ESC European Society of Cardiology

European Heart Journal (2020) **41**, 4103–4110
doi:10.1093/eurheartj/ehz896

CLINICAL RESEARCH
Intensive cardiac care and acute coronary syndromes

Complete revascularization reduces cardiovascular death in patients with ST-segment elevation myocardial infarction and multivessel disease: systematic review and meta-analysis of randomized clinical trials

Rita Pavasini [1], Simone Biscaglia [1], Emanuele Barbato[2], Matteo Tebaldi [1], Dariusz Dudek[3,4], Javier Escaned[5], Gianni Casella [6], Andrea Santarelli[7], Vincenzo Guiducci [8], Enrique Gutierrez-Ibanes [9,10], Giuseppe Di Pasquale[6], Luigi Politi [11], Andrea Saglietto [12], Fabrizio D'Ascenzo[12], and Gianluca Campo [1,4]*

[1]Cardiovascular Institute, Azienda Ospedaliero Universitaria di Ferrara, Via Aldo Moro 8, Ferrara 44124, Italy; [2]Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Via Pansini, Naples 80131, Italy; [3]Institute of Cardiology, Jagiellonian University Medical College, ul. Sw Anny 12, Krakow 31-008, Poland; [4]Maria Cecilia Hospital, GVM Care & Research, Via Corriera 1, Cotignola 48033, Italy; [5]Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Calle del Prof Martin Lagos s/n, Madrid 28040, Spain; [6]U.O.C. Cardiologia, Ospedale Maggiore, Largo Nigrisoli 2, Bologna 40133, Italy; [7]Cardiovascular Department, Infermi Hospital, Viale Luigi Settembrini 2, Rimini 47923, Italy; [8]Interventional Cardiology Unit, S. Maria Nuova Hospital, Viale Risorgimento 80, Reggio Emilia 42123, Italy; [9]Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, CIBERCV, Calle del Dr Esquerdo 46, Madrid 28007, Spain; [10]Universidad Carlos III, Calle Madrid 126 Madrid 28903 Spain; [11]Cardiologia Interventistica, ASST Rhodense, Corso Europa 250, Rho 20024, Italy; and [12]Division of Cardiology, A.O.U. Città della Salute e della Scienza, University of Turin, Corso Bramante 88/90, Turin 10126, Italy

Received 4 September 2019; revised 18 October 2019; editorial decision 28 November 2019; accepted 29 November 2019; online publish-ahead-of-print 31 December 2019

See page 4111 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz956)

Aims The aim of this work was to investigate the prognostic impact of revascularization of non-culprit lesions in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease by performing a meta-analysis of available randomized clinical trials (RCTs).

Methods and results Data from six RCTs comparing complete vs. culprit-only revascularization in STEMI patients with multivessel disease were analysed with random effect generic inverse variance method meta-analysis. The endpoints were expressed as hazard ratio (HR) with 95% confidence interval (CI). The primary outcome was cardiovascular death. Main secondary outcomes of interest were all-cause death, myocardial infarction (MI), and repeated coronary revascularization. Overall, 6528 patients were included (3139 complete group, 3389 culprit-only group). After a follow-up ranging between 1 and 3 years (median 2 years), cardiovascular death was significantly reduced in the group receiving complete revascularization (HR 0.62, 95% CI 0.39–0.97, I^2 = 29%). The number needed to treat to prevent one cardiovascular death was 70 (95% CI 36–150). The secondary endpoints MI and revascularization were also significantly reduced (HR 0.68, 95% CI 0.55–0.84, I^2 = 0% and HR 0.29, 95% CI 0.22–0.38, I^2 = 36%, respectively). Needed to treats were 45 (95% CI 37–55) for MI and 8 (95% CI 5–13) for revascularization. All-cause death (HR 0.81, 95% CI 0.56–1.16, I^2 = 27%) was not affected by the revascularization strategy.

Conclusion In a selected study population of STEMI patients with multivessel disease, a complete revascularization strategy is associated with a reduction in cardiovascular death. This reduction is concomitant with that of MI and the need of repeated revascularization.

Keywords Complete revascularization • Culprit-only revascularization • ST-segment elevation myocardial infarction • Mortality

* Corresponding author. Tel: +390532236450, Email: cmpglc@unife.it

Introduction

Several studies have been published to understand if in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease it would be better to limit the revascularization to the culprit lesion or to extend it to non-culprit lesions. These trials were mainly focused on small populations and with sample size not powered enough to obtain conclusive evidence.[1–11] To overcome these limitations several meta-analyses have been carried out.[12,13] However, they displayed several limitations and did not achieve an adequate sample size for reliable estimation in cardiovascular death. Recently, the Complete vs. Culprit-only Revascularization to Treat Multi-vessel Disease After Early Percutaneous coronary intervention for STEMI (COMPLETE) study has been published.[14] The coprimary outcomes of the study were the composite of cardiovascular death or myocardial infarction (MI) and the composite of cardiovascular death, MI, or ischaemia-driven revascularization.[14] Although it is the largest randomized clinical trial (RCT) on the topic, including more than 4000 patients, it is still unpowered for cardiovascular mortality.

Therefore, the aim of this study was to investigate the prognostic impact, especially in terms of cardiovascular death, of revascularization of non-culprit lesions in patients with STEMI and multivessel disease by performing a meta-analysis of available RCTs.

Methods

We developed a systematic review and meta-analysis following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement.[15–18] The protocol registration application for this study was performed, on an international prospective register for systematic reviews (PROSPERO), on 17 August 2019.

