Evidence Accumulated Regarding Therapeutic strategy of older STEMI patients (EARTH-STEMI) collaborative initiative

Review methods were amended after registration. Please see the revision notes and previous versions for detail.

Citation

Rita Pavasini, Gianluca Campo, Simone Biscaglia, Giuseppe Biondi-Zoccai. Evidence Accumulated Regarding Therapeutic strategy of older STEMI patients (EARTH-STEMI) collaborative initiative. PROSPERO 2022 CRD42022367898 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022367898

Review question

Several randomized clinical trials (RCTs) investigated the benefit of complete revascularization over culprit-only treatment strategy in patients admitted to hospital for ST-segment elevation myocardial infarction (STEMI). These RCTs supported the benefit of complete revascularization strategy in the overall population, but some reports suggested that this could be not confirmed in older STEMI patients. The FIRE trial (ClinicalTrials.gov NCT03772743) has been designed to address this clinical question, namely if complete revascularization is able to reduce hard endpoints in older (aged 75 years and older) patients with myocardial infarction (MI) (both STEMI and no ST-segment elevation MI) and multivessel coronary artery disease. The integration of the FIRE findings with that from older STEMI patients from previous RCTs (namely COMPARE-ACUTE, DANAMI-PRIMULTI, CVLPRIT, COMPLETE, etc) may further contribute to definitively clarify the best revascularization strategy for older STEMI patients. Therefore, the aim of this meta-analysis is to obtain individual patient data from all available RCTs on this issue to perform a patient-level meta-analysis on a large population of older patients with STEMI and multivessel disease.

The review questions is to assess the superiority of complete versus culprit only revascularization in older patients (aged >=75 years) with STEMI and multivessel disease:

1) in the composite of all-cause mortality, reinfarction and ischemia-driven revascularization

2) in the composite of cardiovascular death and reinfarction

3) in the occurrence of singular endpoints (cardiovascular death, all-cause death, myocardial infarction, stroke, major bleedings, contrast-induced acute kidney injury, ischemia-driven revascularization).

Searches [1 change]

We will search MEDLINE, the Cochrane Library, Google Scholar and BioMed Central electronic databases in October 2022. This will be supplemented by searching in the reference list of included studies and the reference lists of relevant reviews.

Only papers published in English and in peer reviewed journal will be included. Data from abstracts or posters will be excluded, as well as studies with less than 20 patients of the subset of interest (STEMI patients with multi-vessel disease aged >= 75 years). Medical subject heading strategy (MeSH) will be used to search for the following search terms: ((complete revascularization) OR (culprit only revascularization) AND (multivessel coronary artery disease) AND ((ST elevation myocardial infarction) OR (STEMI) OR (ST elevation MI))). Citations will be assessed by two independent reviewers. Citations considered eligible will be assessed as full-text. In case of divergences a third reviewer will be asked to reach consensus.

Outcome of the search strategy will be integrated with the finding of the FIRE trial, whom data will be available for

summer 2023 and the database is on charge of the investigator of the current meta-analysis proposal.

Types of study to be included

Randomized clinical trials.

Condition or domain being studied

Revascularization strategy in older patients (aged >=75 years) with STEMI and multivessel coronary artery disease.

Participants/population

STEMI patients with multivessel coronary artery disease and aged 75 years or older.

Intervention(s), exposure(s)

Complete revascularization.

Comparator(s)/control

Culprit lesion only revascularization.

Main outcome(s)

Composite of Patient-Oriented Cardiac Event (POCE, all-cause mortality, reinfarction and ischemia-driven revascularization) at the longest available follow-up.

Measures of effect

The principal measure of effect will be the hazard ratio with 95% confidence interval, except if event times are unavailable in which case the odds ratio with 95% confidence interval will be used.

Additional outcome(s)

- Composite of cardiovascular death and reinfarction at the longest available follow-up.

- Composite of cardiovascular death; all-cause death; myocardial infarction; stroke; major bleedings; contrast-induced acute kidney injury; ischemia-driven revascularization. All adverse events will be estimated at the longest available follow-up.

Measures of effect

The principal measure of effect will be the hazard ratio with 95% confidence interval, except if event times are unavailable in which case the odds ratio with 95% confidence interval will be used.

Data extraction (selection and coding)

Two unblinded reviewers will independently screen titles and abstracts for inclusion. They will then independently review the full text of potentially relevant articles to determine the adherence to the inclusion and exclusion criteria. Differences of opinion will be resolved by consensus.

Data on study characteristics will be abstracted. Being the present meta-analysis focused on older STEMI patient (aged >=75 years), individual patient data of this specific subset will be asked to the corresponding author of RCTs selected by the search strategy. In particular the following variables will be asked: baseline characteristics (gender, age, height, weight, country of randomization); frailty assessment (if available); medical history (diabetes, cigarette smoking,

hypercholesterolemia, hypertension, liver disease, peripheral artery disease, previous MI, previous PCI, previous coronary artery bypass grafting, prior stroke, prior bleeding, history of chronic kidney disease, chronic lung disease); laboratory at baseline (creatinine, hemoglobin, white cell count); medication at baseline (aspirin, P2Y12 inhibitors, ACE inhibitors/ARB, beta-blockers, statins, proton pump inhibitors); clinical presentation (Killip class), procedural data (multivessel disease, two vessel disease, left main involvement, number of stents used, thromboaspiration, IABP, contrast media volume, radiation exposure, procedure time length, vascular access), kind of revascularization (complete, culprit only), time of revascularization, use of coronary physiology to assess non culprit lesion, duration of participation in the study and reason for end; vital status; adverse events death (cardiovascular, vascular, non- cardiovascular), myocardial infarction, stent thrombosis, stroke, bleeding, repeated revascularization. In case the requested data was not provided by the principal investigator, the reason for this will be recorded (unavailability versus others) and will be disclosed in the publication.

