The Second Strategic Reperfusion Early After Myocardial Infarction (STREAM-2) study optimizing pharmacoinvasive reperfusion strategy in older ST-elevation myocardial infarction patients

Peer-reviewed author version

Armstrong, Paul W.; BOGAERTS, Kris; Welsh, Robert; Sinnaeve, Peter R.; Goldstein, Patrick; Pages, Alain; Danays, Thierry & Van de Werf, Frans (2020) The Second Strategic Reperfusion Early After Myocardial Infarction (STREAM-2) study optimizing pharmacoinvasive reperfusion strategy in older ST-elevation myocardial infarction patients. In: The American heart journal, 226 , p. 140 -146.

DOI: 10.1016/j.ahj.2020.04.029
Handle: http://hdl.handle.net/1942/34620

The Second Strategic Reperfusion Early After Myocardial Infarction (STREAM-2) Study

Optimizing pharmaco-invasive reperfusion strategy in older STEMI patients

Short Title: STREAM-2 Study

Paul W. Armstrong, MD[a], Kris Bogaerts, PhD[b], Robert Welsh, MD[a] , Peter R. Sinnaeve, MD, PhD[c], Patrick Goldstein, MD[d] , Alain Pages, MD[e], Thierry Danays, MD[f] and Frans Van de Werf, MD, PhD[c], on behalf of the STREAM 2 Study Groups (appendix)

[a] The Canadian Virtual Coordinating Centre for Global Collaborative Cardiovascular Research {Canadian VIGOUR Centre}, University of Alberta, Edmonton, Canada

[b] Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BioStat), KU Leuven, Leuven and University Hasselt, Hasselt, Belgium

[c] Dept. of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

[d] Emergency Department and SAMU, Lille University Hospital, Lille, France

[e] Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany

[f] TDC, Aix en Provence, France

ClinicalTrials.gov Identifier: NCT02777580

Address for correspondence:

Frans Van de Werf, MD, PhD

KU Leuven, Department of Cardiovascular Sciences

Herestraat 49, B-3000 Leuven, Belgium

frans.vandewerf@kuleuven.be

Abstract

Background

The Strategic Reperfusion Early after Myocardial Infarction (STREAM) study demonstrated that a pharmaco-invasive strategy was at least as effective as primary PCI (pPCI) in patients presenting early with ST-elevation myocardial infarction (STEMI). The current trial is a response to the finding that reduced intracranial hemorrhage (ICH) in patients ≥75 years occurred after halving the dose of tenecteplase. Additionally, a subsequent analysis of full dose tenecteplase or alteplase in the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT) trials demonstrated a steep increase in bleeding events beginning around the age of 60 years.

Methods

STREAM-2 will compare the efficacy and safety of a novel pharmaco-invasive strategy as compared to routine pPCI in STEMI patients ≥60 years presenting within 3 hours from symptom onset. In the pharmaco-invasive arm patients will receive half-dose tenecteplase, as soon as possible before transport to a PCI center. In the pPCI arm, patients will be treated according to optimal standard of care defined by local practice. The key criteria for efficacy will be the number of patients achieving ≥ 50 % ST-segment resolution before and after PCI in lead with maximal ST elevation at baseline and the clinical endpoints of death, congestive heart failure, shock or re-infarction, rescue PCI and aborted myocardial infarction, both singularly and as a composite at 30 days. Key safety criteria are total stroke, ICH and major non-intracranial bleeds. Approximately 600 patients will be randomized (400 to pharmaco-invasive treatment and 200 to pPCI). An interim analysis is planned after 300 patients are enrolled to consider adapting the trial to include a larger sample size aimed at undertaking a formal confirmatory trial.

Discussion

The study will provide new insights aimed at establishing an effective and safer pharmaco-invasive treatment for the growing population of older STEMI patients who cannot undergo timely pPCI.

