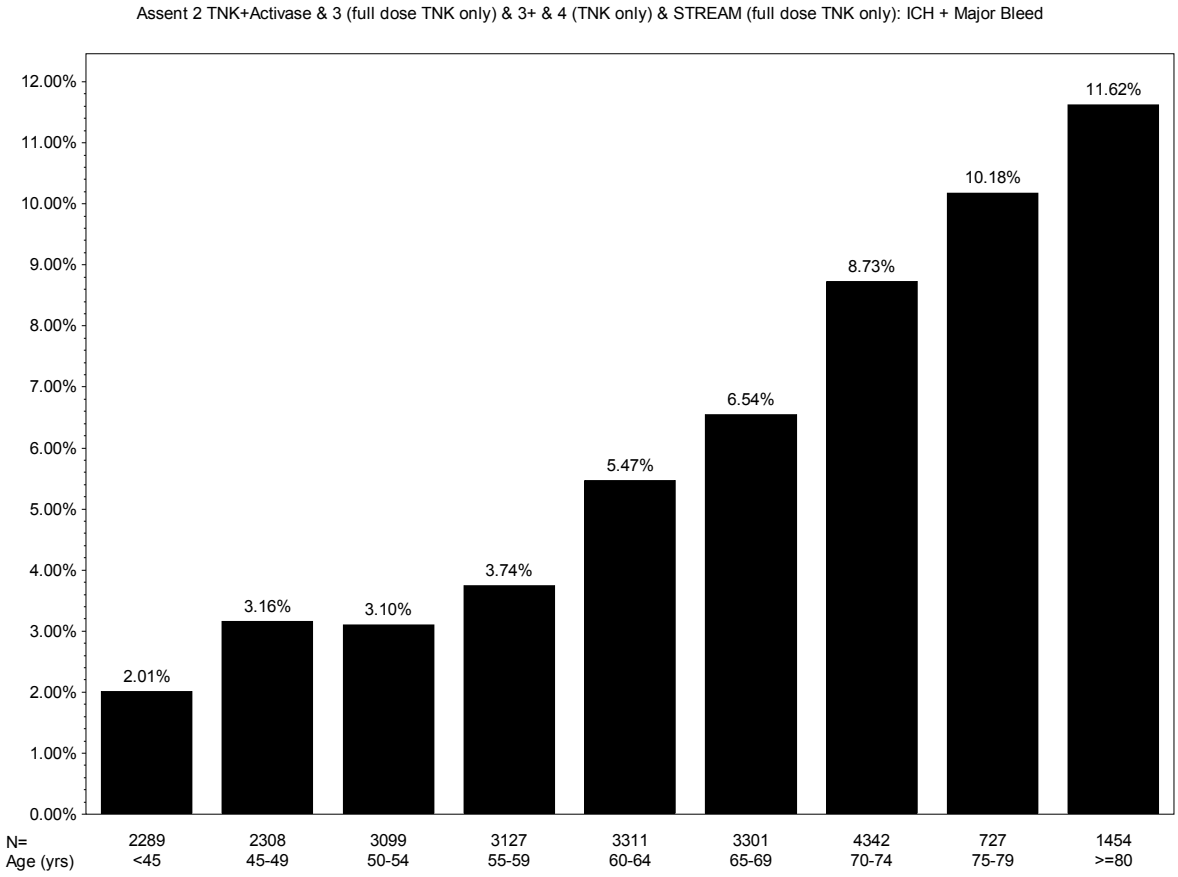


Figure 3: ICH and major non-intracranial bleeding



These data indicate that the risk of major bleeding and/or ICH begins to increase around the age of 60 years. Based on all of the above considerations the STREAM-2 protocol has been amended in order to include patients ≥ 60 years with no upper age limit. The benefit of earlier reperfusion would be expected to translate into a lower % cardiogenic shock, congestive heart failure and improved long-term survival as already suggested by the STREAM-1 study.16

The current trial will therefore evaluate the safety and efficacy of a treatment strategy designed to reflect optimal clinical practice that includes early fibrinolysis and appropriate contemporary adjunctive medical therapy followed by coronary intervention, as required ('lyse now, stent later')[43], or standard PPCI with adequate medical therapy in patients ≥ 60 years with STEMI presenting less than 3 hours after symptom onset.

1.4 BENEFIT / RISK ASSESSMENT

Patients assigned to the PhI group will receive tenecteplase combined with antiplatelet

(acetylsalicylic acid), antithrombin (enoxaparin) treatment and clopidogrel 300 mg. Thereafter they will undergo cardiac catheterisation within 6-24 hours or rescue coronary intervention as required and, if indicated, stent implantation.

As previously indicated, fibrinolysis is a well-established treatment recommended by clinical guidelines. The main risk associated with fibrinolytic treatment is bleeding. Patients will be carefully screened to minimise bleeding risk. Hence in the current study, patients ≥60 years, who are known to have an increased bleeding risk[44], will receive half-dose tenecteplase. As was the case in STREAM-1, the initial bolus of enoxaparin will be omitted to conform to the evidence-based strategy of the ExTRACT trial[25, 27, 29] which supports this approach as safe and effective. Based on the study of Larson et al[20] attesting to the safety of ½ dose fibrinolytic and a 600 mg loading dose of clopidogrel in elderly patients, clopidogrel 300 mg will be administered in Group PhI. In addition, patients with low body weight (i.e. below 55 kg) will be excluded to minimise the small but definitive risk of ICH noted from prior trials. Insufficient reperfusion or vessel reocclusion after fibrinolysis will be addressed, as per current guidelines, by measuring ST-segment resolution. Patients who do not show ECG and/or clinical evidence of adequate reperfusion 90 min after bolus tenecteplase will undergo prompt rescue PCI.

Patients randomised to PPCI will be treated in accordance with international PCI guidelines in the prehospital setting. PPCI is a routine treatment in patients with STEMI and will therefore serve as a comparator to the PhI arm. It has been shown to be safe and effective in securing and maintaining coronary artery patency. Patients with contraindications will be excluded.

During the course of the trial a Data Safety Monitoring Board (DSMB) will review, on a regular basis and whenever necessary, all safety data and evaluate the patients' safety and possible risks. The DSMB will report to the Executive Committee and is entitled to recommend any measures required to secure the patients' safety.

2. TRIAL OBJECTIVES

2.1 GENERAL AIM

This study will evaluate the efficacy of 2 reperfusion strategies based on ST-segment resolution in patients ≥ 60 years presenting with acute STEMI within 3 hours of symptom onset in a pre-hospital setting/community hospital. Following randomisation to a strategy of early (pre-hospital) tenecteplase and additional enoxaparin and a loading dose of clopidogrel, patients will undergo cardiac catheterisation within 6-24 hours with timely coronary intervention as appropriate (or by rescue coronary intervention if required) in Group PhI. Patients randomized to group PPCI will receive concomitant antithrombotic treatment according to local practice. The efficacy will be evaluated by ST-segment resolution (cfr infra), TIMI flow grades and need for rescue PCI (in PhI group).

Clinical events i.e. death, shock, heart failure, recurrent MI and aborted MI will be recorded and assessed as single or composite endpoints for evaluation as noted in the statistical analytical plan. All statistical tests on clinical events are of exploratory nature based on descriptive p-values with estimation of 95% confidence limits for formal statistical hypotheses generation. For comparison the same composite clinical event rates (for example the composite of death, shock, congestive heart failure and re-infarction = primary endpoint of STREAM-1) will be analysed (see APPENDICES).

2.2 EFFICACY ENDPOINT

The trial is of exploratory nature with the aim to examine the potential benefits of this pharmaco-invasive strategy. Therefore, no confirmatory statistical hypothesis is pre-specified. All statistical tests are of exploratory nature based on descriptive p-values with accompanying 95% confidence limits for formal statistical hypotheses generation. Efficacy for early reperfusion will be evaluated by the number of patients achieving ≥ 50 % ST-segment resolution before and after PCI in lead with maximal ST elevation at baseline; % rescue PCI; TIMI flow grades.

An intent-to-treat analysis of all randomised patients will be carried out. After 50 % of the planned recruitment a formal interim analysis will be performed by the DSMB to evaluate and advise the Executive Committee on the feasibility and justification of enlarging the sample size with provision to proceed with a confirmatory trial.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN - DESCRIPTION

The current trial is designed as an open-label, prospective, randomised, parallel, comparative international multi-centre trial.

In patients ≥ 60 years with acute ST-elevation myocardial infarction randomised within 3 hours of onset of symptoms, the efficacy and safety of a strategy of early fibrinolytic treatment with half-dose tenecteplase and additional antiplatelet and antithrombin therapy followed by catheterisation within 6-24 hours or rescue coronary intervention as required will be compared to a strategy of PPCI according to local standards.

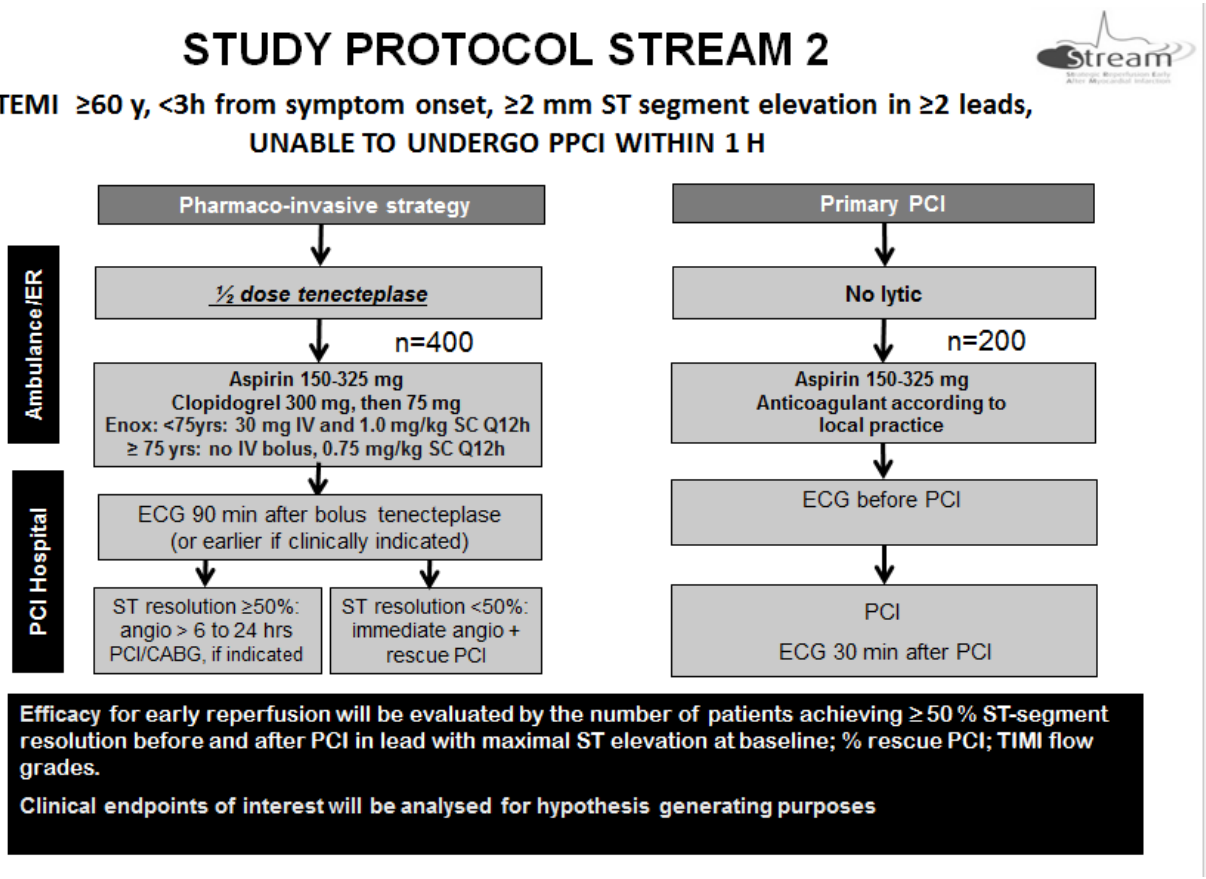


Figure 4: Overall Trial Design

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Although several studies and registries have compared fibrinolytic treatment with PPCI in patients with acute myocardial infarction, limited trial data are available in older patients ≥60 years regarding the strategy of early fibrinolysis followed by PCI versus a strategy of PPCI, in particular in the pre-hospital setting.[5, 10, 18, 42] Moreover, limited data exists concerning the efficacy and safety of a loading dose of clopidogrel combined with fibrinolytic therapy in such patients.