The integrity of individual patient-level data will be checked by evaluating internal data consistency and completeness, baseline imbalance, randomization integrity, follow-up details, and censoring patterns. Any discrepancy will be checked with the principal trial investigators/corresponding authors.

Risk of bias (quality) assessment

The quality of included will be appraised by two unblinded reviewers using the Cochrane Collaboration tool for assessing the risk of bias (RoB 2.0). We evaluated for each RCT the risk of analytical, selection, detection, reporting and attrition bias (expressed as low, or high risk of bias, as well as unclear risk in case of inability to ascertain the underlying risk of bias). In case of disagreement, it will be solved by discussion and consulting a third author for arbitration if no consensus can be achieved.

Strategy for data synthesis

We will first describe our systematic review results at a study level, reporting study and patient characteristics, and frequencies across included studies. We will then conduct an individual patient level meta-analysis.

Baseline and procedural continuous variables will be summarized by means (SD), categorical variables by counts (%). The pre-specified primary analysis will be based on a one-step approach to model the data from all trials simultaneously using a random-effects Cox regression model stratified by trial. Pre-specified sensitivity analyses of the primary endpoints will be based on a two-step approach using an inverse-variance random-effects model and a DerSimonian-Laird random-effects model to combine trial-level estimates. Between-trial heterogeneity will be estimated from the two-step fixed-effect and random-effect model using I^2. Treatment effects will be principally derived as HRs and 95% CIs, assuming constant hazard. In case the underlying assumption of proportional hazards in the Cox model for the primary endpoints from randomization through latest available follow-up will not be met, comparisons between treatments will be performed by logistic regression with follow-up time included as covariate for adjustment. All analyses will be conducted in the intention-to-treat population.

Analysis of subgroups or subsets

- Impact of sex in complete vs culprit only revascularization in older adults

- Impact of diabetes in complete vs culprit only revascularization in older adults

- Age (<85 vs ≥85 years old)

- Comorbidities (PAD, COPD, CKD, cancer, stroke, bleeding, BMI, frailty assessment)

- Non culprit lesion located on LAD vs. different coronary vessel location

- Impact of time delay to primary PCI

- Angiographic vs. physiology assessment of non-culprit coronary lesion

All subgroup analyses will be coupled with interaction tests.

Contact details for further information

Rita Pavasini

pvsrti@unife.it

Organisational affiliation of the review

UO Cardiologia, Azienda Ospedaliera Universitaria di Ferrara, Cona, Ferrara, Italy

Review team members and their organisational affiliations

Dr Rita Pavasini. Cardiovascular Institute, Azienda Ospedaliera Universitaria di Ferrara

Professor Gianluca Campo. UO Cardiologia, Azienda Ospedaliera Universitaria di Ferrara, Cona, Ferrara, Italy

Dr Simone Biscaglia. UO Cardiologia, Azienda Ospedaliera Universitaria di Ferrara, Cona, Ferrara, Italy

Professor Giuseppe Biondi-Zoccai. Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

Collaborators [1 change]

Professor Emanuele Barbato. Departement of Clinical and Molecular Medicine, Sapienza University, Roma, Italy

Professor Peter C. Smits. Department of Cardiology, Maasstad Ziekenhuis, Rotterdam, the Netherlands

Professor Raul Moreno. Cardiology Department, Interventional Cardiology Section, University Hospital La Paz, 28046 Madrid, Spain

Professor Javier Escaned. Hospital Clínico San Carlos, IDISSC, and Universidad Complutense de Madrid, Madrid, Spain

Professor Shamir R. Metha. Population Health Research Institute McMaster University and Hamilton Health Science, Hamilton, Canada

Professor Gerry McCann. Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom

Professor Thomas Engstroem. Department of Cardiology, Rigshospitalet University of Copenhagen, Copenhagen, Denmark

Professor Islam Elgendy. Gill Heart & Vascular Institute, University of Kentucky, Lexington, USA

Professor Felix Böhm. Department of Medicine, Division of Cardiology, Karolinska Institutet, Stockholm, Sweden

Type and method of review

Individual patient data (IPD) meta-analysis, Intervention, Meta-analysis, Systematic review

Anticipated or actual start date

16 October 2022

Anticipated completion date [1 change]

02 September 2024

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Italy

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Acute Kidney Injury; Aged; Coronary Artery Disease; Hemorrhage; Hospitals; Humans; Randomized Controlled Trials as Topic; ST Elevation Myocardial Infarction; Stroke

Date of registration in PROSPERO

25 October 2022

Date of first submission

16 October 2022

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note

The conclusion of the meta-analysis has been delayed, waiting for the data of the FULL-REVASC study.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

25 October 2022

02 November 2022

31 July 2023