ClinicalTrials.gov Identifier: NCT02777580

Keywords: Fibrinolysis, ST elevation myocardial infarction, reperfusion, elderly, primary percutaneous coronary intervention

Introduction

In the first Strategic Reperfusion Early after Myocardial Infarction (STREAM) study, we established that prehospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early presenting ST-elevation myocardial infarction (STEMI) who could not undergo primary percutaneous coronary intervention (pPCI) within one hour after the first medical contact [1]. The rates of the primary composite outcome of death, shock, heart failure or reinfarction at 30 days were similar irrespective of whether a pharmaco-invasive or pPCI strategy were employed. Mortality was also similar in both treatment groups at 1 year [2].

Importantly, because of an excess of intracranial hemorrhage (ICH) in patients ≥75 years, the original STREAM protocol was amended after 21% of the intended enrolment in order to halve the dose of the weight-adapted bolus tenecteplase in this cohort. Although no further ICH occurred in the remaining 97 patients receiving a pharmaco-invasive treatment, the relationship between this reduction in dose and efficacy was unclear given the modest sample size [3]. Recognizing that excess ICH was also observed in patients ≥70 years in STREAM-1, we also included this cohort. We also employed a loading dose of 300 mg clopidogrel as used safely this population by others [4].

Additional impetus for the current study was generated by recent broader global uptake of a pharmaco-invasive strategy [5,6] and encouraging results of new clinical trial and registry data comparing a pharmaco-invasive and pPCI strategy [7-15]. Some of this work underscores the continuing challenges in estimating times to pPCI [16] and in achieving timely pPCI: hence, these delays not only persist but extract a significant morbidity and mortality penalty even in well-established networks and centers [9,10]. Accordingly, we designed a new investigative study to compare the efficacy and safety of a pharmaco-invasive strategy (including a loading dose of 300 mg clopidogrel as adjunct to half-dose tenecteplase) with pPCI in elderly STEMI patients.

Methods

The trial is an exploratory open-label, prospective, randomized (in a ratio of 2:1, pharmaco-invasive: pPCI), parallel, comparative, international multicenter trial aimed at examining the potential benefits of this pharmaco-invasive strategy in older patients. 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 pPCI in lead with maximal ST-elevation at baseline; % rescue PCI, TIMI flow grades and clinical endpoints (death, congestive heart failure, shock, reinfarction and aborted MI). An intent-to-treat analysis of all randomized patients will be carried out. After 50% of the planned recruitment, a formal interim analysis will be performed by the Data Safety and Monitoring Board (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. The study is an academic, investigator initiated effort sponsored by Leuven Research & Development (LRD) at the University of Leuven, Belgium and supported by Boehringer Ingelheim GmbH.

Although the first patient enrolled in STREAM-2 was in August 2017, subsequent enrollment was slow and adversely affected by the selective nature of the population as well as contractual and regulatory issues that delayed participation of several countries. During this interval we performed a systematic review of bleeding complications from our prior work with full dose tenecteplase and alteplase in almost 24,000 patients from the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT) [17-20] and STREAM-1 [1] trials to further inform the protocol design. This revealed that the risk of major bleeding and/or intracranial hemorrhage begins to increase around the age of 60 years (Figure 1). Accordingly, we amended the original protocol on July 16, 2018 and broadened the admissible age entry to all STEMI patients ≥60 years which corresponds to the mean age of patients in STREAM-1.