Search strategy

Two expert cardiologists (R.P., S.B.) independently and systematically searched (MESH strategy) MEDLINE, Cochrane Library, Google Scholar, and Biomed Central for RCTs comparing complete vs. culprit-only revascularization in STEMI patients with multivessel disease. The terms searched were: (complete revascularization) AND ((STEMI) OR (ST-elevation myocardial infarction)), OR ((non-culprit lesion) AND (primary percutaneous coronary angioplasty)) AND ((randomized) AND ((clinical) OR (controlled)) trial). Details of the search strategy are reported in the Supplementary material online. The research was carried out in August 2019. The data of the COMPLETE trial[14] have been published online on 1 September 2019 and they have been added to the analysis carried out in August 2019.

Selection criteria

The shortlisted studies were retrieved as full articles and appraised independently by two unblinded reviewers (G.C. and R.P.), with divergences solved after consensus, according to the following inclusion criteria: (i) English language; (ii) enrolment of STEMI patients; (iii) reperfusion strategy by primary percutaneous coronary intervention (PCI); (iv) randomized treatment allocation; (v) comparison of complete vs. culprit-only revascularization plus optimal medical therapy; (vi) at least 50 patients per arm; (vii) availability of the individual outcome data of cardiovascular death, all-cause death, MI, coronary revascularization, and contrast-induced acute kidney injury (CI-AKI); (viii) data published in peer-reviewed journal; and (ix) follow-up length ≥1 year. Exclusion criteria were: (i) duplicate reports failing to report additional or extended clinical outcomes, (ii) equivocal or non-random treatment allocation; (iii) grey literature; and (iv) only abstract or posters.

Data abstraction, endpoints

The reviewers (R.P., S.B., and G.C.) independently extracted data from full texts and published appendixes. The following information was retrieved: year of publication, journal, number of patients included, time of the enrolment, follow-up length, source for follow-up, inclusion and exclusion criteria, presence of a blinded adjudication committee for adverse event, age, sex, cardiovascular risk factors, cardiovascular history and comorbidities, clinical presentation, extension of coronary artery disease, and medical treatment. The primary outcome was cardiovascular death. Secondary outcomes were: (i) all-cause death; (ii) MI; (iii) repeated coronary revascularization; and (iv) CI-AKI. Definitions of the study endpoints are detailed for each study in the Supplementary material online, *Tables* 1s and 2s.

Internal validity and quality appraisal

The quality of the studies was appraised by two unblinded reviewers (R.P. and S.B.) following the Cochrane Collaboration. For each RCT, we evaluated 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).

Data analysis and synthesis

Continuous variables were reported as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as number and percentage. For each outcome, the pooled event rate (ER) with 95% confidence interval (CI) was calculated. Standard errors were calculated by the formula: root squared (ER*(1-ER)/sample size). Being necessary to pool time-to-event endpoints from studies with considerable heterogeneity in the follow-up duration, the hazard ratio (HR) values for the outcomes of interest were extrapolated. Hazard ratio values for cardiovascular death, all-cause death, reinfarction, and repeated revascularization were available for all studies, except for the study by Politi *et al.*[11] Then, the corresponding author was contacted. The author accepted to calculate and share the HR values for the present meta-analysis. Therefore, HR values for the outcomes of interest were pooled together. Regarding CI-AKI, we did not consider it as an outcome time-dependent, being strictly related to study procedures occurring soon after MI. Then, CI-AKI was expressed as risk ratio (RR) with 95% CI. For the analyses of ER, HR, and RR, DerSimonian and Laird random effects model was used with heterogeneity being taken from the inverse-variance fixed-effect model.[19] Statistical heterogeneity was assessed using Cochran's Q test and I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and >75% high heterogeneity.[20] Sensitivity analyses were also performed repeating the meta-analysis of the primary outcome removing one study at a time. Because of the small number of studies included in this meta-analysis ($n = 6$) it was not possible to perform publication bias and meta-regression analyses.[21] Prometa (Internovi, Cesena, Italy) and RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) softwares were used for statistical analyses.

