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Systematic Review/Meta-analysis

Early Complete Revascularization in Hemodynamically Stable Patients With ST-Segment Elevation Myocardial Infarction and Multivessel Disease

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ABSTRACT

Background: The optimal strategy and timing of revascularization in hemodynamically stable patients with ST-segment elevation myocardial infarction and multivessel disease is unknown. We performed a systematic review and meta-analysis to explore the comparative efficacy and safety of early complete revascularization vs culprit-only or staged revascularization in this setting.

Methods: We searched the literature for randomized clinical trials that assessed this issue. Early complete revascularization was defined as a complete revascularization achieved during the index procedure or within 72 hours. Efficacy outcomes were major adverse cardiovascular events, myocardial infarction, repeat revascularization, and all-cause mortality. Safety outcomes were all bleeding events, stroke, and contrast-induced acute kidney injury.

Results: Nine randomized clinical trials with a total of 2837 patients were included; 1254 received early complete revascularization and

RÉSUMÉ

Contexte: On ignore quelle est la stratégie optimale et le moment le plus approprié pour la revascularisation chez les patients stables sur le plan hémodynamique qui ont subi un infarctus du myocarde avec élévation du segment ST et présentent une atteinte polyvasculaire. Nous avons effectué une revue systématique et une méta-analyse en vue de comparer l'efficacité et l'innocuité d'une revascularisation complète précoce et d'une revascularisation de la seule artère en cause ou par étapes chez les patients présentant ces caractéristiques.

Méthodologie: Nous avons effectué une recension de la littérature traitant des essais cliniques à répartition aléatoire pertinents. Une revascularisation complète précoce a été définie comme étant une revascularisation effectuée au cours de l'intervention initiale ou dans les 72 heures de celle-ci. Les paramètres d'évaluation de l'efficacité étaient les événements cardiovasculaires indésirables majeurs, l'infarctus du myocarde, la revascularisation répétée et la mortalité toutes

Multivessel coronary disease is found in 40%-50% of patients with ST-segment elevation myocardial infarction (STEMI)[1] and is associated with worse clinical outcomes and increased mortality.[2] In patients with STEMI there is overwhelming evidence of the benefit of treating the infarct-related artery with primary percutaneous coronary intervention (pPCI), whereas the best strategy and timing to additional nonculprit coronary stenoses is still unsettled.[3] Data coming from observational studies did not show any benefit from early complete revascularization, that was rather associated with an increased mortality risk in patients with STEMI.[4] These results were probably mainly related to unmeasured confounders and selection bias, because unstable patients with more deteriorated conditions were more likely to receive early complete revascularization. On the contrary, recent randomized clinical trials (RCTs) reported a benefit of early complete revascularization in terms of preventing major adverse cardiovascular events (MACE) without potential additional risk.[5-8]

The latest release of European guidelines on myocardial revascularization reinforced the importance of complete revascularization, however, the best timing and modality (angiography-guided or ischemia-guided) to define coronary lesions to be targeted by percutaneous coronary intervention (PCI) is still unknown. In the updated European Society of

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1583 were treated with other revascularization strategies. After a mean follow-up of 15.3 ± 9.4 months early complete revascularization was associated with a lower risk of major adverse cardiovascular events (relative risk [RR], 0.51; 95% confidence interval [CI], 0.41-0.62; $P < 0.00001$; number needed to treat = 8), myocardial infarction (RR, 0.59; 95% CI, 0.40-0.87), and repeat revascularization (RR, 0.39; 95% CI, 0.28-0.55) without any difference in all-cause mortality and in safety outcomes compared with culprit-only or staged revascularization. Moreover, fractional flow reserve-guided complete revascularization reduced the incidence of repeat revascularization compared with angiography-guided procedure ($\chi^2 = 4.36$; $P = 0.04$).
Conclusions: Early complete revascularization should be considered in hemodynamically stable patients with ST-segment elevation myocardial infarction and multivessel disease deemed suitable for percutaneous interventions. Fractional flow reserve-guided complete revascularization might be superior to angiography-guided procedures in reducing need for further interventions.