Figure 1A

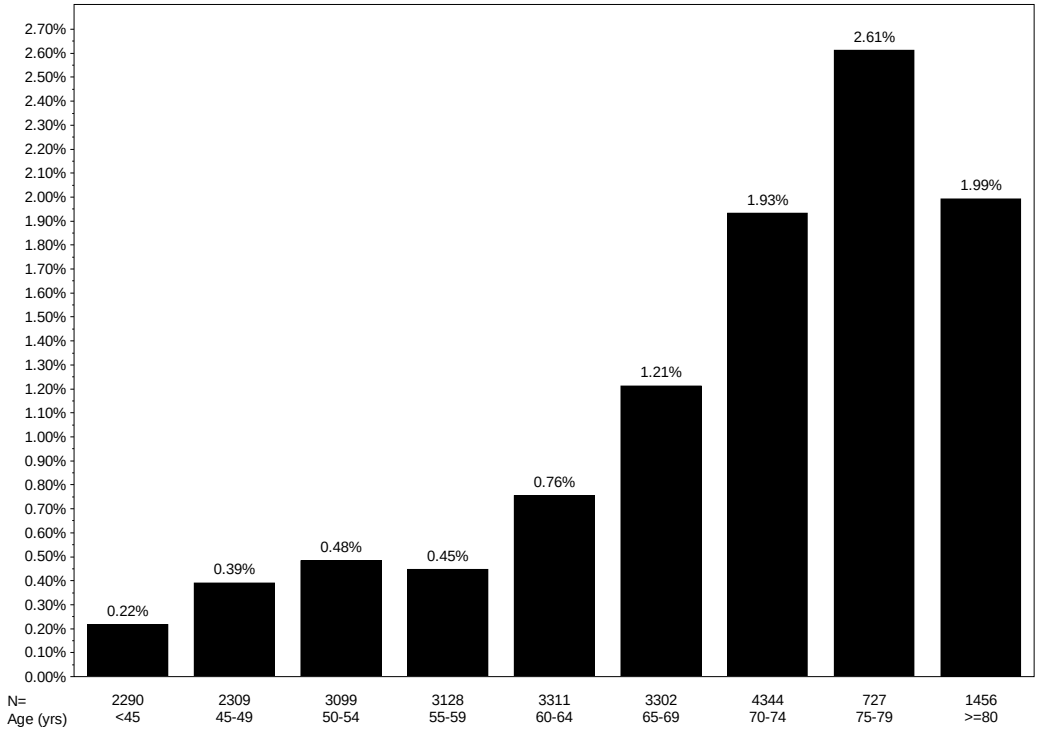

Figure 1B

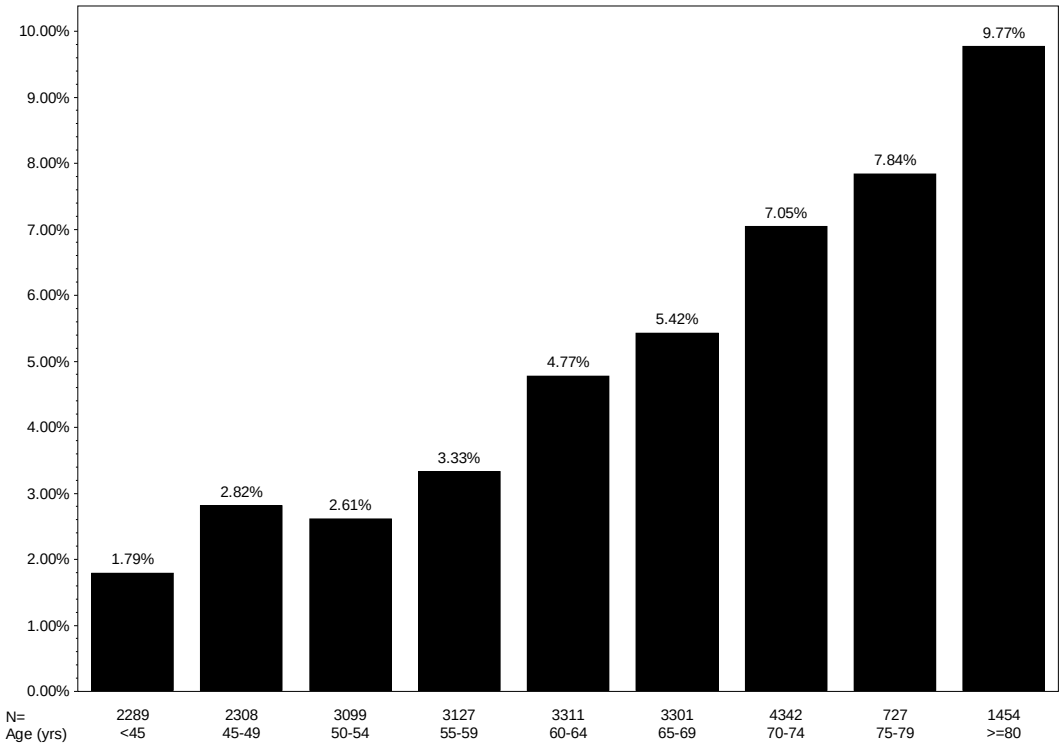

Figure 1: The incidence of intracranial hemorrhage (A) and intracranial hemorrhage plus major bleeding complications (B) in the ASSENT and STREAM-1 trials with full dose tenecteplase or alteplase.

Data are unadjusted for covariables and displayed as percentages according to age. N values are shown below each histogram.

Hence, in the amended protocol described herein, approximately 600 patients (400 patients to group pharmaco-invasive and 200 patients to group pPCI) are to be enrolled with the expectation that a minimum of 100 patients ≥70 years of age will be randomized to the pharmaco-invasive arm (Figure 2).