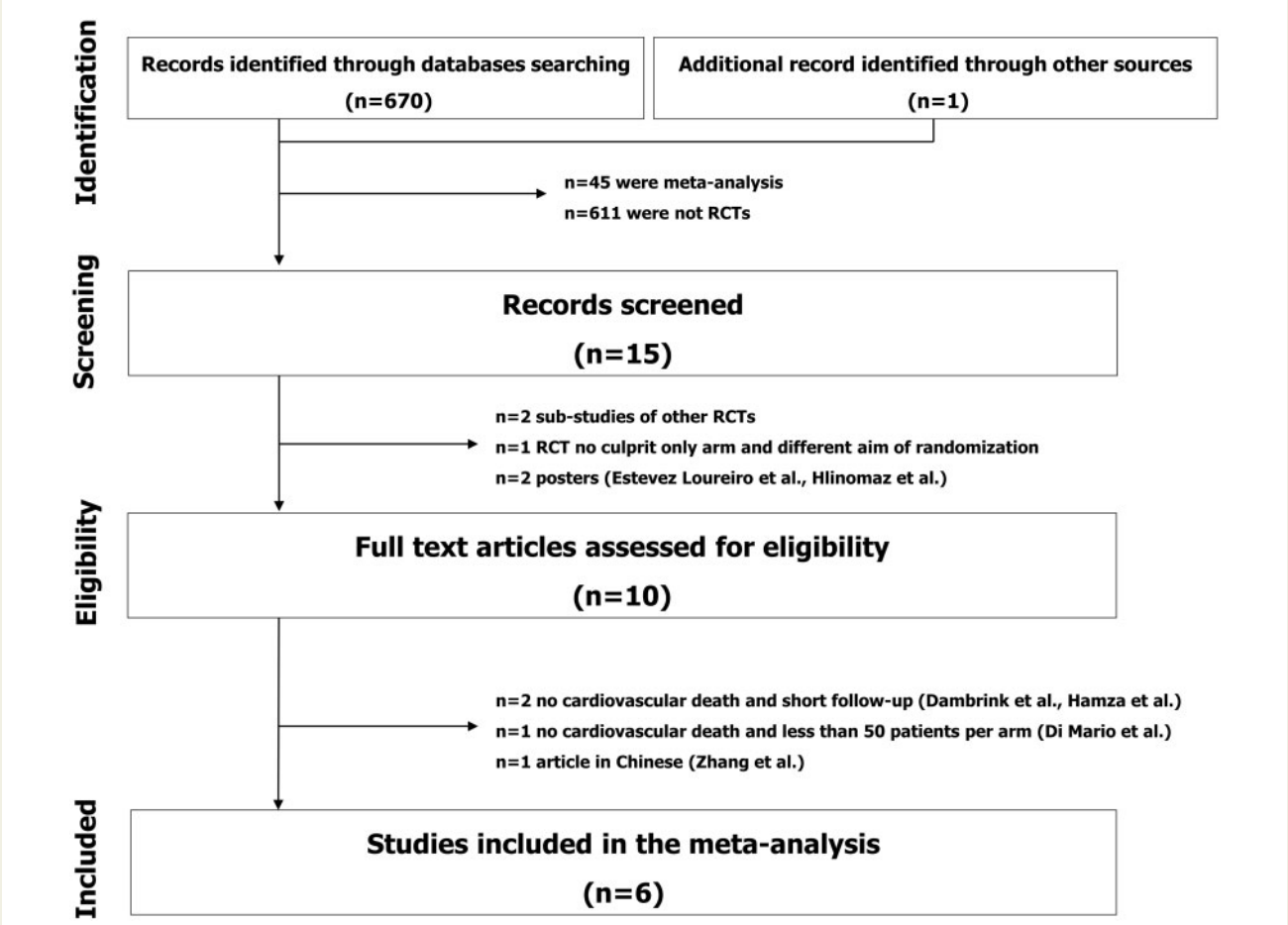


Figure 1 Outline of the search strategy. RCT, randomized clinical trial.

Results

Search results and study selection

The database search yielded 670 records (*Figure 1*). The COMPLETE trial was added to screened records.[14] After the first evaluation of title and abstract 15 records were screened. Two studies were excluded as they focused on a sub-analysis of the main trial.[4,5] One was excluded because it looked at a sub-analysis of an RCT randomizing bivalirudin vs. heparin plus a glycoprotein IIb/IIIa inhibitor, where the comparison was between complete revascularization in a single procedure vs. staged procedure.[22] The studies of Estevez Loureiro *et al.* and Hlinomaz *et al.* investigated the topic of interest and have been previously included in a similar meta-analysis.[6,7,12] However, we excluded them because data were only presented in international meetings but were not published in peer-reviewed journals in English.[6,7] As a result, 10 studies were analysed as full text. The studies of Hamza *et al.* and Dumbrink *et al.* did not report data about cardiovascular death and the follow-up was shorter than 1 year.[1,2] The culprit-only arm of the study of Di Mario *et al.*[3] included less than 50 patients and no clear information about cardiovascular death was reported. Lastly, the study of Zhang *et al.*[8] has been published only in Chinese. For these reasons, the previous four full texts have been excluded. Therefore, six RCTs were included (*Figure 1*).[4,5,9–11,14] The studies were the COMPLETE,[14] CvLPRIT (Complete vs. Lesion-only Primary PCI),[9] PRAMI (Preventive Angioplasty in Acute Myocardial Infarction),[4] Compare-Acute,[5] DANAMI-3-PRIMULTI (Third DANish study of primary PCI in patients with ST-elevation Myocardial Infarction and multivessel disease: treatment of culprit lesion only or complete revascularization),[10] and Politi *et al.*[11] trials. Except for the study of Politi *et al.*,[11] all RCTs were multicentre, registered in public websites and the adverse events were adjudicated by independent blinded committees. Then, the overall quality of included studies is to be considered high (Supplementary material online, *Figure 1s* and *Table 3s*).

Patients characteristics

The six studies include 6528 STEMI patients with multivessel disease. Overall, 3139 of them were randomized to complete revascularization, whereas 3389 to culprit-only. Mean age was 63 ± 11 vs. 63 ± 10 ($P = 0.9$), respectively. The main characteristics of the study population are detailed in *Table 1*. In all studies, patients randomized to culprit-lesion-only PCI strategy received guideline-based medical therapy. Repeated angiography was admitted only in the presence of recurrence of symptoms and documentation of ischaemia