causes confondues. Les paramètres d'évaluation de l'innocuité étaient les événements hémorragiques totaux, les accidents vasculaires cérébraux et l'insuffisance rénale aiguë induite par les produits de contraste.
Résultats : Neuf essais cliniques à répartition aléatoire menés auprès de 2837 patients au total ont été inclus; 1254 patients avaient été traités par revascularisation complète précoce et 1583, par une autre stratégie de revascularisation. Après une période de suivi moyenne de 15,3 ± 9,4 mois, la revascularisation complète précoce était associée à un risque plus faible d'événement cardiovasculaire indésirable majeur (risque relatif [RR], 0,51; intervalle de confiance [IC] à 95 %, de 0,41 à 0,62; $p < 0,00001$; nombre de sujets à traiter = 8), d'infarctus du myocarde (RR, 0,59; IC à 95 %, de 0,40 à 0,87) et de revascularisation répétée (RR, 0,39; IC à 95 %, de 0,28 à 0,55) sans aucune différence sur le plan de la mortalité toutes causes confondues et des paramètres d'évaluation de l'innocuité comparativement à la revascularisation de la seule artère en cause ou à la revascularisation par étapes. De plus, la revascularisation complète guidée par la mesure de la réserve coronaire a entraîné une réduction de l'incidence des revascularisations répétées comparativement à l'intervention guidée par angiographie ($\chi^2 = 4,36$; $p = 0,04$).
Conclusions : La revascularisation complète précoce devrait être envisagée chez les patients stables sur le plan hémodynamique qui ont subi un infarctus du myocarde avec élévation du segment ST, qui présentent une atteinte polyvasculaire et chez lesquels une intervention percutanée est indiquée. La revascularisation complète guidée par la mesure de la réserve coronaire pourrait s'avérer supérieure aux techniques guidées par angiographie pour réduire la nécessité d'interventions futures.

Cardiology guidelines on STEMI and on myocardial revascularization the indication for complete revascularization in hemodynamically stable patients was shifted from class IIb[9] to class IIa.[3,10] Similarly, American College of Cardiology Foundation/American Heart Association guidelines on STEMI changed this indication from class III[11] to class IIb.[12]

The aim of the present study was to assess whether early complete revascularization can improve clinical outcomes in hemodynamically stable patients with STEMI and multivessel coronary disease compared with staged or culprit-only revascularization and to analyze what is the best test to guide revascularization in this setting.

Methods

Study identification

We systematically searched Medline, Embase, and the Cochrane database for RCTs that evaluated the comparative efficacy and safety of early complete revascularization vs culprit-only or staged revascularization in hemodynamically stable patients with STEMI and multivessel coronary artery disease.

For the present analysis we considered early complete revascularization as a complete revascularization achieved during the index procedure or same hospitalization within 72 hours. Whereas staged revascularization was defined as PCI of the culprit lesion during the index procedure and complete revascularization obtained after 72 hours. In comparison, culprit-only revascularization was identified as infarct-related artery-only treatment performed during the index procedure.

To be eligible for inclusion, studies had to report on ischemic events (MACE, nonfatal myocardial infarction [MI], stroke, and/or any myocardial revascularization), bleeding events (defined as any type of bleeding event), all-cause mortality and/or contrast-induced acute kidney injury (CI-AKI).

The following key words were used for our research: "acute coronary syndrome" or "myocardial infarction" and "revascularization" and "multivessel." Searches were limited to English language RCTs. Moreover, we considered reference letters, reviews, other meta-analyses, and editorials to identify potentially eligible studies. The process was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

Study selection

Two independent investigators (F.A. and F.F.) reviewed all titles and abstracts and selected the ones with the potential characteristics to be included in the final analysis. Selected abstracts were further reviewed as full texts and additional studies were identified by scanning their references; discrepancies were resolved by consensus.