The groups of interest are:

- Group PhI: fibrinolytic treatment with half-dose tenecteplase combined with clopidogrel 300 mg and followed by catheterisation within 6-24 hours or rescue coronary intervention as required.

- Group PPCI: PPCI according to local standards.

3.3 SELECTION OF TRIAL POPULATION

Patients with ST-elevation acute myocardial infarction (STEMI) within 3 hours of symptom onset in the pre-hospital setting will be randomised to Group PhI for a strategy of early pre-hospital/ER community hospital fibrinolysis or to PPCI, if the eligibility criteria mentioned below are met.

Approximately 600 patients (400 patients to group PhI and 200 patients to group PPCI) will be enrolled in approximately 65 sites located in different countries (for sample size calculation see section 7). A minimum of 100 patients ≥ 70 years of age will be randomized to the PhI arm

3.3.1 Inclusion criteria

1. Age equal or greater than 60 years
2. Onset of symptoms < 3 hours prior to randomisation
3. 12-lead ECG indicative of an acute STEMI (ST-elevation will be measured from the J point; scale: 1 mm per 0.1 mV):
   - ≥ 2 mm ST-elevation across 2 contiguous precordial leads (V1-V6) or leads I and aVL for a minimum combined total of ≥ 4 mm ST-elevation
     or
   - ≥ 2 mm ST-elevation in 2 contiguous inferior leads (II, III, aVF) for a minimum combined total of ≥ 4 mm ST-elevation
4. Informed consent received

3.3.2 Exclusion criteria

1. Expected performance of PCI < 60 minutes from diagnosis (qualifying ECG) or inability to arrive at the catheterisation laboratory within 3 hours
2. Previous CABG
3. Left bundle branch block or ventricular pacing
4. Patients with cardiogenic shock - Killip Class 4
5. Patients with a body weight < 55 kg (known or estimated)
6. Uncontrolled hypertension, defined as sustained blood pressure ≥ 180/110 mm Hg (systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg) prior to randomisation
7. Known prior stroke or TIA
8. Recent administration of any i.v. or s.c. anticoagulation within 12 hours, including unfractionated heparin, enoxaparin, and/or bivalirudin or current use of oral anticoagulation (i.e. warfarin or a NOACs)
9. Active bleeding or known bleeding disorder/diathesis
10. Known history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery) or recent trauma to the head or cranium (i.e. < 3 months)

11. Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current myocardial infarction)
12. Clinical diagnosis associated with increased risk of bleeding including known active peptic ulceration and/or neoplasm with increased bleeding risk
13. Known severe renal insufficiency
14. Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
15. Known acute pericarditis and/or subacute bacterial endocarditis
16. Known acute pancreatitis or known severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
17. Dementia
18. Previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 7 days
19. Known allergic reactions to tenecteplase, clopidogrel, enoxaparin and aspirin
20. Inability to follow the protocol and comply with follow-up requirements or any other reason that the investigator feels would place the patient at increased risk if the investigational therapy is initiated.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of investigational products

Tenecteplase (Metalyse®) manufactured by Boehringer Ingelheim (Metalyse®) or Genentech Inc. (TNKase®), will be taken off the shelf or made available according to local regulations. Vials contain either 50 mg or 40 mg of tenecteplase lyophilized powder and excipients, L-arginine, phosphoric acid and polysorbate 20, for reconstitution with sterile water from a 10 mL or 8 mL vial, respectively

Clopidogrel will be taken of the shelf. Tablets contain 75 mg of clopidogrel for oral use. 1 tablet containing 300 mg clopidogrel can be given as loading dose instead of 4 tablets of 75 mg.

4.1.2 Methods of assigning patients to treatment groups

Immediately after screening in the pre-hospital setting, eligible patients will be randomised 2:1 to the pharmaco-invasive therapy or to PPCI.

Randomisation will be performed centrally by means of an interactive voice response system (IVRS), which has to be called by the investigator or an authorised member of site staff.

4.1.3 Selection of doses in the trial

Tenecteplase is given in a weight-adjusted dose regimen as described in the following section (4.1.4) according to the Basic Product Information.[45] Based on the strategy used by Larson et al.[20] and after balancing the risks versus benefits the dose has been adapted for patients ≥ 60 years of age who will receive half dose tenecteplase. As described below, the strategy of measuring ST-segment resolution at 90-minutes after fibrinolysis, or earlier if clinically indicated and performing rescue PCI, if appropriate, in Group PhI is considered to provide an optimal balance between efficacy and safety.

Based on the results of the ASSENT-3 and ExTRACT trials (please refer to section 1.2 for details) reduced dose of LMWH enoxaparin will be used in the current trial.).[25, 26] In the ExTRACT trial, the dose of enoxaparin was reduced for patients of at least 75 years of age, which resulted in positive overall results for this age group. To conform to these results the initial intravenous bolus of enoxaparin will be omitted and a reduced daily dose of enoxaparin (0.75 mg/kg instead of 1 mg/kg) will be administered in this trial for patients of at least 60 years of age.

As described in section 1.2, the dose of clopidogrel in group PhI chosen in this trial (300 mg p.o. initial loading dose followed by 75 mg p.o. qd.) is based on the results of CLARITY, COMMIT and STREAM-1.[16, 20, 28, 29]

Acetylsalicylic acid is used as routine treatment after acute myocardial infarction and has been shown to be beneficial when combined with tenecteplase in several trials.[24, 26] Recent guidelines recommend 150 – 325 mg p.o. given immediately, followed by 75 – 100 mg once daily with lifelong treatment unless it is contraindicated.

As for the sequence of treatments, the required dose of tenecteplase administered as a single intravenous bolus over 5-10 seconds should be the first drug injected. Next, the s.c. dose of enoxaparin and then the oral drugs, i.e. clopidogrel and acetylsalicylic acid, should be given.

Pharmacological treatment will be followed by timely coronary angiography after 6 hours but within 24 hours of the start of fibrinolytic therapy and, if required, PCI or, in case of insufficient ST resolution at 90 min (or earlier if clinically indicated), rescue PCI. The time window of 6-24 hours between the start of fibrinolysis and catheterisation avoids interventions when there is still the pro-thrombotic effect of the lytic agent on the one hand and, on the other hand, minimalizes the risk of spontaneous reocclusion after successful fibrinolysis. The decision on rescue PCI will, however, be taken 90 min (or earlier if clinically indicated) after injection of tenecteplase according to the ST resolution.[35] Rescue PCI will be centrally adjudicated in the core ECG laboratory.

In the PPCI arm, patients will receive antithrombotic treatments as soon as possible according to local standards and international guidelines.

Please also refer to section 1.2 for details.

4.1.4 Selection and timing of doses for each patient

4.1.4.1 Group PhI

Pre-PCI hospital (ambulance/ER community hospital) treatment:

Acetylsalisylic acid
Acetylsalicylic acid is expected to be administered routinely to all patients: a loading dose of 150-325 mg p.o. if not on acetylsalisylic acid already. Alternatively, if the patient is unable to ingest tablets, the initial dose may be given intravenously (80 to 250 mg i.v.). If a patient has already taken acetylsalicylic acid within 12 hours prior to screening the patient will start with acetylsalicylic acid the next day (maintenance dose: 75 to 100 mg).

Tenecteplase
50 or 40 mg of drug reconstituted in sterile water (10 or 8 ml respectively) for injection will be given as single weight-adjusted i.v. bolus over 5 - 10 seconds according to the following scheme:

Weight (kg)	Dose (mg)	Dose (ml)
≥55 to <60	15.0 mg	3.0 ml
≥60 to <70	17.5 mg	3.5 ml
≥70 to <80	20.0 mg	4.0 ml
≥80 to <90	22.5 mg	4.5 ml
≥90	25.0 mg	5.0 ml

The total dose of tenecteplase is injected into an intravenous line of normal saline, as close to the insertion site as possible, using aseptic technique. The total dose is to be injected as a rapid intravenous bolus over 5 - 10 seconds. The intravenous line is to be flushed with normal saline immediately after injection of the tenecteplase bolus to ensure complete drug delivery. Tenecteplase must not be administered in dextrose or Ringer's solution.
The same i.v. line may be used for administration of other medication after flushing the line with a sufficient amount of normal saline prior to the subsequent intravenous injection.

Enoxaparin
< 75 years:
- 30 mg i.v. bolus
- S.c. injections of 1.0 mg/kg every 12 hours until hospital discharge (4 days); the first injection should be given within 15 min of the bolus
- For the first two s.c. injections, a maximum of 100 mg should not be exceeded

≥ 75 years:
- No bolus;
- S.c. injections of 0.75 mg/kg every 12 hours until hospital discharge or for a maximum of

4 days; the first injection should be given immediately
- For the first two s.c. injections, a maximum of 75 mg per injection should not be exceeded

For patients of any age with a creatinine clearance < 30 ml/min, s.c. injections of 0.75 mg/kg will be given in intervals of 24 hours.

Clopidogrel
- 300 mg p.o. initial loading dose (either 4x75 mg or a single 300 mg dose)
- 75 mg p.o. once daily as maintenance dose

In-PCI hospital treatment:

Patients randomised in the ER of a community hospital will be transferred immediately to the PCI hospital after receiving study medication. This is needed to ensure timely rescue coronary intervention if required.[46] Only community hospitals without a catheterization lab and who have an established transfer protocol with a PCI hospital can participate in the study.

The patient should be admitted to either the emergency department, coronary care unit or catheterisation laboratory (as per local practice).

Assessment of reperfusion (by ECG) and evaluation of clinical symptoms will be done 90 min after injection of tenecteplase or earlier if clinically indicated.

ENOXAPARIN

Continuation of enoxaparin started at randomisation:

<75 years: 1.0 mg/kg SC (max 100 mg) every 12 h (i.v. bolus already given at randomisation) ≥75 years: 0.75mg/kg SC (max 75 mg) every 12 h

Prior to **catheterisation** enoxaparin should be given according to the following scheme (please also refer to chapter 4.2.2 for restrictions).