Figure 2

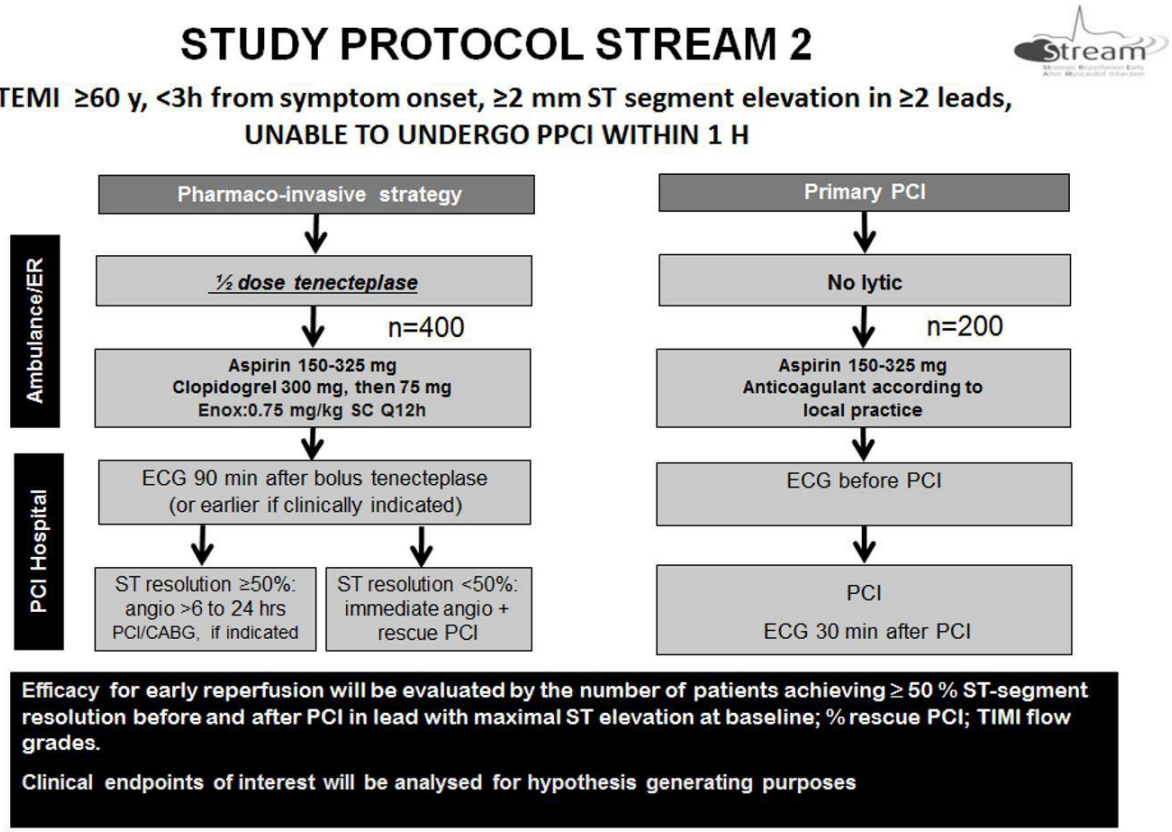

Figure 2: The STREAM 2 protocol

The inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Age equal or greater than 60 years
Onset of symptoms < 3 hours prior to randomization
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 (V_1-V_6) 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
Exclusion criteria
Expected performance of PCI < 60 minutes from diagnosis (qualifying ECG) or inability to arrive at the catheterization laboratory within 3 hours
Previous CABG
Left bundle branch block or ventricular pacing
Patients with cardiogenic shock - Killip Class 4
Patients with a body weight < 55 kg (known or estimated)
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 randomization
Known prior stroke or TIA

Recent administration of any IV or SC anticoagulation within 12 hours, including unfractionated heparin, enoxaparin, and/or bivalirudin or current use of oral anticoagulation (i.e. warfarin or a NOACs)
Active bleeding or known bleeding disorder/diathesis
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)
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)
Clinical diagnosis associated with increased risk of bleeding including known active peptic ulceration and/or neoplasm with increased bleeding risk
Known severe renal insufficiency
Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
Known acute pericarditis and/or subacute bacterial endocarditis
Known acute pancreatitis or known severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
Dementia
Previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 7 days
Known allergic reactions to tenecteplase, clopidogrel, enoxaparin and aspirin
Inability to follow the protocol, comply with follow-up requirements or other reasons leading to increased risk of the investigational therapy

ECG, electrocardiogram; STEMI, ST-elevation myocardial infarction, CABG, Coronary artery bypass graft surgery; SC, subcutaneous; BP, blood pressure; TIA, transient ischemic attack; NOAC, novel oral anticoagulant.