Data extraction

Data were extracted from the selected studies concerning: study design, sample size, patient characteristics,

Table 1. Study characteristics

	HELP AMI 2004	PRIMA 2004	Politi et al.[19]	PRAMI 2013	Tarasov et al.[22]	CVLRIT 2015	DANAMI-3-PRIMULTI 2015	Hamza et al.[7]	COMPARE-ACUTE 2017
Follow-up, months	12	6	30	23	6	12	27	6	12
Early complete revascularization	During pPCI	During pPCI	During pPCI	During pPCI	During pPCI	During pPCI (64%) or in-hospital	FFR-guided ($\leq$ 0.80 or $>$ 90% stenosis) complete revascularization in an additional PCI procedure 2 days after the initial PCI and before discharge	During pPCI or in-hospital within 72 hours	Ischemia-guided (FFR $\leq$ 0.80) generally during the same intervention (83.4%); it could be delayed at the operator's discretion but had to be performed during the index hospitalization and preferably within 72 hours
Other revascularization strategy	Culprit-only during pPCI	Culprit-only during pPCI and staged procedure	Culprit only during pPCI/ staged	Culprit-only during pPCI	Culprit-only during pPCI and then staged PCI	Culprit-only during pPCI	Culprit-only during pPCI	Culprit-only during pPCI	Culprit-only during pPCI. FFR was performed in noninfarct-related arteries. Clinically indicated elective revascularizations performed within 45 days after pPCI (7.6%) were not counted as events
Significant stenosis definition	N/A	Angiographic criteria ($>$ 70% diameter stenosis)	Angiographic criteria ($>$ 70% diameter stenosis)	Angiographic criteria ($\geq$ 50% diameter stenosis)	Angiographic criteria ($\geq$ 70% diameter stenosis)	Angiographic criteria (70% diameter stenosis in 1 plane or $>$ 50% in 2 planes)	Angiographic and/or functional criteria (50%-90% diameter stenosis and FFR $\leq$ 0.80 or $>$ 90% diameter stenosis)	Angiographic criteria ($\geq$ 80% diameter stenosis)	Angiographic and functional criteria ($\geq$ 50% diameter stenosis and FFR $\leq$ 0.80)
Bleeding definition	N/A	TIMI	N/A	N/A	N/A	N/A	Periprocedural bleeding requiring transfusion or surgery	TIMI	N/A
MACE definition	N/A	All-cause mortality, nonfatal MI or target vessel revascularization	All-cause mortality, nonfatal MI, rehospitalization for ACS or repeat coronary revascularization (only if unplanned in the staged group)	Death from cardiac causes, nonfatal MI or refractory angina	All-cause mortality, nonfatal MI or repeat coronary revascularization	All-cause mortality, nonfatal MI, heart failure or ischemic-driven revascularization	All-cause mortality, nonfatal MI or ischemia-driven revascularization	All-cause mortality, nonfatal MI or ischemia-driven revascularization.	All-cause mortality, nonfatal MI, repeat revascularization or cerebrovascular events
Repeat revascularization definition	PCI or CABG	PCI or CABG	Ischemia driven revascularization	PCI or CABG	Target vessel revascularization	Ischemia driven revascularization	Ischemia driven revascularization	Ischemia driven revascularization	PCI or CABG (80% defined appropriate)

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; COMPARE-ACUTE, **Compa**rison Between FFR Guided **Re**vascularization Versus Conventional Strategy in **Acute** STEMI Patients With MVD; CVLRIT, **C**omplete **vs** **L**esion Only **Pr**imary PCI **T**rial; DANAMI-3-PRIMULTI, Third **Dan**ish Study of Optimal **A**cute Treatment of Patients With STE**MI**: **Pri**mary PCI in **Multi**vessel Disease; FFR, fractional flow reserve; HELP AMI, **He**pacoat for Cu**lp**rit or Multivessel Stenting for **A**cute **M**yocardial **I**nfarction; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not available; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention; PRAMI, **Pr**eventive **A**ngioplasty in Acute **M**yocardial **I**nfarction; PRIMA, Primary Angioplasty in Patients With Multivessel Disease with Acute Myocardial Infarction; TIMI, **T**hrombolysis **i**n **M**yocardial **I**nfarction.