If cath before 2nd s.c. enoxaparin dose: 0.3 mg/kg iv enoxaparin
If cath after 2 or more s.c. enoxaparin doses and ≤ 8 hr after last dose: no additional enoxaparin
If cath after 2 or more s.c. enoxaparin doses and > 8 hr after last dose: 0.3 mg/kg iv enoxaparin

After sheath removal: further use of s.c.enoxaparin is at the discretion of investigator (e.g. in patients where anti-thrombin treatment is indicated, as in atrial fibrillation etc.)

- Clarifications:

- If catheterisation is performed ≤ 8 hours after the second or any later s.c. enoxaparin dose, no additional i.v. enoxaparin should be given (see box above).

- If catheterisation is performed > 8 hours from the second or any later s.c. enoxaparin dose, additional 0.3 mg/kg of i.v. enoxaparin should be administered.

If a closure device is used, the sheath should be removed at the end of the PCI; however, if no closure device is used, the sheath should be removed at least 6 h after the last intravenous or subcutaneous dose of enoxaparin.

After sheath removal further use of s.c. enoxaparin is at the discretion of the investigator (e.g. in patients where antithrombin treatment is indicated, as in atrial fibrillation etc.). If longterm oral anticoagulation is needed (eg because of atrial fibrillation) aspirin may be stopped (at the discretion of local investigator).

Important Note: For patients who received enoxaparin according to the protocol a change to a different type of heparin (e.g., unfractionated heparin) before or during catheterisation should be avoided (cf. 4.2.2).

CLOPIDOGREL
The maintenance dose of clopidogrel (75 mg p.o. per day) should be continued for 1 year.

CATHETERISATION: for details please refer to section 6.2.2.1.

4.1.4.2 Group PPCI

Pre-PCI hospital (ambulance/ER community hospital) treatment:

Acetylsalisylic acid
Acetylsalicylic acid is expected to be administered routinely to all patients at a dose of 150-325 mg p.o. Alternatively, if the patient is unable to ingest tablets, the initial dose may be given intravenously (80 to 150 mg i.v.). If a patient has already taken acetylsalicylic acid within 12 hours prior to screening the patient will start with acetylsalicylic acid the next day (maintenance dose: 75 to 100 mg).

P2Y12 antagonist
A P2Y12 antagonist is to be administered according to local practice and international guidelines. Prasugrel should not be administered to any patient ≥ 75 years of age. cfr FDA product label.

Antithrombin treatment according to local standards and in accordance with international PCI guidelines (e.g., unfractionated heparin/ enoxaparin/ bivalirudin).

In-PCI hospital treatment:
At the receiving PCI hospital transfer to the catheterisation laboratory should be organised as soon as possible as per local practice and in accordance with the protocol timelines. The patient should be admitted preferably directly to the catheterisation laboratory.

Standard PPCI
Standard PPCI procedure following angiography (use of additional GP IIb/IIIa antagonists is at the investigator's discretion). As per current guidelines, only PCI of the infarct related vessel should be performed. PCI of non-infarct related vessels is NOT recommended. For details please refer to section 6.2.2.2.

4.1.5 Blinding

This is an open-label trial. All treatment strategies will be performed in an unblinded manner.

4.1.6 Study medication

No study kits will be provided and medications will be taken "off the shelf" or made available according to local regulations. All medications to be administered in the study are commercially available in the participating countries. Investigators will be asked to make sure that study medications are available in ambulances/ERs of community hospitals. All concomitant or rescue treatment(s) taken during the course of the trial must be recorded in the source documents (e.g. patient files).

4.2 ADDITIONAL THERAPIES

4.2.1 Rescue medication and additional treatments

Protamine (sulphate or hydrochloride) administered as a slow i.v. injection (1 mg protamine per 1 mg of enoxaparin) may be used to neutralise the effect of enoxaparin (maximum effect: 60 % of the anti-Xa-activity).

4.2.2 Restrictions

Enoxaparin and heparin
Patients who received enoxaparin should not be administered a different type of heparin prior to catheterisation (and vice versa) as this may result in excessive anticoagulation well above therapeutic levels.[47, 48] If heparin was initially used for PPCI patients, subsequent treatment should not be switched to enoxaparin prior to catheterisation.

Prior to catheterisation a dose of 0.3 mg/kg i.v. enoxaparin should be given to patients in Group PhI, unless the last subcutaneous dose of enoxaparin was given within the previous 8 hrs.

GP IIb/IIIa antagonists
GP IIb/IIIa antagonists should not be used in Group PhI except if required for bail-out situations in the catheter laboratory. The use of GP IIb/IIIa antagonists in PPCI arm is at the investigator's discretion in accordance with STEMI/PCI guidelines and local standards.

4.3 TREATMENT COMPLIANCE

As all study treatments will be given out of hospital by the emergency physician and/or by experienced paramedics (as per local regulations) or in the ER of a community hospital by physicians and nursing staff, few compliance problems are foreseen. The only reasons for deviations from the treatment schedule in the protocol are considered to take place in emergency situations, for patients' safety, or due to the rare events of dosing mistakes by the study team.

Information on dosing will be collected in the eCRF.

5. OBSERVATIONS

All observations that represent or contribute to a trial endpoint are listed in the Trial Flow Chart. Observations will be taken during different trial periods: the pre-PCI hospital (including ambulance/ER community hospital), the in-PCI hospital period, end of trial (30 days) and the follow-up period (1-year), respectively, as described below. Data have to be recorded on appropriate written or electronic source data, e.g. ambulance file, patient file, hospital chart, electronic ECG recording or printout, laboratory print-out, or any trial-specific worksheet. All required data will be transcribed into the eCRF.

If needed, worksheets and instruction leaflets will be made available to the ambulance or hospital staff to facilitate data collection and ensure sample collection required for diagnostic and baseline purposes.

Please refer to section 8.2.4 for further details regarding source documents.

5.1 EVALUATION OF EFFICACY

ST-segment resolution on the ECG taken 90 min (or earlier if clinically indicated) after bolus tenecteplase and in both arms on the ECG taken in the PCI hospital before and 30 min after first catheterization (PCI), % rescue PCI and TIMI flow grades.

5.1.1 ECGs to be taken/analysed

Twelve-lead ECGs at screening/baseline for initial diagnosis in all patients and subsequently:

- In PhI group:

  - 90 min (or earlier if clinically indicated) after bolus tenecteplase
  - Immediately before and 30 minutes after the catheterization procedure (with or without PCI/stenting).
  - In case of rescue/urgent PCI, ECGs will be taken immediately before the procedure and 30 minutes after the end of the procedure.
- In PPCI group: an ECG will be taken before PCI procedure and 30 min after the PCI procedure.

In all patients, additional ECGs will be recorded before hospital discharge or on day 4, whichever occurs first. Serial ECGs should be taken in case of symptoms of recurrent ischaemia or reinfarction (see tables 4 and 5). ECGs will be centrally adjudicated.

ECG changes will be used to determine:

- Infarct size: It will be calculated at hospital discharge or day 4 whichever is earlier) using Selvester QRS scoring system[49] previously used in the ASSENT-3/3 Plus and ASSENT-4 PCI studies.[23, 42]

5.1.2. Clinical events

Death, shock, heart failure, recurrent MI, rescue PCI and aborted MI will be recorded and assessed as single or composite endpoints for evaluation as noted in the statistical analytical plan. All statistical tests on clinical events are of exploratory nature based on descriptive p-values with estimation of 95% confidence limits for formal statistical hypotheses generation.

For definitions of clinical events: see APPENDICES

5.2 SAFETY RECORDING

5.2.1 General assessment of safety

During screening and baseline the patient's condition is assessed. Results of routine observations – demographic data, medical history and concomitant diseases, physical assessment, vital signs, concomitant treatments – will be a part of the check for patient eligibility.

- Medical history/current diseases:
  Data on previous and current relevant diseases will be collected, in particular information about any cardiovascular disease, hypertension, diabetes mellitus or renal insufficiency.
- Concomitant therapy:
  Any chronic/concomitant antihypertensive, antiplatelet or anticoagulant treatment or otherwise significant therapy at screening and during the course of the study will be recorded.

- Physical assessment:
  It will be done as routine procedure at screening and will be used as check for patient eligibility. It comprises assessment of heart, lung, abdomen, etc. and should be recorded in the source documents. Results will not be collected in the eCRF.
- Vital signs:
  Assessment of systolic and diastolic blood pressure and heart rate.
- Haematology:
  Haematology laboratory samples (at least haemoglobin, haematocrit, erythrocytes, leucocytes and platelets) will be taken at baseline pre-hospital or, if this is not possible, on hospital arrival, and before hospital discharge according to the local hospital procedures. Values will be recorded in the eCRF as categories relative to the local reference ranges (i.e., below/within/above normal range). In case of bleeding or relevant laboratory abnormalities during the in-hospital period (until discharge) the laboratory values will be cross-checked with baseline values and with adverse events reports.
- Renal function:
  Serum creatinine level (as per Cockcroft-Gault formula) should be measured at the first occasion to rule out renal insufficiency. In Group PhI patients with a creatinine clearance of < 30 ml/min, the dose of subsequent enoxaparin injections should be adjusted as described in section 4.1.4.1)[27] .
- Cardiac markers:
  Troponin I/T (or CK, CK-MB) will be measured at baseline, i.e. pre-hospital or on arrival at ER of the community hospital, as well as 8-12 hrs and 24 hrs after randomisation. If symptoms suggest occurrence of recurrent myocardial ischaemia or reinfarction during in-hospital stay, marker levels should be determined to confirm the diagnosis. Individual values will not be recorded in the eCRF, for the qualifying myocardial infarction only peak values expressed as times exceeding upper limit of normal will be recorded (cf. also section 5.1.2).
- 12-lead ECG:
  For ECG measurements please refer to section 5.1.2.
- TIMI flow grade:
  TIMI flow grade of the infarct-related artery (IRA) will be assessed by standard angiographic measurement during routine catheterisation in PhI Group or, for the PPCI Group, before PCI (first contrast injection) and after PCI (last contrast injection) as measured by the local investigator.
- Killip class:
  Killip class will be determined before randomisation to check for patient eligibility. In case the ambulance staff consists of paramedics only, the responsible PI (or sub-investigator) must make sure the staff is sufficiently trained to perform the Killip classification. In the exceptional case that the Killip classification cannot be done at randomisation, it will be done upon arrival at the hospital.

- Adverse events:

  Expected adverse events (AEs) related to tenecteplase are listed in the current version of the Tenecteplase Investigator Brochure[50], filed in the Investigator Site File.

  Adverse events will be recorded according to the following procedure until day 30 (cf. Figure 2):

  All adverse events (serious and non-serious) need to be reported in the eCRF.