In the pharmaco-invasive group, half-dose, weight-adapted tenecteplase (dosing in appendix) will be given with aspirin 150-325mg, clopidogrel 300mg: subcutaneous enoxaparin 0.75mg/kg will be administered as soon as possible after ECG diagnosis, and followed by catheterization within 6-24 hours or rescue coronary intervention as required. Subsequently, aspirin will be maintained at 75-100mg, clopidogrel at 75mg daily and enoxaparin 0.75mg/kg S.C. every 12 hours until hospital discharge or for a maximum of 4 days (adjusted to once daily in patients with a creatinine clearance <30 ml/min).

In the pPCI group, all patients are to receive aspirin, a P2Y12 antagonist and anti-thrombin treatments according to local standard of care and guidelines. Additional glycoprotein IIb/IIIa antagonists use is at the discretion of local investigators.

ECGs will be taken at several time points: first medical contact, 60-90 min after bolus tenecteplase, before and after PCI, in case of reinfarction and at discharge.

A summary of the study efficacy and safety endpoints are shown in Table 2.

Table 2. Efficacy and Safety Endpoints [For definitions see ref 21]

EFFICACY
Numbers patients achieving ≥ 50 % ST-segment resolution before and after PCI in lead with maximal ST elevation at baseline (Core ECG Laboratory)
% confirmed rescue PCI (is a clinical efficacy endpoint)
TIMI flow grades assessed by investigator
Clinical events (assessed as single or composite endpoints)
Death
Shock
Heart failure
Recurrent MI
Aborted MI
SAFETY (assessed as single or composite endpoints)
Total stroke (fatal, disabling, nondisabling)

Disabling stroke
Ischemic stroke
Intracranial hemorrhage
Nonintracranial bleeds (total, major, minor, and blood transfusions)
Serious clinical events (resuscitated ventricular fibrillation, repeat target vessel recanalization)

ECG, electrocardiogram; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; MI, myocardial infarction.