Table 1 Baseline characteristics

	COMPLETE (*N* = 4041)	Compare-Acute (*N* = 885)	CvLPRIT (*N* = 296)	DANAMI-3-PRIMULTI (*N* = 627)	Politi *et al.* (*N* = 214)	PRAMI (*N* = 465)
Patients	2025/2016	590/295	146/150	313/314	84/130	234/231
Age (years)	62 ± 11/62 ± 11	61 ± 10/62 ± 10	65 ± 12/65 ± 11	63 ± 10/64 ± 10	66 ± 13/64 ± 11	62 ± 10/62 ± 9
Male (%)	79/81	76/79	77/85	81/80	76/78	81/76
CV risk factors (%)						
Hypertension	51/49	48/46	36/37	47/41	76/78	81/76
Diabetes	20/19	16/15	14/13	13/9	24/16	21/15
Dyslipidaemia	39/38	30/32	24/28	NA	NA	NA
Smoking	39/41	49/41	27/34	48/51	NA	45/50
Comorbidities (%)						
Prior MI	8/7	7.5/8		5/9		7/8
Prior PCI	7/7	8/9	2/4	NA	NA	NA
Prior stroke	3/3	4/3	NA	NA	NA	4/4
Renal failure	2/2	1/1	1/1	NA	24/25	NA
Culprit lesion (MI location) (%)						
LM	0.2/0.2	0.3/0.2	0/0	NA	NA	NA
LAD (anterior)	34/34	24/36	32/34	(36/33)	(42/46)	(39/29)
LCx (postero-lateral)	16/18	21/18	31/31	(6/3)	NA	(6/4)
RCA (inferior)	50/47	45/46	37/35	(57/62)	NA	(55/66)
General data (%)						
Killip class II–IV	11/11	5/5	9/7	6/7	5/6	NA
3-vessel disease	23/24	33/31	25/21	32/31	25/48	33/39
Medical therapy (%)						
Aspirin	100/100	98/98	97/99	98/96	96/98	100/100
P2Y12 inhibitor	100/100	98/98	98/94	98/99	92/97	100/100
Beta-blocker	89/88	91/91	93/93	91/92	81/80	92/88
ACEi/ARB	85/86	88/92	96/97	44/45	48/56	91/93
Statin	97/98	98/98	99/100	98/99	88/90	97/95

In each column, percentages are culprit-only group/complete groups, respectively.
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; CV, cardiovascular; LAD, left anterior descending; LCx, left circumflex; LM, left main; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; RCA, right coronary artery.

(Supplementary material online, *Table 4s*). The study design of PRAMI, CvLPRIT, and Compare-Acute trials[4,5,9] strongly recommended the treatment of non-culprit lesions at the time of the index procedure, after successful treatment of the culprit lesion. This recommendation was followed in >99%, 64%, and 83% of the patients of the complete arm, respectively. In the study of Politi *et al.*,[11] non-culprit lesions were treated in 50% of cases immediately during index procedure and in 50% in a staged procedure. On the contrary, treatment of non-culprit lesions was recommended by the protocol in a staged procedure in the DANAMI-3-PRIMULTI and COMPLETE trials.[10,14] The identification of non-culprit lesions requiring PCI was angio-based in the PRAMI, CvLPRIT, and Politi *et al.*[4,9,11] trials. In the COMPLETE trial, non-culprit lesions showing a dimeter stenosis >70% were directly treated with PCI, whereas those with a diameter between 50% and 70% were investigated with pressure wires.[14] Overall, physiology-guided PCI was used for only 37 of 2612 lesions.[14] Intracoronary physiology assessment with fractional flow reserve (FFR) was mandatory before revascularization of non-culprit lesions in the DANAMI-3-PRIMULTI and Compare-Acute trials.[5,10]

Primary outcome

After a median follow-up of 2 years (range 1–3 years), cardiovascular death occurred in 185 patients. The pooled event rate was 2.9% (95% CI 1.9–4.4%, I^2 80%). Overall, the occurrence of cardiovascular death was significantly reduced in patients randomized to complete revascularization (HR 0.62, 95% CI 0.39–0.97, I^2 = 29%) (*Figure 2*, Supplementary material online, *Table 5s*). The number needed to treat (NNT) to prevent one cardiovascular death was 70 (95% CI 36–150) (*Take home figure*).

Secondary outcomes

All-cause mortality occurred in 307 patients (pooled event rate 4.8%, 95% CI 3.3–6.9%, I^2 73%). All-cause mortality was not affected by revascularization strategy (HR 0.81, 95% CI 0.60–1.10, I^2 = 14%) (*Figure 3*). In the follow-up, 381 patients suffered from reinfarction. The pooled event rate was 5.0% (95% CI 3.9–6.5%, I^2 73%) and it was significantly reduced in patients randomized to complete revascularization (HR 0.65, 95% CI 0.53–0.80, I^2 = 0%) (*Figure 4*). The NNT to