  In addition an SAE form must be completed and submitted within 24 hours for any SERIOUS adverse event:

  - related to study treatment (Tenecteplase, Clopidogrel, catheterisation/PCI)
  - not related to study treatment AND not on the list of the STEMI related events

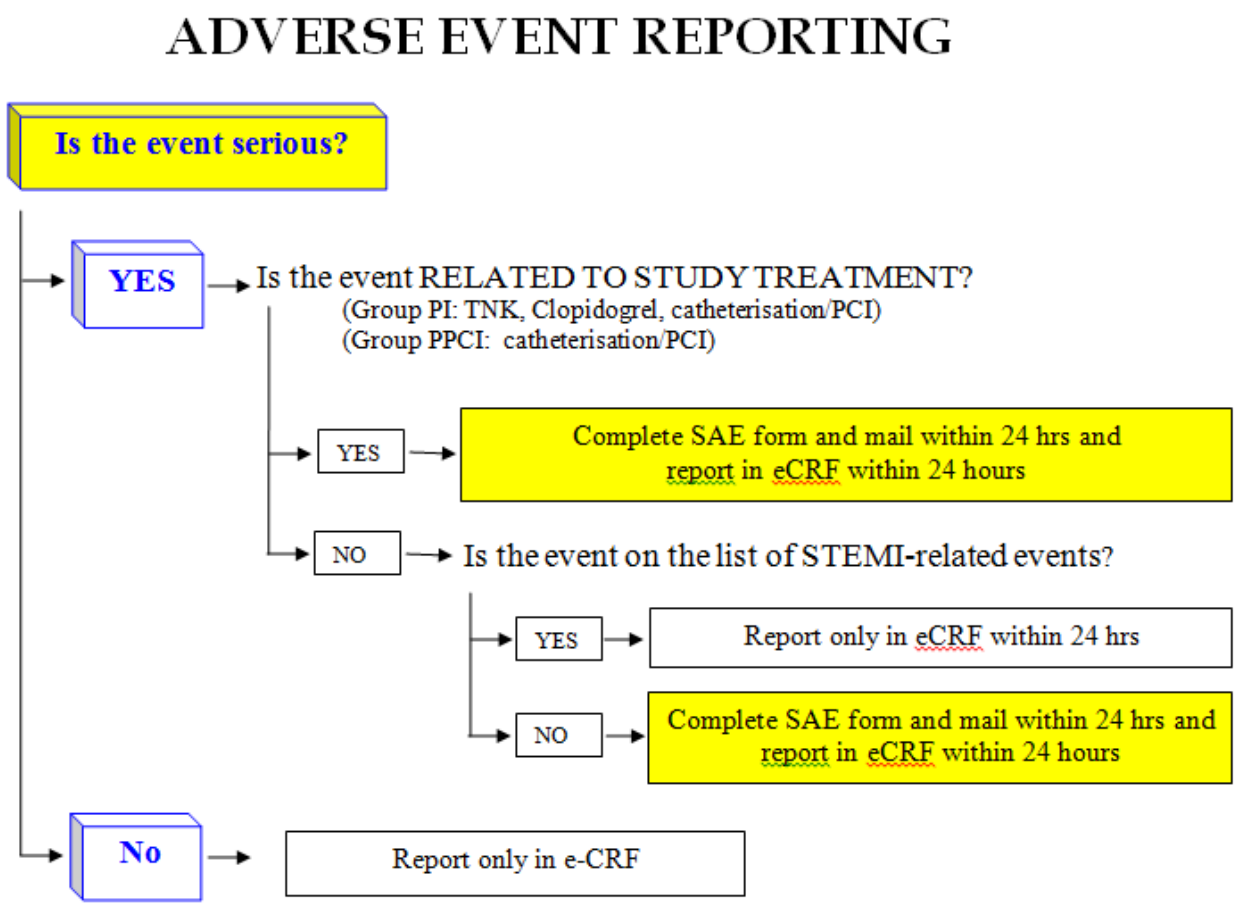


Figure 5: Adverse Event Reporting

During screening/baseline, the patient's condition is assessed; any relevant changes from

baseline will be noted subsequently in the source data (cf. section 8.2.4 for details).
Patients and investigators will be required – according to the procedure described above –to report spontaneously any AEs as well as the time of onset, end and seriousness of these events. A carefully written record of all AEs shall be kept by the investigator in charge of the trial. All events, including those persisting after trial completion must be followed up until they have resolved or have been sufficiently characterised.

Definitions and requirements for documentation and reporting of AEs and SAEs during a trial are provided in sections 8.4.1.

Worsening of pre-existing conditions

- Expected fluctuations or expected deterioration of the underlying disease will not be recorded as an AE. Worsening of the disease under study will be recorded as an AE if one of the following criteria is met.
  - Worsening of disease meets the criteria for an SAE.
  - Treatment is required (concomitant medication is added or changed).
  - The investigator believes a patient has shown a clear, unexpected deterioration from baseline symptoms.
- The same criteria as above apply to recording of AEs resulting from worsening of other pre-existing conditions. Pre-existing conditions are not recorded as AEs if they do not meet the criteria above. Specifically, the following will not be recorded as an AE:
  - Pre-existing conditions present at baseline, which remain unchanged during the trial.
  - Expected fluctuations or expected deterioration of a pre-existing condition.

Vital Signs, ECG and Laboratory test results qualifying as AE

Changes in safety tests including blood pressure, pulse rate, ECG and laboratory tests will be recorded as AEs, if:

- they are not associated with an already reported AE, symptom or diagnosis
  or
- treatment is required (concomitant medication is added or changed)

5.2.2 Specific safety recording within 30 days

Specific safety events to be recorded in this trial will be:

- Clinically suspected stroke (total (fatal, disabling, non-disabling); ischaemic; intracranial haemorrhage)

  Patients experiencing any new neurological deficit at any time after randomisation (up to day 30) are to be taken for immediate (within 24 hours) computed tomography scanning (CT) or

magnetic resonance imaging (MRI) to determine whether a stroke or intracranial haemorrhage (ICH) has occurred. CT is preferred, but MRI is also acceptable. In addition, all patients concerned should also be seen by a neurologist who may assist with the completion of the necessary documentation.
If, in case of a fatal stroke and no imaging was done, an autopsy should be performed whenever possible.
Detailed information on the stroke (date and time of onset, type, method of detection, outcome) will be collected in the eCRF.
If a stroke occurs after discharge (up to day 30) or after referral to another hospital, the investigator and/or study team ought to use their best efforts to obtain the required information from that hospital.

All strokes will be centrally adjudicated by the Stroke Review Panel (cf. section 8.10).

- Non-intracranial bleeds (total, major, minor, and blood transfusions):
  Any reported bleeding, i.e. minor or major bleeds or any bleeding requiring blood transfusion, will be collected in the eCRF to assess the safety of the treatment. Serious bleeds will be reported as serious adverse events as described in section 5.2.1. All bleeds will be recorded in the eCRF. For bleed categories please refer to Appendices.
- Serious cardiac events:
  Serious clinical events such as stent thrombosis, reinfarction, CHF, cardiogenic shock will be recorded in the eCRF. For all serious adverse events requiring expedited reporting according to the procedure described in section 5.2.1 a special eSAE form must be completed in addition and must be submitted for further distribution to the Coordinating Center within 24 hours of the investigator becoming aware of the event (see section 8.4.1).

5.3 OTHER RECORDINGS

5.3.1 Duration of hospitalization

- Total duration of hospital stay (PCI hospital and possibly community hospital):
  Days from initial admission to PCI hospital until discharge home or referral to a rehabilitation centre or nursing home will be calculated. Patients coming from a community hospital can be transferred back to the referring community hospital after PCI.
- Duration of rehospitalisation started until and including day 30 day:
  The duration of any rehospitalisation subsequent to discharge from index hospitalisation that commenced within 30 days of randomisation (i.e., starting at the latest on day 30) will be counted.

5.3.2 Evaluations at 1 year

- All-cause mortality:
  The patient's vital status at day 365 has to be evaluated. In case of the patient's death between

day 31 and day 365, the date and primary cause of death will be collected retrospectively at the 1-year follow up.

- Rehospitalisation:
  If a patient is readmitted to the hospital for cardiovascular reasons between day 31 up to and including day 365, the date(s) and primary reason(s) must be recorded in the eCRF.

5.3.3 Evaluations specific for group PhI

- Need for recue PCI

  ST resolution will be calculated according to methods described by Armstrong et al.[51] and will also be used to determine the adherence to ECG criteria for rescue.

  Rescue coronary intervention is anticipated in approximately 25 to 30 % of patients receiving pharmacologic reperfusion therapy, if ST-segment resolution at 90 minutes (or earlier, if clinically indicated), is <50 % in the lead showing the greatest ST-segment elevation noted at baseline (randomisation) with the ECG measured from J-point *with or without* clinical symptoms.

  All rescue or urgent coronary interventions (as defined in section 6.2.2.1) will be centrally adjudicated to ensure protocol adherence with feedback provided to investigators as warranted.

5.4 APPROPRIATENESS OF MEASUREMENTS

All methods selected as efficacy and safety assessments in this trial are standard methods and/or widely used in trials on myocardial infarction.

A strong step-wise correlation has been demonstrated across the lytic trials between the degree of ST-segment resolution and clinical outcome.[52, 53] More recently analysis of resolution of maximal post-lysis ST-segment elevation from the single lead showing maximal initial ST-elevation has been shown to discriminate clinical outcomes following fibrinolysis for STEMI. Adoption of a 50 % cut-off for ST-segment resolution appears to confer similar sensitivity for prediction of death or development of heart failure (around 90 %) to that of <70% maximal ST resolution threshold, with fewer false positive results (specificity around 60% at the 50 % threshold). A single criterion of <50% ST-segment resolution in the lead with previous maximal ST-elevation acquired 90 minutes after fibrinolysis equips physicians and nursing staff with a simple, convenient and reasonably accurate bed-side tool to diagnose lytic failure.

5.5 DATA QUALITY ASSURANCE

This trial will be conducted according to the principles of the International Conference on Harmonisation (ICH), Declaration of Helsinki (2013), Good Clinical Practice (GCP), the applicable national and international laws and guidelines and all applicable standard operating procedures (SOPs). The following measures will be taken to ensure accurate, consistent, complete and reliable data:

- All required trial documents will be distributed to every trial site and kept in the Investigator Site File (ISF). Site initiation will be performed by the CRO / ARO to assure a high quality and standardisation across sites (and countries).
- Trial teams at the sites will be trained on protocol requirements, trial procedures, adverse event reporting, and remote data capture.
- ECGs for assessment of ST resolution, clinical and ECG data for assessment of aborted infarction, and clinical and imaging data for assessment strokes will be centrally adjudicated.
- Monitoring: Data captured in the eCRF will be verified against source data by CRAs. The identity and informed consent as well as SAE reporting will be checked. A risk based monitoring approach will be implemented.
- The trial sites are to use validated and calibrated equipment (ECG) as required.
- Auditing (internal and, if required by any regulatory authorities, external) can be performed as necessary.
- Coding (e.g., according to MedDRA for adverse events) will be performed.
- Data quality review meetings (DQRMs) will be held at regular intervals to check for data accuracy across sites and discrepancies will be handled.

6. INVESTIGATIONAL PLAN

Prerequisites:

During the site selection process the qualification of a trial site for participation in the trial has to be determined. Sites (ambulances or ER of community hospitals) must be experienced in fibrinolysis and have access to a hospital with a catheterisation laboratory providing 24/7 PPCI service. (e.g., by hub and spoke relationship) to ensure the performance of delayed or timely rescue PCI, as required (Group PhI), or of PPCI according to the protocol. Each site enrolling patients will be assigned an individual site number and IVRS code.