Statistical Methods

Approximately 600 patients are planned to be randomized with 400 receiving pharmaco-invasive therapy and 200 pPCI. A minimum of approximately 100 patients ≥70 years of age will be randomized to the pharmaco-invasive arm. An important secondary analysis will be to combine data from the latter group with similar data from STREAM-1 in order to have a more reliable estimate of the efficacy and safety of the pharmaco-invasive strategy in these patients. The analysis of ECG data, angiographic data and clinical events will be described in a detailed statistical analysis plan. Although the study of 600 patients is not powered to show a difference in clinical events, given the older 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-myocardial infarction ranged between 18% and 20% for pharmaco-invasive and pPCI groups. Bleeding complications in this age group were 1.7% and 0% for ICH and 8.8% and 7% for non-intracranial major bleeding, respectively. If the study is adapted into a confirmatory trial after the interim analysis at 300 patients, a primary hypothesis on a combined clinical endpoint will be pre-specified. If extension is recommended, the trial will proceed without interrupting recruitment and will be subsequently analysed as one single trial.

Trial Organization

During the site selection process, the qualification of a trial site for participation in the trial is determined and sites (ambulances or emergency units of community hospitals) must be experienced in fibrinolysis. Additionally, access is required to a hospital with 24/7 pPCI service. (e.g., by hub and spoke relationship) to ensure timely rescue PCI, as required (pharmaco-invasive group), or of pPCI according to the protocol. Each site enrolling patients will be assigned an individual site number. Randomization will be performed by an Interactive Voice Response or an Interactive Web Response System.

An Executive and Steering Committee (see appendix) are responsible for the overall conduct of the trial and will have full access to the database after concluding the trial. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of this paper. The results will be analyzed independently by the Executive Committee. An independent DSMB, who will review safety data regularly provided by the Leuven Safety group, will monitor the study. An independent Stroke Review Panel will perform a final blinded central evaluation and classification of documented clinically suspected strokes. ECGs for assessment of ST-resolution, clinical and ECG data for assessment of the need for rescue PCI and aborted infarction will be centrally adjudicated at the core ECG Laboratory in the Canadian VIGOUR Centre in Edmonton (Canada), University of Alberta. The study is international in scope and includes the following countries: Australia, Brazil, Canada, Chile, France, Mexico, Montenegro, Romania, Russia, Serbia and Spain. Additional countries are expected to join the trial. In Australia, Canada and France, an academic research organization will be responsible for site initiating and monitoring. In all other countries this will be done by Confidence Pharmaceutical Research LLC (a global clinical research organization).

Discussion

Although current STEMI guidelines continue to define pPCI as the preferred therapy, they rest upon the ability to deliver timely pPCI. Despite this latter caveat, experience over the last decade -including that in

large urban areas where many cardiac interventional facilities exist- it is clear that the time from first medical contact or ECG diagnosis to pPCI and overall ischemic times frequently exceed recommended guidelines as shown in multiple registries [8,9,10,12-15]. When this occurs, it imposes a penalty for patients defined by larger infarct sizes and subsequently expressed by excess heart failure, cardiogenic shock and mortality [8,9,22,23]. The reasons for the inability to consistently achieve timely pPCI are multifactorial and include; i) patient related delay such as self-presentation to a community hospital or calling an emergency number, ii) system issues related to pre- and in-hospital delays, iii) unpredictable environmental issues affecting timely transport by road and/or air, iv) unfettered availability of the pPCI facility, and, v) challenges in vascular access at the interventional sites. Importantly, these delays have been accentuated by some opinion leaders who have discouraged any use of fibrinolytic therapy, often because of perceived excess of bleeding risks, especially in older patients. As a consequence in many developed countries the recent generation of cardiovascular care providers are unfamiliar with fibrinolytic therapy and therefore reluctant to administer it. Ironically, this devolution of STEMI care has occurred during the renaissance in the acute care of stroke, exhorting early fibrinolysis in appropriately selected patients without an upper age limit [24].