Table 2. Baseline characteristics

	HELP AMI 2004	PRIMA 2004	Politi et al.[19]	PRAMI 2013	Tarasov et al.[22]	CVLPRIT 2015	DANAMI-3-PRIMULTI 2015	Hamza et al.[7]	COMPARE ACUTE 2017
Number of patients	69	92	214	474	89	296	627	100	885
Age (years)	63.9	65.9	65.2	62.0	58.8	65.0	63.5	54.3	61.3
Male sex, %	87.0	73.9	77.6	76.6	64.0	81.1	80.7	84.0	77.2
Hypertension, %	42.0	50.0	43.5	39.5	44.4	35.5	44.0	31.0	47.2
Diabetes, %	18.8	32.6	23.8	17.5	23.6	13.2	11.3	100	15.5
Dyslipidemia, %	43.5	85.9	N/A	N/A	N/A	34.1	N/A	45.0	30.6
Smoker, %	71.0	40.2	N/A	46.6	N/A	29.4	73.7	75.0	46.0
Ejection fraction, %	48.5	43.4	46	N/A	51.5	45.5	50	46.5	N/A
Three-vessel disease, %	34.8	N/A	32.2	N/A	44.9	22.6	31.4	31.0	32.2
Drug-eluting stent, %	0	0	9.8	35.2 (only early complete PCI group considered)	100	90.5	93.8	100	32.9 (only early complete PCI group considered)
Previous PCI, %	20.3	16.3	N/A	7.4 (previous MI)	7.9 (previous MI)	3.0	7.0 (previous MI)	7.0	7.8
Anterior MI, %	53.6	45.7	43.9	32.9	38.2 (LAD culprit)	35.8	34.6	47.0 (LAD culprit)	35.1
Renal impairment, %	N/A	N/A	26.6	N/A	N/A	0.7	N/A	N/A	1.1

COMPARE ACUTE, **Compar**ison Between FFR Guided **Re**vascularization Versus Conventional Strategy in **Acute** STEMI Patients With MVD; CVLRIT, **Complete vs L**esion Only **P**rimary PCI **T**rial; DANAMI-3-PRIMULTI, Third **Dan**ish Study of Optimal **Acute** Treatment of Patients With STE**MI**: **Pri**mary PCI in **Multi**vessel Disease; HELP AMI, **He**pacoat for Cul**prit** or Multivessel Stenting for **A**cute **M**yocardial **I**nfarction; LAD, left anterior descending artery; MI, myocardial infarction; N/A, not available; PCI, percutaneous coronary intervention; PRAMI, **Pr**eventive **A**ngioplasty in Acute **M**yocardial Infarction; PRIMA, Primary Angioplasty in Patients With Multivessel Disease with Acute Myocardial Infarction.

revascularization strategy, dual antiplatelet therapy, bleeding definition, MACE definition, repeat revascularization definition, CI-AKI definition, length of follow-up, and end points of interest. Discrepancies were resolved by discussion and consensus among the authors.

End points

The efficacy outcomes were MACE, nonfatal MI, all-cause mortality, and repeat revascularization. The safety outcomes were any type of bleeding irrespective of the bleeding definition used, stroke, and CI-AKI. As shown in Table 1, MACE and repeat revascularization were defined using different definitions among the studies. We considered MACE as defined by each study (Table 1). In comparison, we considered any repeat myocardial revascularization regardless of the indication (ie, urgent or scheduled), the modality (ie, coronary artery bypass grafting or PCI), and the vessel involved (ie, target vessel revascularization or other vessels), because this was the most homogeneous definition used across the studies (Table 1).

Assessment of data quality

The quality of the RCTs taken into account was analyzed using the Cochrane Collaboration Risk of Bias Tool.[14] The following domains were evaluated: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. For each domain the pooled risk of bias was determined.