Before an ambulance site commences enrolling patients, the composition of the ambulance staff involved in pre-hospital trial procedures should be clearly established. In instances where an ambulance vehicle is staffed entirely with paramedics, the principal investigator will confirm that the diagnosis of STEMI as well as the acquisition of consent and initiation of pre-hospital treatment is undertaken with appropriate ethical and regulatory authorisation as established in the region and/or country participating. In addition, the principal investigator must ensure that the staff is able to make any trial-related diagnoses as, e.g. congestive heart failure and cardiogenic shock and to perform the trial procedures according to protocol. Patient eligibility criteria will be provided in a translated comprehensible version for use by paramedics. Similarly in the ER of community hospitals the principal investigators must ensure that the staff of the emergency department is

familiar with the existence and details of the protocol.

6.1 VISIT SCHEDULE

The trial consists of the following periods:

- Pre-PCI hospital: screening/baseline assessments, informed consent, randomisation, early study treatment
- In-PCI hospital period: continuation of trial treatment as necessary
- Discharge: pre-discharge assessments
- End of trial (day 30): check for AEs and rehospitalisations
- 1-year follow-up: check for vital status and rehospitalisations for cardiovascular reasons.

All assessments per visit are listed in the Trial Flow Chart and are described in section 6.2 and, in more detail, section 5.

6.2 TRIAL PROCEDURES AT EACH VISIT

6.2.1 Pre-PCI hospital period

As soon as the ambulance arrives at the scene or the patient arrives at the emergency department of a community hospital, the patient will be screened for eligibility and enrolled by the investigator or authorised ambulance staff. Routine and/or rescue procedures are performed according to local practice and established guidelines. The following assessments will be done (for details of the individual assessments please refer to the Flow Chart and to section 5.2):

- Informed consent, demographic data, medical history/current diseases; physical assessment, vital signs (blood pressure for evaluation of exclusion criterion 6), concomitant therapy; haematology, renal function, troponin I/T (CK/CK-MB) (if pre-hospital blood samples are taken); twelve-lead ECG, Killip class; inclusion/exclusion criteria, randomisation, and administration of trial medication.

Randomisation and treatment allocation

- Patients will be randomised by authorised staff by means of an interactive voice response system (IVRS). A study number will be given by the system after recording a minimal set of data (gender, date of birth, informed consent, inclusion/exclusion criteria).
- For patients randomized to PhI arm tenecteplase should be given first followed by enoxaparin, aspirin (if not yet on aspirin) and clopidogrel.

For a detailed description of study treatment please refer to section 4.1.4 of this protocol.

Following randomisation and administration of study treatments, immediate transfer to the PCI hospital must be arranged.

The following documents/samples should accompany any patient when transferred to the receiving PCI hospital:

- Diagnostic/baseline ECG, either as a paper copy or transferred electronically
- Any ambulance files or worksheets in the ambulance/ER community hospital where the required source data are recorded
- Baseline blood samples for diagnostic cardiac markers/enzymes (troponin I/T or CK/CK-MB), haematology, and renal function, if taken on scene/pre-hospital. In case no blood samples are taken on scene/pre-PCI hospital, they should be taken immediately after arrival at the receiving PCI hospital.

6.2.2 In-PCI hospital period (including day of discharge)

The "in-PCI hospital period" starts with the patient's arrival at the PCI hospital.

A patient is considered admitted to hospital when he/she reaches the hospital alive and medical responsibility is taken over by the PCI hospital medical team (irrespective of whether it occurs in the emergency room, the coronary care unit (CCU), the intensive care unit (ICU) or any other ward/unit).

- If not already taken before, baseline blood samples for diagnostic cardiac markers (Troponin I/T or CK/CK-MB), renal function, and haematology should be taken as soon as possible after hospital arrival.
- Patients will then receive further treatment according to the treatment group they have been randomised to.

6.2.2.1 Group PhI

Assessment of reperfusion

At the receiving PCI hospital patients should be admitted to either the emergency department, coronary care unit or catheterisation laboratory (as per local practice) to assess reperfusion.

The patient's need for rescue coronary intervention will be assessed by both ECG and evaluation of clinical symptoms 90 min (or earlier if clinically indicated) after injection of tenecteplase. These patients may undergo coronary intervention immediately, if indicated, in accordance with the protocol criteria described below.

An additional ECG should be taken before starting the procedure. If there are clinical or electrocardiographic signs of reperfusion that have occurred after the previous ECG, the planned coronary intervention may be postponed.

Cardiac Catheterisation

- If ST-segment resolution is ≥ 50 % in the qualifying lead (that had the maximum initial ST-segment elevation in the baseline ECG), diagnostic coronary angiography (followed by

elective PCI +/- stenting, if indicated) should be performed no sooner than 6 hours, but within 24 hours after administration of tenecteplase. This will be considered as planned catheterisation according to protocol

- If ST-segment resolution is < 50 % relative to the ST-segment elevation in the qualifying lead at baseline, irrespective of the presence or absence of clinical symptoms, rescue coronary intervention should be performed promptly.
- If any of the following indications require coronary intervention (irrespective of previous ST-segment resolution), urgent coronary intervention is indicated at any time:
    - haemodynamic instability (presence of any of the following requiring inotropic support: sustained hypotension, cardiogenic shock, or congestive heart failure)
    - refractory ventricular arrhythmias requiring cardioversion or pharmacological treatment
    - worsening ischaemia
    - progressive or sustained ST-segment elevation which, in the judgement of the investigator, requires immediate coronary intervention

All rescue and urgent coronary interventions will be adjudicated by an independent clinical expert as previously described.[19] Feedback to participating sites regarding adherence to protocol defined indications for rescue will be provided as appropriate.

Further ECG measurements

Further ECG measurements are listed in Table 4.

Table 4: Overview of ECG measurements in Group PhI

Timing of ECG	Location	Reason for ECG
Baseline	Pre-PCI hospital: on site/ambulance/ER community hospital	ECG for assessment of STEMI entry criteria
90 min after bolus tenecteplase or earlier if indicated	In-PCI hospital: emergency dept. or CCU	Assessment of reperfusion
In case of catheterisation (with or without PCI/stenting) or rescue or urgent PCI, respectively: - immediately before - and 30 min after the end of the procedure.	In-PCI hospital: catheter laboratory	Re-assessment of reperfusion

Timing of ECG	Location	Reason for ECG
Any time, if indicated (serial ECGs)	In-PCI hospital	Verification of ischaemia or reinfarction
At 4 days or hospital discharge whichever comes first	In-PCI hospital	Assessment infarct size using QRS score

Collection of data
During the patient's stay in hospital (i.e., until and including the day of discharge) the following data will be collected:

- Concomitant therapy
- Troponin I/T (CK/CK-MB) 8-12 hrs and 24 hrs after randomisation, respectively, and also at any time in case of signs and symptoms suggestive of recurrent myocardial ischaemia or reinfarction
- 12-lead ECG (please refer to Table 4)
- Data on catheterisation/coronary intervention(s)
- TIMI flow grade (before PCI and at the end of the angiographic procedure)
- Any occurrence of adverse events, and serious adverse events/serious clinical events

The following assessments will be performed on the **day of discharge from hospital** (or transfer to a rehabilitation centre or nursing home)

- Blood test for haematology as per hospital routine
- 12-lead ECG (cf. Table 4)
- Any occurrence of adverse events, and serious adverse events/serious clinical events

6.2.2.2 Group PPCI

Patients randomized to PPCI will receive medical treatment before, during and after PPCI according to established local standards. Additional GP IIb/IIIa antagonists may be given at the investigator's discretion.

During the in-hospital period several 12-lead ECGs will be taken as summarised in Table 5.

Table 5: Overview of ECG measurements in PPCI Group C

Timing of ECG	Location	Reason for ECG
Baseline	Pre-hospital: on site/ambulance/ER community hospital	ECG for assessment of STEMI entry criteria

Timing of ECG	Location	Reason for ECG
Immediately prior to PCI after arrival in PCI hospital	In-PCI hospital: catheter laboratory	Assessment of pre-PCI patency
30 min after the end of the intervention	In-PCI hospital	Reassessment of reperfusion
Any time, if indicated (serial ECGs)	In-PCI hospital	Verification of ischaemia or reinfarction
At 4 days or hospital discharge whichever comes first	In-PCI hospital	QRS score for infarct size

During the patient's stay in hospital, data on PPCI will be collected. All further assessments during the initial hospitalisation and prior to the patient's discharge from hospital (or transferral to a rehabilitation centre or nursing home) are identical to those assessed in Group PhI (please refer to the above paragraph, 6.2.2.1).

6.2.3 End of trial and follow-up period

6.2.3.1 End of trial (day 30)

The end-of-trial visit will take place at day 30. Data may however be collected until and including day 37. If a visit at the outpatient clinic is not possible the patients may be contacted by phone. The following data will be collected:

- Data on any rehospitalisation occurring after hospital discharge up to (including) day 30
- Any occurrence of adverse events, and serious adverse events/serious clinical events since hospital discharge or (if the patient is still hospitalised) that have not yet been recorded

6.2.3.2 Follow-up

Data for the 1-year follow up should be collected at day 365 (up to and including day 395). The required evaluations may be assessed via phone (if a physical visit is not performed) or can also be obtained from medical records.

The following data will be collected at 1-year: vital status/all-cause mortality and rehospitalisation for cardiovascular reasons (since day 30).

6.3 REMOVAL OF PATIENTS FROM THERAPY ASSESSMENT

As soon as the patient is randomised, the patient is considered a trial participant irrespective of

whether he or she received any trial-specific treatment or not.

A patient may withdraw from the trial at any time without the need to justify the decision.

In case of withdrawal all data collected until (and including) the day of withdrawal will be kept in the trial database. Furthermore vital status at 30 days and 1 year will be collected.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN/MODEL

The trial is a prospective, multi-centre, international, randomised (2:1), open-label, parallel-group comparison, conducted for investigating the efficacy and safety of

A. Study treatment (Group PhI)

B. Primary PCI according to local standards (Group PPCI)

in patients with acute myocardial infarction randomised < 3 hours from symptom onset.

The principal aim of the trial is to evaluate the safety and efficacy in the 2 treatment groups measured by ST segment resolution, TIMI flow grades, and clinical events as listed in section 2.1.

7.2 PLANNED ANALYSES

Baseline characteristics will be tabulated and differences among the two treatment groups will be examined by means of descriptive statistics.

The primary analysis is an intent-to-treat analysis of all randomised patients. Patients will be analysed according to the treatment group to which they were randomised, irrespective of which study drug was given or if any study drug was received.

7.2.1 Interim analyses

After 50 % of the planned recruitment a formal interim analysis will be performed by the Data and Safety Monitoring Board (DSMB) to evaluate and advise the Executive Committee on the feasibility of enlarging the sample size and to turn the study into a confirmatory trial. Continuous safety monitoring will be done by the DSMB with particular emphasis on the incidence of systemic bleeding and intracranial haemorrhage (ICH); details are documented in the DSMB charter.

7.3 HANDLING OF MISSING DATA

No imputation of missing data is foreseen. Best efforts will be made to collect complete data for the clinical events of interest. Distribution of the missing data will be checked across groups.