The results of STEAM-1, coupled with encouraging data from a number of international registries and clinical trials have inspired the current protocol. The incorporation of STREAM-1 results into current STEMI guidelines, and welcome scaling of its results internationally where enhanced STEMI care remains a crucial unmet need, are future impetus to demonstrate that the pharmaco-invasive strategy being tested is not only effective but also safe in older patients. [5,6].

Acknowledgements

The editorial assistance of Krista Bogaert, Katleen Vandenberghe and Lisa Soulard is appreciated.

Disclosures

The study is sponsored by Leuven Research & Development at the University of Leuven (KU Leuven) Belgium and supported by a grant from Boehringer Ingelheim GmbH to KU Leuven. The executive committee was responsible for the design and conduct of the trial. The academic authors vouch for the integrity and completeness of the data and analyses.

Paul W. Armstrong has served as a consultant for Bayer and Merck. He has received research grants from CSL, Boehringer-Ingelheim, Bayer and Merck. Kris Bogaerts received consultancy fees through his institution from Boehringer Ingelheim GmbH. Robert Welsh has received research funding and honoraria from Astra Zeneca, Bayer, Boerhinger Ingelheim GmbH, and Pfizer. Peter Sinnaeve received Speaker's and consultancy fees from Boehringer-Ingelheim. Patrick Goldstein reports travel support and lecture fees from Boehringer Ingelheim GmbH. Alain Pages is an employee of Boehringer Ingelheim GmbH. Thierry Danays is a former employee of Boehringer Ingelheim France, received consultancy fees from Boehringer Ingelheim GmbH. Frans Van de Werf received study grants to institution and lectures fees from Boehringer Ingelheim GmbH.

References:

1. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction. N Engl J Med. 2013;368:1379-1387. https://doi.org/10.1056/NEJMoa1301092

2. Sinnaeve PR, Armstrong PW, Gershlick AH, et al. ST–Segment-Elevation Myocardial Infarction Patients Randomized to a Pharmaco-Invasive Strategy or Primary Percutaneous Coronary Intervention. Circulation 2014;130:1139–45. https://doi.org/10.1161/CIRCULATIONAHA.114.009570

3. Armstrong PW, Zheng Y, Westerhout CM, et al. 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;169:890–8. https://doi.org/10.1016/j.ahj.2015.03.011

4. Larson DM, Duval S, Sharkey SW, et al. 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;33:1232–40. https://doi.org/10.1093/eurheartj/ehr403

5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2018;39:119–77. https://doi.org/10.1093/eurheartj/ehx393

6. Wilson H, Jollis J, Alexanderson E. Scaling STEMI Care Internationally: ACC's Global STEMI Quality Improvement Initiative. J Am Coll Cardiol 2018;72:2528–30. https://doi.org/10.1016/j.jacc.2018.10.012

7. Pu J, Ding S, Ge H, et al. Efficacy and Safety of a Pharmaco-Invasive Strategy with Half-Dose Alteplase Versus Primary Angioplasty in ST-Segment-Elevation Myocardial Infarction: EARLY-MYO Trial Circulation. 2017;136:1462–73. https://doi.org/10.1161/CIRCULATIONAHA.117.030582

8. Bainey KR, Armstrong PW, Zheng Y, et al. Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction in Clinical Practice: Insights From the Vital Heart Response Registry. Circ Cardiovasc Interv. 2019;12:e008059. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008059

9. Scholz KH, Maier SKG, Maier LS, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic istability: Results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J. 2018;39:1065–74. https://doi.org/10.1093/eurheartj/ehy004

10. Danchin N, Popovic B, Puymirat E, et al. Five-year outcomes following timely primary percutaneous intervention, late primary percutaneous intervention, or a pharmaco-invasive strategy in ST-segment elevation myocardial infarction: the FAST-MI programme. Eur Heart J. 2019;ehz665 https://doi.org/10.1093/eurheartj/ehz665

11. Welsh RC, Van de Werf F, Westerhout CM, et al. 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. 2015;114:811–9. https://doi.org/10.1016/j.amjcard.2014.06.011