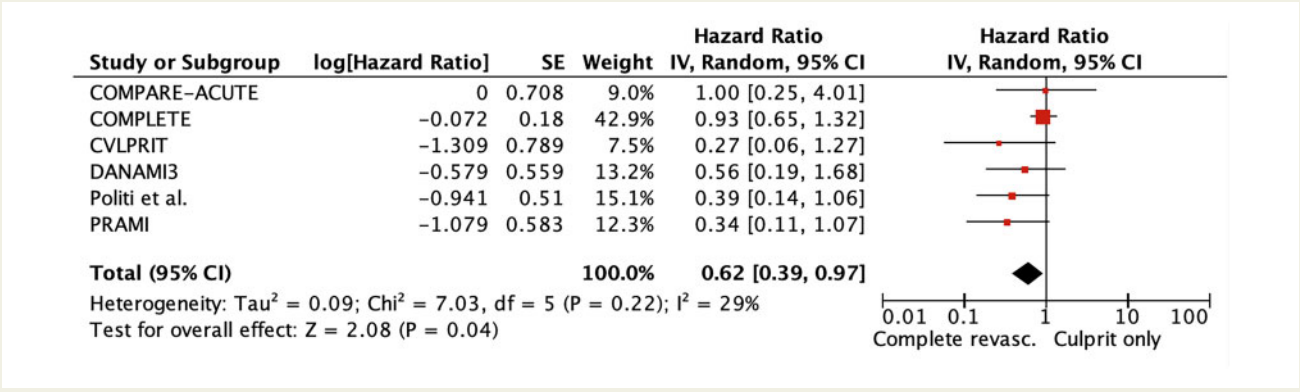
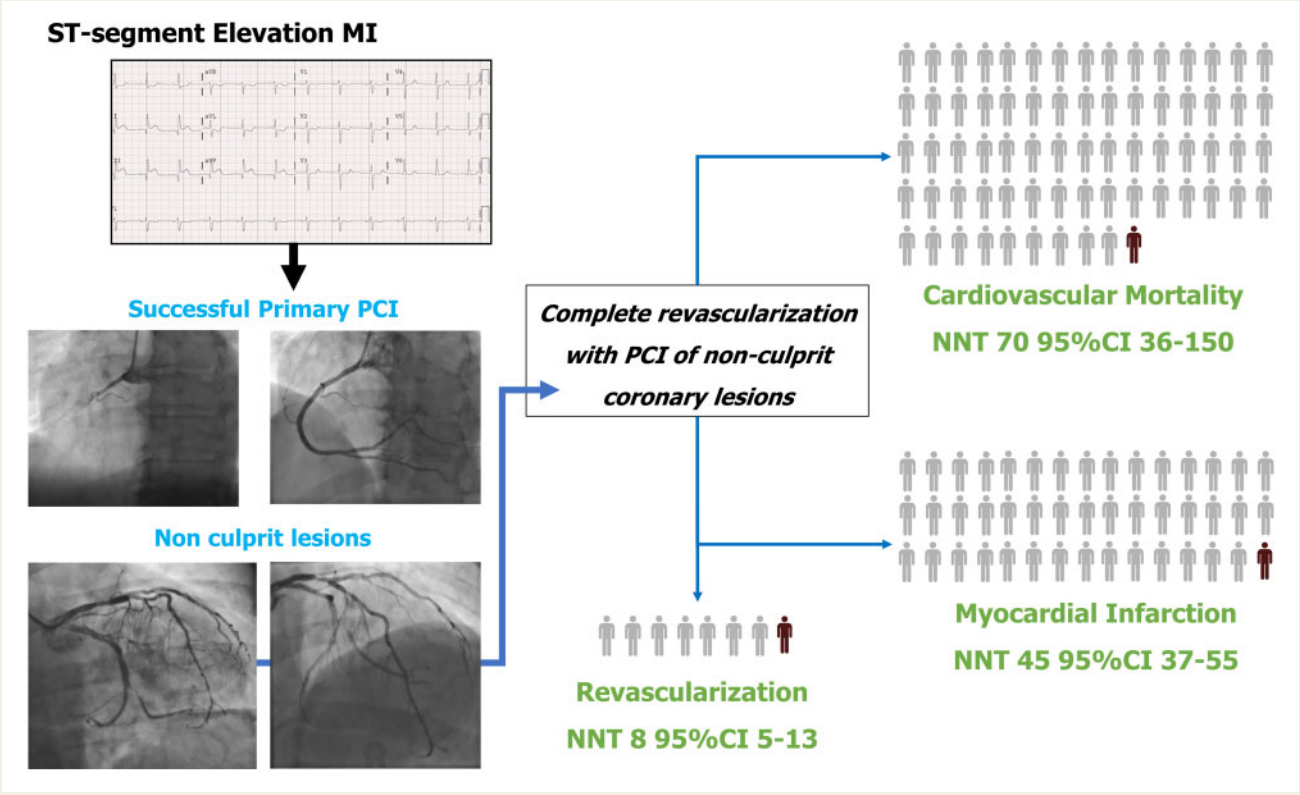


Figure 2 Summary plot for cardiovascular death.



Take home figure Benefit associated with complete revascularization of non-culprit lesions. MI, myocardial infarction; NNT, number needed to treat; PCI, percutaneous coronary intervention.

prevent one reinfarction was 45 (95% CI 37–55) (*Take home figure*). Repeated revascularization was the most common adverse event, occurring in 568 patients (pooled event rate 11.7%, 95% CI 6.4–20.4%, I^2 98%). As expected, it was significantly lower in the complete group (HR 0.29, 95% CI 0.22–0.38, I^2 = 36%) (*Figure 5*). The NNT to prevent one repeated revascularization was 8 (95% CI 5–13) (*Take home figure*). The complete revascularization strategy was not associated with a significant increase in the occurrence of CI-AKI (RR 1.19, 95% CI 0.76–1.87, I^2 = 0%) (Supplementary material online, *Figure 2s*).

Sensitivity analysis

Sensitivity analysis with the 'leave-one-out approach' showed that data about cardiovascular death was confirmed also after the removal of Compare-Acute or COMPLETE trials, but not removing data from the other studies (Supplementary material online, *Table 6s*).

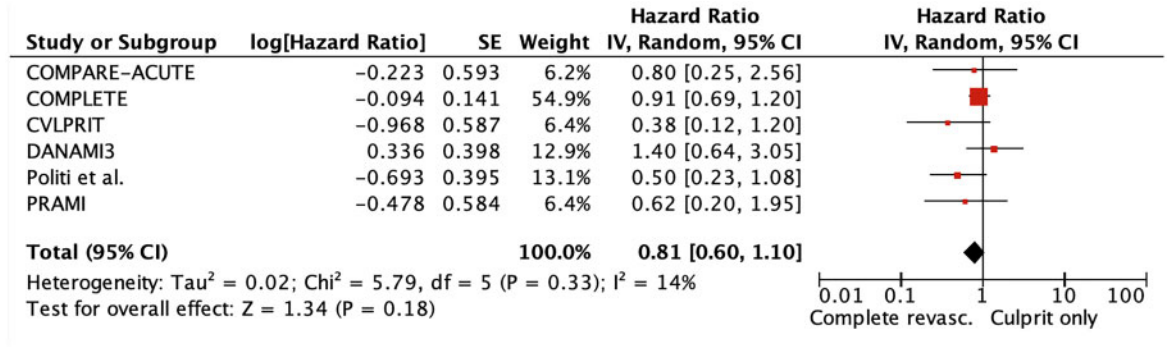


Figure 3 Summary plot for all-cause death.