7.4 RANDOMISATION

The randomisation will be stratified by centre and, within the centres, performed in blocks to ensure balanced distribution of the treatment groups at any time. Randomisation will be available daily for 24 hours via a centralised telephone Interactive Voice Response System (IVRS) or web randomization. Each site (ambulance/ER of community hospital) will be provided with a telephone number and a PIN code that will connect them to a computerised script identifying the treatment group. For details on the use of IVRS see the manual in the Investigator Site File.

Patients are considered randomised as soon as the treatment group has been assigned.

7.5 DETERMINATION OF SAMPLE SIZE

As mentioned before this is a hypothesis generating trial. No primary hypothesis or primary endpoint have been formulated. Approximately 600 patients are planned to be randomized with 400 receiving PhI therapy and 200 PPCI. A minimum of approximately 100 patients ≥ 70 years of age will be randomized to the PhI arm. The aim is to combine ECG and angiographic data from the latter group with similar data from STREAM-1[16, 18] in order to have a more reliable estimate of the efficacy of the PhI strategy in elderly patients. The analysis of ECG data, angiographic data and clinical events will be described in detail in the statistical analysis plan. Although the study of 600 patients is not powered to show a difference in clinical events, given the elderly nature of the population there will be ample efficacy and safety events to observe. They will be reported along with their 95% confidence limits. For reference, in patients ≥ 60 years from STREAM-1 the 30 day composite of death, shock, heart failure and re-MI ranged between 18 and 20 % for PhI and PPCI groups. Bleeding data in this age group were 1.7 % and 0 % ICH and 8.8 % and 7 % non-intracranial major bleeding respectively. If the study would turn into a confirmatory trial after the interim analysis a primary hypothesis on a combined clinical endpoint will be pre-specified.

8. ADMINISTRATIVE MATTERS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of 2013 in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant SOPs.

The applicable international and local laws and treatment guidelines will be adhered to.

A no fault insurance cover will be provided and explained in the informed consent form.

8.1 ETHICS

8.1.1 Institutional Review Board or Independent Ethics Committee

The trial will not be initiated before the clinical trial protocol (CTP) and informed consent and

patient information form have been reviewed and received approval from the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and approval by the Competent Authority (CA) or applicable regulatory authority as required by local laws and regulations. Should a CTP amendment be made that needs IRB/IEC approval and authority notification/approval, the changes in the CTP will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and received approval / favourable opinion from the local IRB/IEC and the CA or applicable regulatory authority, as required by local laws and regulations. A CTP amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing that the regulatory authority and IRB / IEC are notified as soon as possible and an approval is requested. CTP amendments exclusively for logistical or administrative changes may be implemented with notification of the IRB / IEC and CA or competent authority only.

The constitution of the IRB/IEC must meet the requirements of the participating countries. A list of the IRB/IEC members, with names and qualifications, needs to be provided by the IRB/IEC to the investigator or, if applicable, sponsor.

8.1.2 Informed Consent and Patient Information

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) or initial verbal and subsequent written consent according to the regulatory and legal requirements of the participating country. Each signature must be dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by the study sponsor in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorised monitors (CRA) or Clinical Quality Assurance auditors appointed by the sponsor, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

Should a CTP amendment become necessary, the patient consent form and patient information form may need to be revised to reflect the changes to the CTP. It is the responsibility of the investigator or, if applicable, sponsor to ensure that an amended consent form is reviewed and has received approval / favourable opinion from the IRB / IEC and CA or applicable regulatory authority, as required by local laws and regulations, and that it is signed by all patients subsequently entered in the trial and those currently in the trial, if affected by the amendment.

8.2 RECORDS

8.2.1 Drug accountability

The local investigator or pharmacist must maintain records of the delivery and use of medications for the study.

8.2.2 Case Report Forms (CRFs)

All of the clinical data will be captured via electronic data capture (EDC) using Open Clinica, a web-based application. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (Ref: 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded.

Electronic CRFs (eCRFs) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. Relevant medical history prior to enrolment will be documented at the baseline visit. The eCRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the eCRF by name. Appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

8.2.3 Source documents

According to ICH/GCP source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigative site and will be verified to the eCRF by the CRA when indicated.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Current medical records must also be available.

8.2.4 Direct access to source data / documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data / documents. ECRFs and all source documents, including progress notes and copies of laboratory and medical test results, must be available at all times for review by the sponsor's clinical trial monitor and inspection by health authorities. The on-site monitor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the source documents to the eCRF.

8.3 QUALITY ASSURANCE AUDIT

A quality assurance audit of this trial may be conducted by the sponsor or sponsor's designees. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation that is relevant to this clinical trial.

8.4 PROCEDURES

8.4.1 Adverse events

An **adverse event** (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

A **serious adverse event** (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason representing a significant hazard, which is comparable to the aforementioned criteria.

Adverse events occurring during the course of the clinical trial (i.e. from signing the informed consent onwards through the observational phase) will be collected, documented and reported by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File and in section 5.2.1 of the trial protocol. Figure 2 in section 5.2.1 of the trial protocol shows an overview of the adverse event reporting.

Reporting of serious adverse events (SAE)s:

On an SAE form:
For the following events an SAE form (in addition to entering the SAE data in the eCRF) will need to be completed and emailed for expedited reporting:

- Serious and treatment-related SAEs
- Serious, not treatment-related and not mentioned on the 'list of STEMI-related events'

For each SAE, the investigator will provide the onset, end, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will also determine the relationship of the investigational drug to all SAEs.

The basis for judging the causal relationship between the investigational product and the SAE is described below.

Causal relationship*	
Yes	There is a reasonable causal relationship between the study drug administered and the AE.

No	There is no reasonable causal relationship between the study drug administered and the AE.

*Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

These completed SAE forms need to be emailed within 24 hours (1 workday) after the Investigator (or any member of the study team) has become aware of the event. Timelines are the same for initial reports and for follow-up reports.

Upon receipt of these SAE forms the treatment relationship, the category classification, listedness and seriousness of reported SAE cases will be assessed. Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), will be done according to local regulatory requirements within the required timelines.

In the eCRF:

Any SAE, whether or not considered related to the study medication, and whether or not the study medication has been administered, must be reported immediately in the eCRF.

Reporting of non-serious adverse events:

Non-serious events need to be recorded in the eCRF

8.5 RULES FOR AMENDING PROTOCOL

All CTP amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol. This also applies to any local amendment that may become necessary. Amendments need to be submitted to the IRB / IEC for review/approval and to the competent authority (CA) or the applicable regulatory authority for approval/ notification, as described in section 8.1.1.

8.6 DISCONTINUATION OF THE TRIAL

The sponsor who initiated the study reserve the right to discontinue the trial at any time for the following reasons (please also refer to section 8.10):

1.) Failure to meet expected enrolment goals,
2.) Emergence of any efficacy/safety information that could significantly affect continuation of the trial or any other administrative reasons,
3.) Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

8.7 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.8 PUBLICATION POLICY

This study represents an investigator initiated effort supported by a pharmaceutical company and research foundations, and as such, the parties agree that the recommendation of the pharmaceutical company concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation whenever these recommendations are related to their drugs.

The Executive Committee in conjunction with the Steering Committee will prepare a manuscript(s) plan to ensure timely and high quality presentation and publication of the study results and provide this also to the pharmaceutical company for due consideration.

Investigators are encouraged to propose additional analyses from the final available data. All proposed publications and presentations by investigators or their personnel and associates resulting from or relating to this study must be submitted to the Executive Committee in conjunction with the Steering Committee for review and approval prior to submission for publication or presentation. Manuscripts submitted for publication must be in compliance with applicable laws and regulations regarding patient privacy.

8.9 COMPLETION OF TRIAL

The IEC/competent authority in each participating EU member state and any other countries where notification is required needs to be notified about the end of the trial (last patient out) or early termination of the trial.

8.10 STUDY COMMITTEES

Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will monitor the accruing safety and outcome data.

The DSMB will be composed of independent cardiologists including at least one interventional

cardiologist and one independent biostatistician.

The DSMB will review safety data. The DSMB will also conduct analyses of the data at the request of the Steering Committee and/or Executive Committee. The DSMB analyses and operations will be formally separated from the sponsor, pharmaceutical companies, the investigators and the Steering/Executive Committee. The DSMB will advise the executive committee- by giving recommendations on the trial continuation or aspects of the study conduct. After recruiting 50 % of the planned population a formal interim analysis will be performed by the DSMB to evaluate and advise the Executive Committee on the feasibility of increasing the sample size in order to turn the study into a confirmatory trial. The tasks of the DSMB will be described in detail in the DSMB charter.

Stroke Review Panel

An independent Stroke Review Panel will perform a final evaluation and classification of documented clinically suspected strokes.

The Stroke Review Panel members will include an independent neurologist and a neuroradiologist.

All the clinically suspected stroke events will be reviewed by the Stroke Review Panel blinded to the allocated treatment. On the basis of the stroke event documentation the Stroke Review Panel will assess and classify each stroke event as primary haemorrhagic or ischaemic or unclassifiable.

The classification of the strokes will be made available for the periodical DSMB reviews.

Executive Committee

The Executive Committee is composed of F. Van de Werf (co-chair), P.W. Armstrong (co-chair), Peter Sinnaeve (co-PI), Robert Welsh (co-PI), P. Goldstein. It provides scientific direction of the study and assesses the study progress. The Executive Committee is assisted by the Steering Committee. The Executive Committee Chairmen are responsible for communicating with the DSMB when appropriate.

The Executive Committee meets periodically by telephone or webcast.

Steering Committee

The Steering Committee is composed of the Executive Committee and members from all participating countries, usually the national coordinator(s) of every country. The Steering Committee meets periodically at the major international cardiology congresses to assess the progress, provide scientific input and address policy issues and operational aspects of the protocol. At the end of the trial the Steering Committee will meet in a closed session to discuss the trial results.

Operations Committee

The Operations Committee is responsible for all operational management issues in running the study on a daily basis. It is composed of members with operative responsibility for different areas like overall management, regulatory issues, monitoring, safety reporting, data management etc. It interacts closely with the Study Chairmen and the Executive Committee, the local clinical monitors and data management for the day-to-day conduct of the study.

APPENDIX A: CLINICAL EVENTS TO BE RECORDED IN ECRF

Cardiac events within 30 days

- All-cause mortality
- Cardiac mortality
- Cardiogenic shock
- Congestive heart failure
- Recurrent myocardial infarction
- Stent thrombosis
- Rehospitalisation for cardiac reasons
- Rehospitalisation for non-cardiac reasons

Safety events with 30 days

Total stroke, intracranial haemorrhage, ischaemic stroke, haemorrhagic conversion within 30 days

- Procedure related major bleeds (within 48 hours)
- Non-intracranial bleeds (major, minor) and need for blood transfusions up to 30 days

Evaluations at 1 year

- All-cause mortality

APPENDIX B: DEFINITIONS OF CLINICAL EVENTS

B1. BLEEDS

Major bleeds

Severe bleed: a bleed that leads to haemodynamic compromise requiring intervention (e.g. blood or fluid replacement, inotropic support, surgical repair) or life-threatening or fatal bleeds.

Moderate bleed: bleeding requiring transfusion of blood but which does not lead to haemodynamic compromise requiring intervention.

Minor bleeds

Bleeding neither requiring blood transfusion nor leading to haemodynamic compromise.