12. Auffret V, Laurin C, Leurent G, et al. Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction in Patients ≥70 Years of Age. Am J Cardiol. 2020;125:1–10. https://doi.org/10.1016/j.amjcard.2019.09.044

13. Lambert L, Brown K, Segal E, et al. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. JAMA. 2010;303(21):2148–55. https://doi.org/10.1001/jama.2010.712

14. Sim DS1, Jeong MH2, Ahn Y1, et al. Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention in Patients With ST-Segment-Elevation Myocardial Infarction: A Propensity Score-Matched Analysis. Circ Cardiovasc Interv. 2016;9. pii: e003508 https://doi.org/10.1161/CIRCINTERVENTIONS.115.003508

15. Rashid MK, Guron N, Bernick J, et al. Safety and Efficacy of a Pharmacoinvasive Strategy in ST-Segment Elevation Myocardial Infarction: A Patient Population Study Comparing a Pharmacoinvasive Strategy With a Primary Percutaneous Coronary Intervention Strategy Within a Regional System. JACC Cardiovasc Interv. 2016;9:2014–20. https://doi.org/10.1016/j.jcin.2016.07.004

16. Sinnaeve P, Van de Werf F. Primary PCI and the indistinct 120 min time limit. Eur Heart J. 2019;ehz755. https://doi.org/10.1093/eurheartj/ehz755

17. Van de Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. Lancet. 1999;354:716–22. https://doi.org/10.1016/S0140-6736(99)07403-6

18. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: The ASSENT-3 randomized trial in acute myocardial infarction. Lancet 2001;358:605–13. https://doi.org/10.1016/S0140-6736(01)05775-0

19. Wallentin L, Goldstein P, Armstrong PW, et al. 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;108:135–42. https://doi.org/10.1161/01.CIR.0000081659.72985.A8

20. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): Randomised trial. Lancet 2006;367:569–78. https://doi.org/10.1016/S0140-6736(06)68147-6

21. Armstrong PW, Gershlick A, Goldstein P, et al. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study. Am Heart J. 2010;160:30-35.e1. https://doi.org/10.1016/j.ahj.2010.04.007

22. Armstrong PW, Westerhout CM, Welsh RC. Is duration of symptoms is the key modulator of the choice of reperfusion for ST-elevation myocardial infarction. Circulation. 2009;119:1293–303. https://doi.org/10.1161/CIRCULATIONAHA.108.796383

23. Gershlick AH, Westerhout CM, Armstrong PW, et al. Impact of a pharmacoinvasive strategy when delays to primary PCI are prolonged. Heart. 2015;101:692–8. http://dx.doi.org/10.1136/heartjnl-2014-306686

24. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50:e344-e418. https://doi.org/10.1161/STR.0000000000000211

Appendix 1

National Coordinators:

COUNTRY	**Name**
Australia	John French
Brazil	José Saraiva
Canada	Robert Welsh/Kevin Bainey
Chile	Pablo Sepulveda
France	Yves Lambert
Mexico	Alexandra Arias
Montenegro	Ljilja Music
Romania	Gabriel Tatu-Chitoiu
Russia	Oleg Averkov
Serbia	Arsen Ristic
Spain	Fernando Rosell

DSMB members: Dr. Keith Fox, Chairman (Cardiologist), Nicola Danchin (Cardiologist), Jan G.P. Tijssen (Statistician), Dr. Miodrag Ostojic (Invasive Cardiologist), Dr. Freek Verheugt (Cardiologist), Ann Belmans (Liaison Officer)

Leuven Coordinating Centre: Katleen Vandenberghe, Peter Van Rompaey, Anne Luyten

ECG Core Lab CVC University of Alberta: Dr. Kevin Bainey, Tracy Temple, Eric Ly

Appendix 2

Reduced dose of tenecteplase

50 or 40 mg of drug reconstituted in 10 or 8 ml sterile water for injection given as single weight-adapted i.v. bolus over 5 - 10 seconds

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