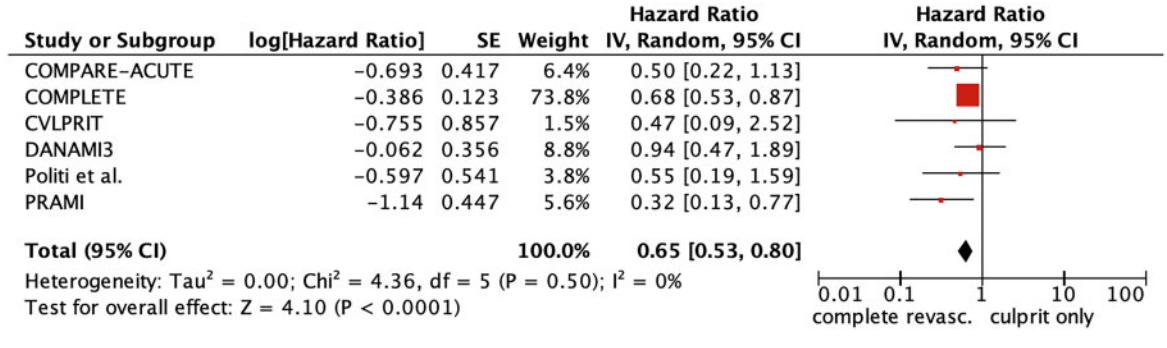


Figure 4 Summary plot for myocardial infarction.

The findings on secondary outcomes were confirmed by sensitivity analysis (Supplementary material online, *Table 6s*).

Discussion

The findings of the present study support that complete revascularization based on PCI of non-culprit lesions reduces cardiovascular mortality and has a positive effect on the recurrence of MI and repeated revascularization. The strength of these conclusions is that they are derived from a study-level analysis of trials including 6528 patients with STEMI and multivessel disease.

Despite multiple improvements in pharmacology and biomedical devices, the overall rate of cardiovascular death in patients with STEMI has not improved for more than 15 years.[23] Some technologies like drug-eluting stents have contributed to decreasing softer endpoints, while others, like thrombus manual aspiration, have failed to reduce cardiovascular mortality. Likewise, the treatment with PCI of non-culprit lesions in STEMI patients with multivessel disease had demonstrated to improve patient outcomes, but not cardiovascular death.[3,5,10,11] In that context, previous RCTs and meta-analyses have highlighted a significant reduction in the risk of recurrence of MI in patients receiving complete revascularization.[4,12,24] However, no solid evidence suggested a benefit in terms of mortality.[12,24] Many reasons might contribute to explain this gap in the evidence. First, strong selection bias is induced by including low-risk study populations. Second, the presence of potential confounding factors such as the timing of the treatment of non-culprit lesions (immediate during the index procedure vs. staged). Third, the length of the follow-up. The median follow-up of the available RCTs is around 2 years, with the longest reaching 3 years. Finally, the main issue is the sample size. As suggested by Elgendy *et al.*,[24] based on the event rate and potential benefit related to complete revascularization, a study population around 7000–8000 patients would be needed in order to achieve sufficient power for mortality.[24] The publication of the COMPLETE trial helps us approach this target.[14] The COMPLETE is the largest study on the topic and it confirmed that the treatment of non-culprit lesions, mainly based on visual estimation, is associated with a significant reduction of the need for repeated revascularization and recurrence of MI.[14] However, also in this landmark trial, no effect was observed in terms of cardiovascular and all-cause mortality.[14] If this lack of benefit is related to unpowered sample size for mortality or to the inclusion of highly selected population is unclear. Indeed, the study population of the COMPLETE trial is relatively young (mean age 62 years) and the complexity of coronary artery disease was low. This population is different from sicker patients seen in the clinical

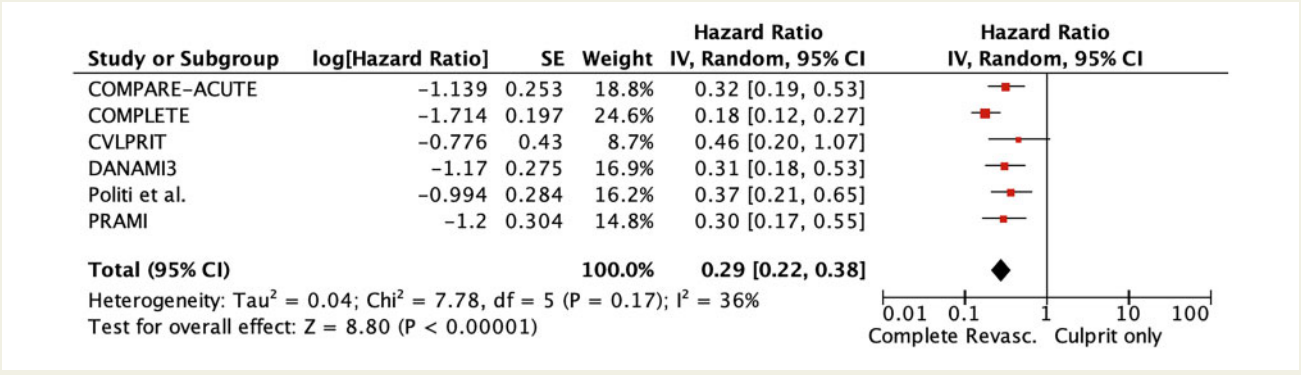


Figure 5 Summary plot for repeated revascularization.

setting and to show a benefit in terms of mortality can be more challenging.