PS Intracranial bleeds will be reported separately

B2. MAJOR CARDIAC EVENTS

Congestive heart failure

A positive diagnosis consists of at least one of the following conditions requiring treatment with diuretics:

- Pulmonary oedema/congestion on chest x-ray without suspicion of a non-cardiac cause;
- Rales >1/3 up from the lung base (Killip class 2 or higher);
- Pulmonary capillary wedge pressure (PCWP) >25 mmHg;
- Dyspnea with pO_2 < 80 mmHg or O_2 sat < 90 % (no supplemental O_2) in the absence of known lung disease

Killip class

I: The absence of rales over the lung fields and the absence of an S3.

II: The presence of rales that do not clear with coughing, over one half or less of the lung fields or the presence of an S3.

III: The presence of rales that do not clear with coughing, over more than half of the lung fields.

IV: Cardiogenic shock.

Cardiogenic shock

Defined as one of the following:

1. Systolic blood pressure < 90 mmHg for at least 30 min (or the need for supportive measures to maintain a systolic blood pressure of > 90 mmHg) in the presence of a heart rate of >60 beats/min

in association with signs of end organ hypoperfusion (cold extremities, low urinary output < 30 ml/h and/or mental confusion);

2. A cardiac index < 2.2 l/min/m^2 in the presence of a pulmonary capillary wedge pressure (PCWP) of >15 mmHg.

Reinfarction

Reinfarction in the absence of a coronary intervention and within 18 hours after randomization:

Recurrent signs and symptoms of ischaemia at rest, accompanied by new or recurrent ST-segment elevations of ≥ 0.1 mV in at least two contiguous leads lasting ≥ 30 min.

Reinfarction related to PCI

≤48 h after the index procedure:

Coronary intervention related myocardial infarction is arbitrarily defined by elevation of cardiac troponin values >5 multiplying 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cardiac troponin values >20% if the baseline values are elevated and are stable or falling. In addition, either symptoms suggestive of myocardial ischemia or new ischemic ECG changes or angiographic findings consistent with a procedural complication or imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

>48 h after the index procedure:

Detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of ischemia;
- New or presumed new significant ST-T changes or new left bundle branch block;
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus eg stent thrombosis by angiography or autopsy

Reinfarction related to cardiac surgery

≤48 h after the index procedure:

Cardiac and non-cardiac surgeries related myocardial infarction are arbitrarily defined by elevation of cardiac troponin values >10 multiplying 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cardiac troponin values >20% if the baseline values are elevated and are stable or falling plus either new pathological Q waves or new left bundle block or angiographic documented new graft or new native coronary artery occlusion or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

>48 h after the index procedure:

Detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of ischemia;
- New or presumed new significant ST-T changes or new left bundle branch;
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy

Aborted myocardial infarction

Aborted myocardial infarction[54] will be assessed by means of ECG as ST-segment resolution relative to baseline value and cardiac marker enzymes as done previously in STREAM-1[55]. Peak levels of troponin I/T (CK/CK-MB) will be collected at baseline, and 8-12 hrs and 24 hrs after randomisation. Quantification of aborted myocardial infarction will be defined as troponin values ≤ 5 times the upper limit of normal (ULN) within 24 hours of randomisation (or CK/CK-MB levels ≤ 2 times ULN). Only peak values of markers of necrosis (expressed as times exceeding the upper limit of normal) will be recorded in the eCRF; the complete set of measured values will however be kept in the source documents.

Rescue PCI post PhI therapy

If ST-segment resolution is <50% relative to the ST-segment elevation in the qualifying lead at baseline, irrespective of the presence or absence or clinical symptoms

Refractory ischaemia

Symptoms of ischaemia with ST-deviation or definite T-wave inversion persisting for at least 10 min despite medical management while in-hospital and not fulfilling the diagnosis of infarction.

Major arrhythmias

Sustained ventricular tachycardia (ventricular tachycardia lasting ≥ 30 seconds or requiring cardioversion or causing symptoms/hypotension), ventricular fibrillation, asystole, atrial fibrillation, 2nd and 3rd degree atrio-ventricular block.

Invasive procedures

Include CABG, PTCA, stent placement, intra-aortic balloon.

Other major cardiac events

Other major cardiac events include sustained hypotension, acute mitral regurgitation, acute ventricular septum defect, pericarditis, pulmonary embolism and tamponade.

Sustained hypotension

SBP < 90 mmHg for > 30 minutes

Rehospitalisation for cardiac reasons

If, after discharge, a patient is readmitted to the hospital until day 30 due to cardiac reasons, this information must be recorded in the eCRF. Any event requiring unscheduled readmission will be considered a serious adverse event (SAE) and recorded as described in section 5.2.1. Only if readmission was scheduled, e.g. because of a routine or planned procedure, will the event leading to rehospitalisation not be considered as a serious adverse event.

Rehospitalisation for non-cardiac reasons

Data about any rehospitalisation for non-cardiac reasons occurring after discharge from initial hospitalisation until day 30 will be collected in the eCRF and have to be recorded on SAE reports in accordance with section 5.2.1. Only if rehospitalisation was scheduled, e.g. because of a routine or planned procedure, will it not be considered as a serious adverse event.

Statistical analysis of clinical events

The analysis will be described in detail in the statistical analysis plan. Clinical events of interest will be assessed as single or composite endpoints for evaluation. All statistical tests on clinical events are of exploratory nature based on descriptive statistics for formal statistical hypotheses generation. For comparison the same composite clinical event rates as in STREAM-1 will be analysed (see APPENDICES). The primary comparisons will be based on the differences between Group PhI and PPCI. Differences between groups and their 95% CI will be calculated. Should a statically significant difference appear in at least one clinical endpoint, i.e. the corresponding CI excludes 0 (no difference), and if there is also consistency for the other endpoints, then this will be considered evidence for a clinically meaningful difference between treatments which should be confirmed in a later study. Should no statistically significant difference be apparent, the CI will be examined to determine to what level a worse outcome can be excluded as has been done with the primary endpoint in STREAM-1.

A formal interim analysis will be performed after 50 % of the planned recruitment. The aim of this analysis is to evaluate the usefulness and feasibility of enlarging the study based on the results.

APPENDIX C

The following adverse events are expected as disease-related events (i.e. related to acute myocardial infarction):

Arrhythmias

All arrhythmias occurring later than 3 hours after fibrinolysis
All arrhythmias in patients who did not receive fibrinolysis

Ischaemia and symptoms of coronary artery disease

Angina pectoris (stable)
Angina pectoris (unstable)
Back pain (of cardiac origin)
Cardiac enzymes (abnormal)
Cardiac markers (abnormal)
Chest pain
Electrocardiogram abnormalities
Myocardial ischaemia
Myocardial reinfarction
Recurrent myocardial ischaemia
ST-elevation
Substernal chest pain
Substernal pain

Artery disorders

Aortic dissection
Coronary artery dissection
Coronary artery disorder
Coronary artery thrombosis
Coronary occlusion
Vascular anomaly

Cardiac failure

Acute pulmonary oedema
Cardiogenic shock
Congestive heart failure
Cor pulmonale
Heart failure
Left heart failure

Pulmonary oedema
Haemodynamic and circulatory shock

Pericardium disorders

Pericardial effusion
Pericarditis

Other cardiac disorders

Acute mitral regurgitation
Acute ventricular septum defect
Cardiac rupture
Cardiomyopathy
Electro-mechanical dissociation

Other events

Deep thrombophlebitis
Hypertension
Livedo reticularis
Peripheral oedema
Peripheral vascular disorder
Syncope
Thrombocytosis
Vascular disorder
Venous thrombosis

9. REFERENCES

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, Group ESD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;**39**(2):119-177.
2. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso JE, Tracy CM, Woo YJ, Zhao DX, Force CAT. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;**127**(4):529-55.
3. Zahn R, Schuster S, Schiele R, Seidl K, Voigtländer T, Meyer J, Hauptmann KE, Gottwik M, Berg G, Kunz T, Gieseler U, Jakob M, Senges J. Comparison of primary angioplasty with conservative therapy in patients with acute myocardial infarction and contraindications for thrombolytic therapy. Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Study Group. Catheter Cardiovasc Interv 1999;**46**(2):127-33.
4. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;**361**(9351):13-20.
5. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, Leizorovicz A, Touboul P, Investigators CoAaPTIaMiC. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation 2003;**108**(23):2851-6.
6. Kalla K, Christ G, Karnik R, Malzer R, Norman G, Prachar H, Schreiber W, Unger G, Glogar HD, Kaff A, Laggner AN, Maurer G, Mlczoch J, Slany J, Weber HS, Huber K, Group VSR. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). Circulation 2006;**113**(20):2398-405.
7. Fernández-Avilés F, Alonso JJ, Peña G, Blanco J, Alonso-Briales J, López-Mesa J, Fernández-Vázquez F, Moreu J, Hernández RA, Castro-Beiras A, Gabriel R, Gibson CM, Sánchez PL, Investigators G-GdAdCIA. Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial. Eur Heart J 2007;**28**(8):949-60.
8. Danchin N, Blanchard D, Steg PG, Sauval P, Hanania G, Goldstein P, Cambou JP, Guéret P, Vaur L, Boutalbi Y, Genès N, Lablanche JM, Investigators U. Impact of prehospital thrombolysis for acute myocardial infarction on 1-year outcome: results from the French Nationwide USIC 2000 Registry. Circulation 2004;**110**(14):1909-15.
9. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Mäkijärvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;**108**(2):135-42.
10. Armstrong PW, Committee WS. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. Eur Heart J 2006;**27**(13):1530-8.

11. Huber K, De Caterina R, Kristensen SD, Verheugt FW, Montalescot G, Maestro LB, Van de Werf F, ESC TFoP-hRTotWGoTot. Pre-hospital reperfusion therapy: a strategy to improve therapeutic outcome in patients with ST-elevation myocardial infarction. Eur Heart J 2005;**26**(19):2063-74.
12. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. JAMA 2000;**283**(20):2686-92.
13. Le May MR, Wells GA, Labinaz M, Davies RF, Turek M, Leddy D, Maloney J, McKibbin T, Quinn B, Beanlands RS, Glover C, Marquis JF, O'Brien ER, Williams WL, Higginson LA. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). J Am Coll Cardiol 2005;**46**(3):417-24.
14. Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R, Investigators RT. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 2005;**353**(26):2758-68.
15. Armstrong PW, Gershlick A, Goldstein P, Wilcox R, Danays T, Bluhmki E, Van de Werf F. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study. Am Heart J 2010;**160**(1):30-35.e1.
16. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med 2013;**368**(15):1379-87.
17. Sinnaeve PR, Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Lambert Y, Danays T, Soulat L, Halvorsen S, Ortiz FR, Vandenberghe K, Regelin A, Bluhmki E, Bogaerts K, Van de Werf F. ST-Segment-Elevation Myocardial Infarction Patients Randomized to a Pharmaco-Invasive Strategy or Primary Percutaneous Coronary Intervention: Strategic Reperfusion Early After Myocardial Infarction (STREAM) 1-Year Mortality Follow-Up. Circulation 2014;**130**(14):1139-45.
18. Armstrong PW, Zheng Y, Westerhout CM, Rosell-Ortiz F, Sinnaeve P, Lambert Y, Lopes RD, Bluhmki E, Danays T, Van de Werf F, investigators S. Reduced dose tenecteplase and outcomes in elderly ST-segment elevation myocardial infarction patients: Insights from the STrategic Reperfusion Early After Myocardial infarction trial. Am Heart J 2015;**169**(6):890-898.e1.
19. Welsh RC, Van de Werf F, Westerhout CM, Goldstein P, Gershlick AH, Wilcox RG, Danays T, Bluhmki E, Lopes RD, Steg PG, Armstrong PW. Outcomes of a Pharmacoinvasive Strategy for Successful Versus Failed Fibrinolysis and Primary Percutaneous Intervention in Acute Myocardial Infarction (from the Strategic Reperfusion Early After Myocardial Infarction [STREAM] Study). Am J Cardiol 2014;**114**(6):811-9.
20. Larson DM, Duval S, Sharkey SW, Garberich RF, Madison JD, Stokman PJ, Dirks TG, Westin RK, Harris JL, Henry TD. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. Eur Heart J 2012;**33**(10):1232-40.
21. Keyt BA, Paoni NF, Refino CJ, Berleau L, Nguyen H, Chow A, Lai J, Peña L, Pater C, Ogez J. A faster-acting and more potent form of tissue plasminogen activator. Proc Natl Acad Sci U S A 1994;**91**(9):3670-4.
22. Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. Clin Pharmacokinet 2002;**41**(15):1229-45.
23. Investigators AotSaEoaNTRA-. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;**358**(9282):605-13.

24. Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, Betriu A, Binbrek AS, Califf R, Diaz R, Fanebust R, Fox K, Granger C, Heikkilä J, Husted S, Jansky P, Langer A, Lupi E, Maseri A, Meyer J, Mlczoch J, Mocceti D, Myburgh D, Oto A, Paolasso E, Pehrsson K, Seabra-Gomes R, Soares-Piegas L, Sùgrue D, Tendera M, Topol E, Toutouzas P, Vahanian A, Verheugt F, Wallentin L, White H, Investigators AotSaEoaNTA-. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999;**354**(9180):716-22.
25. Antman EM, Morrow DA, McCabe CH, Jiang F, White HD, Fox KA, Sharma D, Chew P, Braunwald E, Investigators E-T. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). Am Heart J 2005;**149**(2):217-26.
26. Armstrong PW, Chang WC, Wallentin L, Goldstein P, Granger CB, Bogaerts K, Danays T, Van de Werf F, Investigators A-aA-P. Efficacy and safety of unfractionated heparin versus enoxaparin: a pooled analysis of ASSENT-3 and -3 PLUS data. CMAJ 2006;**174**(10):1421-6.
27. White HD, Braunwald E, Murphy SA, Jacob AJ, Gotcheva N, Polonetsky L, Antman EM. Enoxaparin vs. unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction in elderly and younger patients: results from ExTRACT-TIMI 25. Eur Heart J 2007;**28**(9):1066-71.
28. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E, Investigators C-T. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;**352**(12):1179-89.
29. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS, group CCaMiMITc. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;**366**(9497):1607-21.
30. Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, Cutlip DE, Bates ER, Frederick PD, Miller DP, Carrozza JP, Antman EM, Cannon CP, Gibson CM. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation 2006;**114**(19):2019-25.
31. Asseburg C, Vergel YB, Palmer S, Fenwick E, de Belder M, Abrams KR, Sculpher M. Assessing the effectiveness of primary angioplasty compared with thrombolysis and its relationship to time delay: a Bayesian evidence synthesis. Heart 2007;**93**(10):1244-50.
32. Gershlick AH, Westerhout CM, Armstrong PW, Huber K, Halvorsen S, Steg PG, Ostojic M, Goldstein P, Carvalho AC, Van de Werf F, Wilcox RG. Impact of a pharmacoinvasive strategy when delays to primary PCI are prolonged. Heart 2015;**101**(9):692-8.
33. Kostis WJ, Demissie K, Marcella SW, Shao YH, Wilson AC, Moreyra AE, Group MIDASMS. Weekend versus weekday admission and mortality from myocardial infarction. N Engl J Med 2007;**356**(11):1099-109.
34. Widimský P, Budesínský T, Vorác D, Groch L, Zelízko M, Aschermann M, Branny M, St'ásek J, Formánek P, Investigators PSG. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial--PRAGUE-2. Eur Heart J 2003;**24**(1):94-104.
35. Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. J Am Coll Cardiol 2006;**48**(7):1326-35.
36. Danchin N, Puymirat E, Steg PG, Goldstein P, Schiele F, Belle L, Cottin Y, Fajadet J, Khalife K, Coste P, Ferrieres J, Simon T. Five-year survival in patients with ST-segment-elevation myocardial

infarction according to modalities of reperfusion therapy: the French Registry on Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) 2005 Cohort. Circulation 2014;**129**(16):1629-36.
37. Claeys MJ, de Meester A, Convens C, Dubois P, Boland J, De Raedt H, Vranckx P, Coussement P, Gevaert S, Sinnaeve P, Evrard P, Beauloye C, Renard M, Vrints C. Contemporary mortality differences between primary percutaneous coronary intervention and thrombolysis in ST-segment elevation myocardial infarction. Arch Intern Med 2011;**171**(6):544-9.
38. Vora AN, Holmes DN, Rokos I, Roe MT, Granger CB, French WJ, Antman E, Henry TD, Thomas L, Bates ER, Wang TY. Fibrinolysis use among patients requiring interhospital transfer for ST-segment elevation myocardial infarction care: a report from the US National Cardiovascular Data Registry. JAMA Intern Med 2015;**175**(2):207-15.
39. Pu J, Ding S, Ge H, Han Y, Guo J, Lin R, Su X, Zhang H, Chen L, He B, Investigators E-M. Efficacy and Safety of a Pharmaco-Invasive Strategy With Half-Dose Alteplase Versus Primary Angioplasty in ST-Segment-Elevation Myocardial Infarction: EARLY-MYO Trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment-Elevation Myocardial Infarction). Circulation 2017;**136**(16):1462-1473.
40. Armstrong PW, Welsh RC. Recalibrating Reperfusion Waypoints. Circulation 2017;**136**(16):1474-1476.
41. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, Fleischmann C, Werner GS, Olbrich HG, Ott R, Mudra H, Seidl K, Schulze PC, Weiss C, Haimerl J, Friede T, Meyer T. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J 2018;**39**(13):1065-1074.
42. investigators AotSaEoaNTSwPCIA-P. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet 2006;**367**(9510):569-78.
43. Verheugt FW. Lyse now, stent later: the grace of GRACIA. Lancet 2004;**364**(9439):1014-5.
44. Ahmed S, Antman EM, Murphy SA, Giugliano RP, Cannon CP, White H, Morrow DA, Braunwald E. Poor outcomes after fibrinolytic therapy for ST-segment elevation myocardial infarction: impact of age (a meta-analysis of a decade of trials). J Thromb Thrombolysis 2006;**21**(2):119-29.
45. Basic Product Information on Metalyse®. Boehringer Ingelheim GmbH. BPI No. 0245-03, April 26, 2006.
46. Welsh RC, Goldstein P, Carvalho A, Ostojic MC, Nanas J, Zheng Y, Gershlick A, Danays T, Van de Werf F, Armstrong PW. Impact on Clinical Outcomes of Randomization at Community Hospitals Versus Pre-hospital location in STEMI Patients: Insights From the STREAM Study. Circulation 2015;**132**:A13594.
47. Welsh R. Anticoagulation after subcutaneous enoxaparin is time sensitive in STEMI patients treated with TNK. Can J Cardiol 2007;**23**:Abstr 271C (P09-02136).
48. Drouet L, Bal dit Sollier C, Martin J. Adding intravenous unfractionated heparin to standard enoxaparin causes excessive anticoagulation not detected by activated clotting time: results of the STACK-on to ENOXaparin (STACKENOX) study. Am Heart J 2009;**158**(2):177-84.
49. Hindman NB, Schocken DD, Widmann M, Anderson WD, White RD, Leggett S, Ideker RE, Hinohara T, Selvester RH, Wagner GS. Evaluation of a QRS scoring system for estimating myocardial infarct size. V. Specificity and method of application of the complete system. Am J Cardiol 1985;**55**(13 Pt 1):1485-90.
50. Investigator Brochure on Metalyse® (Tenecteplase). June 5, 2014.
51. Armstrong PW, Siha H, Fu Y, Westerhout CM, Steg PG, James SK, Storey RF, Horrow J, Katus H, Clemmensen P, Harrington RA, Wallentin L. ST-elevation acute coronary syndromes in the Platelet

Inhibition and Patient Outcomes (PLATO) trial: insights from the ECG substudy. Circulation 2012;**125**(3):514-21.
52. Schröder R, Wegscheider K, Schröder K, Dissmann R, Meyer-Sabellek W. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. J Am Coll Cardiol 1995;**26**(7):1657-64.
53. Zeymer U, Schröder R, Tebbe U, Molhoek GP, Wegscheider K, Neuhaus KL. Non-invasive detection of early infarct vessel patency by resolution of ST-segment elevation in patients with thrombolysis for acute myocardial infarction; results of the angiographic substudy of the Hirudin for Improvement of Thrombolysis (HIT)-4 trial. Eur Heart J 2001;**22**(9):769-75.
54. Verheugt FW, Gersh BJ, Armstrong PW. Aborted myocardial infarction: a new target for reperfusion therapy. Eur Heart J 2006;**27**(8):901-4.
55. Maleki ND, Van de Werf F, Goldstein P, Adgey JA, Lambert Y, Sulimov V, Rosell-Ortiz F, Gershlick AH, Zheng Y, Westerhout CM, Armstrong PW. Aborted myocardial infarction in ST-elevation myocardial infarction: insights from the STrategic Reperfusion Early After Myocardial infarction trial. Heart 2014;**100**(19):1543-9.

PROTOCOL APPROVAL PAGE

Study Title: STREAM-2 (STrategic Reperfusion in elderly patients Early After Myocardial Infarction)

I, the undersigned, have read and approve this protocol and agree on its content. This protocol has been developed by the members of the Executive Committee. The information and guidance given in this protocol complies with Good Clinical Practice and all applicable regulatory requirements.

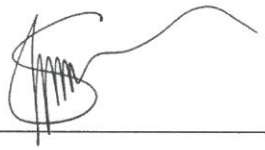
Signatures of the Executive Committee members:

20 April 2021

Frans Van de Werf, MD, PhD (Date)

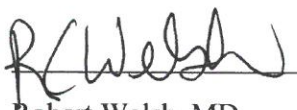
26 April 2021

Paul W. Armstrong, MD (Date)



26 April 2021

Peter Sinnaeve, MD, PhD (Date)



26 APR 21

Robert Welsh, MD (Date)

27 Apr 21

Patrick Goldstein, MD (Date)

INVESTIGATOR PROTOCOL AGREEMENT

STUDY TITLE: STREAM-2 (STrategic Reperfusion in elderly patients Early After Myocardial Infarction)

By signing below I confirm that I have read and understand the protocol and agree to comply with the conduct and terms of the study specified herein and any reference documents in the trial protocol. I agree to assume responsibility for the conduct of the study at this site including complying with the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and all applicable local and federal regulations relating to the conduct of clinical studies and protection of human patients.

Investigator Signature:

_____

Name

_____

Institution

_____