The present study provides an updated and improved assessment of the problem using meta-analytical techniques. To circumvent the limitations of previous meta-analyses, we rigorously selected the inclusion criteria. In agreement with the standards for high-quality meta-analysis, we included only RCTs published in peer-reviewed journals, in English, with at least 50 patients per arm and reporting the number of each hard endpoint. Including the COMPLETE trial, the study population of the present analysis is three times bigger than the previous ones.[14,24] The combination of rigorous inclusion criteria and the publication of the COMPLETE trial gave us adequate statistical power for the current analysis of cardiovascular death. The revascularization of non-culprit lesions reduces cardiovascular mortality with an NNT of 70 (95% CI 36–150, *Take home figure*). It is biologically plausible that the significant reduction of recurrence of MI and the need for repeated revascularization could reduce cardiovascular death. On the other side, we did not find a benefit in terms of all-cause mortality. It is interesting to note that similar findings were observed after 16-year follow-up comparing primary PCI vs. thrombolysis in STEMI patients.[25] We may suppose that the sample size and the risk profile of the study population, as well as the length of the follow-up play a major role. A rate of all-cause mortality around 5% should be considered low, being at least two to three times higher in real-life populations.[26] The challenge of future trials is to understand if a significant reduction of all-cause mortality can be achieved including older, more complex, high-risk study populations. Alternatively, it could be related to the timing of non-culprit lesions PCI. Indeed, the study by Pasceri *et al.*[12] suggested that complete revascularization during primary PCI might be associated with a reduction in total mortality. In the COMPLETE trial, non-culprit lesions treatment was performed either during the index hospitalization or in a further hospitalization within 45 days after MI. The timing of the revascularization did not show any influence on the outcomes.[14] In the COMPLETE trial, immediate PCI of non-culprit lesions in the index procedure was not allowed. Only the ongoing RCTs (NCT03135275, NCT03621501) comparing immediate vs. staged revascularization of non-culprit lesions might clarify if the timing of non-culprit lesions is related to mortality. However, the lack of benefit in terms of all-cause mortality should not be considered a limiting factor, especially in the presence of consistent reduction of cardiovascular death and MI.

An important limitation of several of the studies on this topic is the low implementation of physiology-guided revascularization. Further work needs to be carried out to establish whether the identification of non-culprit lesions requiring PCI must be angio- or physiology-guided and what is the perfect timing for physiology assessment of non-culprit lesions. The Fractional flow reserve vs. Angiography for Multivessel Evaluation (FAME) trial demonstrated that ≈65% and ≈20% of the coronary lesions with diameter stenosis ranging from 50% to 70% and from 71% to 90% are not flow-limiting, respectively.[27] In patients with stable coronary lesions, physiology-guided PCI resulted in a decreased risk of MI as compared to medical therapy.[28] At the same time, some authors suggested that lesions' physiology assessment in the early phase of STEMI may be associated with pitfalls due to concomitant microvascular dysfunction.[29,30] Ongoing trials (i.e. NCT03298659) comparing early (invasive) vs. later (non-invasive) assessment of non-culprit lesions will contribute to define the better management of STEMI patients with multivessel disease.

Limitations

This is a study-level meta-analysis. Although the methodology is well-established and we applied strict criteria for study selection, it would be of paramount importance to confirm our findings with a patient-level meta-analysis. In particular, the availability of additional data and analyses with extended follow-up would be helpful. Moreover, due to the limited number of studies (less than 10), we cannot evaluate potential publication bias and potential confounding factors that might affect outcomes.[21] Finally, we recognize that patients participating in RCTs are different from sicker patients seen in the clinical setting and further studies (NCT03772743, NCT03135275, and NCT03621501) are needed to confirm similar outcomes in patients with a greater risk.

Conclusions

In a highly selected study population of STEMI patients with multivessel disease coming from RCTs, it has been proven that PCI of

non-culprit lesions reduces the occurrence of cardiovascular death. This reduction was concomitant with the one of MI and the need of repeated revascularization.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

Conceived and designed the research: Gianluca Campo, Simone Biscaglia, Rita Pavasini. Acquired the data: Gianluca Campo, Gianni Casella, Andrea Santarelli, Matteo Tebaldi, Simone Biscaglia, Rita Pavasini, Luigi Politi. Performed statistical analysis: Rita Pavasini, Fabrizio D'Ascenzo, Andrea Saglietto. Handled funding and supervision: Gianluca Campo, Giuseppe Di Pasquale. Drafted the manuscript: Gianluca Campo, Simone Biscaglia, Rita Pavasini, Vincenzo Guiducci, Emanuele Barbato. Made critical revision of the manuscript for key intellectual content: Javier Escaned, Emanuele Barbato, Gutierrez-Ibanes Enrique, Dariusz Dudek.

Conflict of interest: none declared.

References

1. Dambrink JH, Debrauwere JP, van 't Hof AW, Ottervanger JP, Gosselink AT, Hoorntje JC, de Boer MJ, Suryapranata H. Non-culprit lesions detected during primary PCI: treat invasively or follow the guidelines? *EuroIntervention* 2010;**5**:968–975.
2. Hamza M, Mahmoud N, Elgendy IY. A randomized trial of complete versus culprit-only revascularization during primary percutaneous coronaryintervention in diabetic patients with acute ST elevation myocardial infarction and multi vessel disease. *J Interv Cardiol* 2016;**29**:241–247.
3. Di Mario C, Mara S, Flavio A, Imad S, Antonio M, Anna P, Emanuela P, Stefano DS, Angelo R, Stefania C, Anna F, Carmelo C, Antonio C, Monzini N, Bonardi M. Single vs multivessel treatment during primary angioplasty: results of the multicentre randomised HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study. *Int J Cardiovasc Intervent* 2004;**6**:128–133.
4. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;**369**:1115–1123.
5. Smits PC, Abdel-Wahab M, Neumann F-J, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional flow reserve guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;**376**:1234–1244.
6. Estevez Loureiro R, Calvino-Santos R, Peteiro J, Bouzas-Mosquera A, Salgado-Fernandez J, Soler-Martin MR. Preventive revascularization does not offer clinical advantage over a selective invasive strategy in patients with ST-segment elevation myocardial infarction and multivessel disease. *Eur Heart J* 2014;**35**:477.
7. Hlinomaz O, Grouch L, Polokova L, Lehar F, Vekov T, Petkov R, Stojnev M, Gřiva M, Sitár J, Rezek M, Novák M, Seménka J, Penkov N. Multivessel coronary disease diagnosed at the time of primary PCI for STEMI: complete revascularisation versus conservative strategy. PRAGUE-13 trial. *Kardiolog Rev* 2015;**17**:214–220.
8. Zhang J, Wang Q, Yang H, Ma L, Fu X, Hou W, Feng J, Liu X. Evaluation of different revascularization strategies for patients with acute myocardial infarction with lesions of multiple coronary arteries after primary percutaneous coronary intervention and its economic evaluation. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2015;**27**:169–174.
9. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;**65**:963–972.
10. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L; Danami-3—Primulti Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;**386**:665–671.
11. Politi L, Sgura F, Rossi R, Monopoli D, Guerri E, Leuzzi C, Bursi F, Sangiorgi GM, Modena MG. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart* 2010;**96**:662–667.
12. Pasceri V, Patti G, Pelliccia F, Gaudio C, Speciale G, Mehran R, Dangas GD. Complete revascularization during primary percutaneous coronary intervention reduces death and myocardial infarction in patients with multivessel disease: meta-analysis and meta-regression of randomized trials. *JACC Cardiovasc Interv* 2018;**11**:833–843.
13. Fortuni F, Crimi G, Angelini F, Leonardi S, D'Ascenzo F, Ferlini M, Rolando M, Raisaro A, Oltrona Visconti L, Ferrario M, Gnecchi M, De Ferrari GM. Early complete revascularization in hemodynamically stable patients with ST-segment elevation myocardial infarction and multivessel disease. *Can J Cardiol* 2019;**35**:1047–1057.
14. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, López-Sendón J, Faxon DP, Mauri L, Rao SV, Feldman L, Steg PG, Avezum Á, Sheth T, Pinilla-Echeverri N, Moreno R, Campo G, Wrigley B, Kedev S, Sutton A, Oliver R, Rodés-Cabau J, Stanković G, Welsh R, Lavi S, Cantor WJ, Wang J, Nakamya J, Bangdiwala SI, Cairns JA. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2019;**381**:1411–1421.
15. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. *Lancet* 1999;**354**:1896–1900.
16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–2012.
17. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration, 2009, http://handbook.cochrane.org.
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–560.
21. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.
22. Kornowski R, Mehran R, Dangas G, Nikolsky E, Assali A, Claessen BE, Gersh BJ, Wong SC, Witzenbichler B, Guagliumi G, Dudek D, Fahy M, Lansky AJ, Stone GW, Horizons AMI, Trial I. Prognostic impact of staged versus "one-time" multivessel percutaneous intervention in acute myocardial infarction: analysis from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol* 2011;**58**:704–711.
23. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, James S, Kellerth T, Lindahl B, Ravn-Fischer A, Rydberg E, Yndigegn T, Jernberg T. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J* 2017;**38**:3056–3065.
24. Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;**10**:315–324.
25. Thrane PG, Kristensen SD, Olesen KKW, Mortensen LS, Bøtker HE, Thuesen L, Hansen HS, Abildgaard U, Engstrøm T, Andersen HR, Maeng M. 16-year follow-up of the Danish Acute Myocardial Infarction 2 (DANAMI-2) trial: primary percutaneous coronary intervention vs. fibrinolysis in ST-segment elevation myocardial infarction. *Eur Heart J* 2019;doi: 10.1093/eurheartj/ehz595.
26. Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, Holmvang L, Clemmensen P, Engstrøm T, Grande P, Saunamäki K, Jørgensen E. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol* 2014;**64**:2101–2108.

27. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010; **55**:2816–2821.
28. Zimmermann FM, Omerovic E, Fournier S, Kelbæk H, Johnson NP, Rothenbühler M, Xaplanteris P, Abdel-Wahab M, Barbato E, Høfsten DE, Tonino PAL, Boxma-de Klerk BM, Fearon WF, Køber L, Smits PC, De Bruyne B, Pijls NHJ, Jüni P, Engstrøm T. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. *Eur Heart J* 2019;**40**:180–186.
29. Thim T, Götberg M, Fröbert O, Nijveldt R, van Royen N, Baptista SB, Koul S, Kellerth T, Bøtker HE, Terkelsen CJ, Christiansen EH, Jakobsen L, Kristensen SD, Maeng M. Nonculprit stenosis evaluation using instantaneous wave-free ratio in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2017;**10**:2528–2535.
30. van der Hoeven NW, Janssens GN, de Waard GA, Everaars H, Broyd CJ, Beijnink CWH, van de Ven PM, Nijveldt R, Cook CM, Petraco R, Ten Cate T, von Birgelen C, Escaned J, Davies JE, van Leeuwen MAH, van Royen N. Temporal changes in coronary hyperemic and resting hemodynamic indices in nonculprit vessels of patients with ST-segment elevation myocardial infarction. *JAMA Cardiol* 2019;doi: 10.1001/jamacardio.2019.2138 [Epub ahead of print].