Statistical analysis

Data were analyzed on an intention to treat basis. Relative risk (RR) and 95% confidence interval (CI) were obtained for each end point with the random effect model. This model was chosen because in our analysis we compared heterogeneous studies with different treatments and population baseline characteristics.[15] Heterogeneity between trials was assessed by measuring inconsistency using the I^2 index, which describes the percentage of total variation across the studies that is due to heterogeneity rather than chance.[16] I^2 values of 25%, 50%, and 75% were attributed to small, moderate, and large amounts of heterogeneity.

For the end points that were significantly different in the 2 groups, absolute risk reduction (ARR) and number needed to treat (NNT) were calculated.

Two subgroup analyses were performed to stratify the results according to modality of revascularization in the "other revascularization strategy" group (staged vs culprit-only revascularization) and according to early complete revascularization strategy (angiography-guided vs fractional flow reserve [FFR]-guided). A sensitivity analysis was performed to verify the consistency of the results depending on the timing of early complete revascularization (mandatory during pPCI vs during pPCI or within 72 hours). In addition, we carried out a leave-one-out sensitivity analysis on the efficacy end points to evaluate if the results were largely affected by a single study. As an additional analysis univariate meta-regression for unadjusted log RR was performed. The potential moderator effect of: year of publication, age, sex, stent type (intended as percentage of drug-eluting stent [DES] implanted),

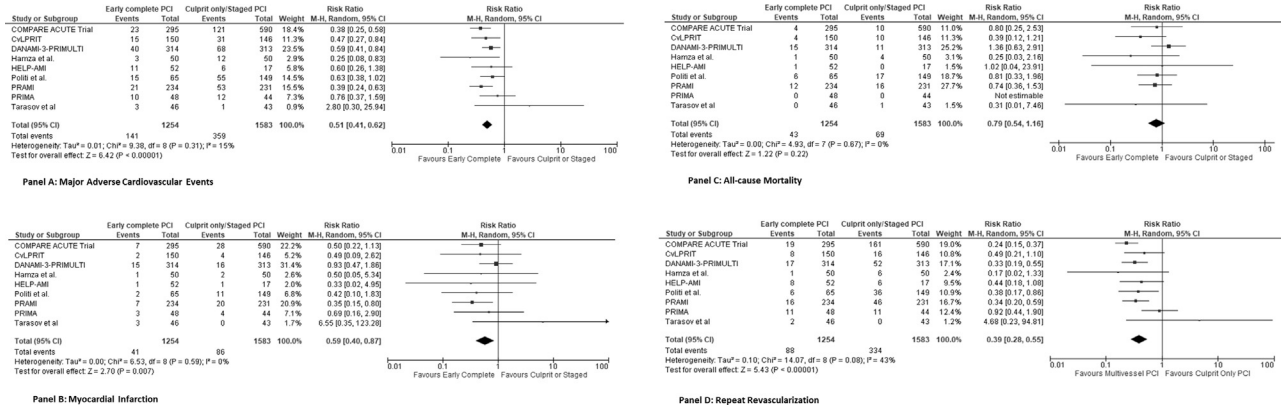


Figure 1. Efficacy end points. Forest plot showing the relative risks with 95% confidence interval of major adverse cardiovascular events (**A**), myocardial infarction (**B**), all-cause mortality (**C**), and repeat revascularization (**D**) in hemodynamically stable patients with acute coronary syndrome treated with early complete revascularization vs culprit-only or staged revascularization. The diamond indicates the point estimate, and the left and right end of the line indicate the 95% confidence interval. PCI, percutaneous coronary intervention.

hypertension, diabetes, smoking status, dyslipidemia, previous PCI, 3-vessel disease, left ventricular ejection fraction, and anterior MI was explored.

Publication bias was assessed using funnel plot and Egger regression tests.

The analyses were performed using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), OpenMeta-Analyst version beta 1.0[17], and Microsoft Excel 2010 (Microsoft Corp, Redmond, WA).

Results

Study and patient characteristics

Overall, 30 full-text studies were screened for eligibility; 9 RCTs[5-8,18-22] met our inclusion criteria and were taken into account for further consideration (Table 1 and Supplemental Fig. S1).

A total of 2837 patients were included; 1254 participants received early complete revascularization and the remaining 1583 were treated with other revascularization strategies

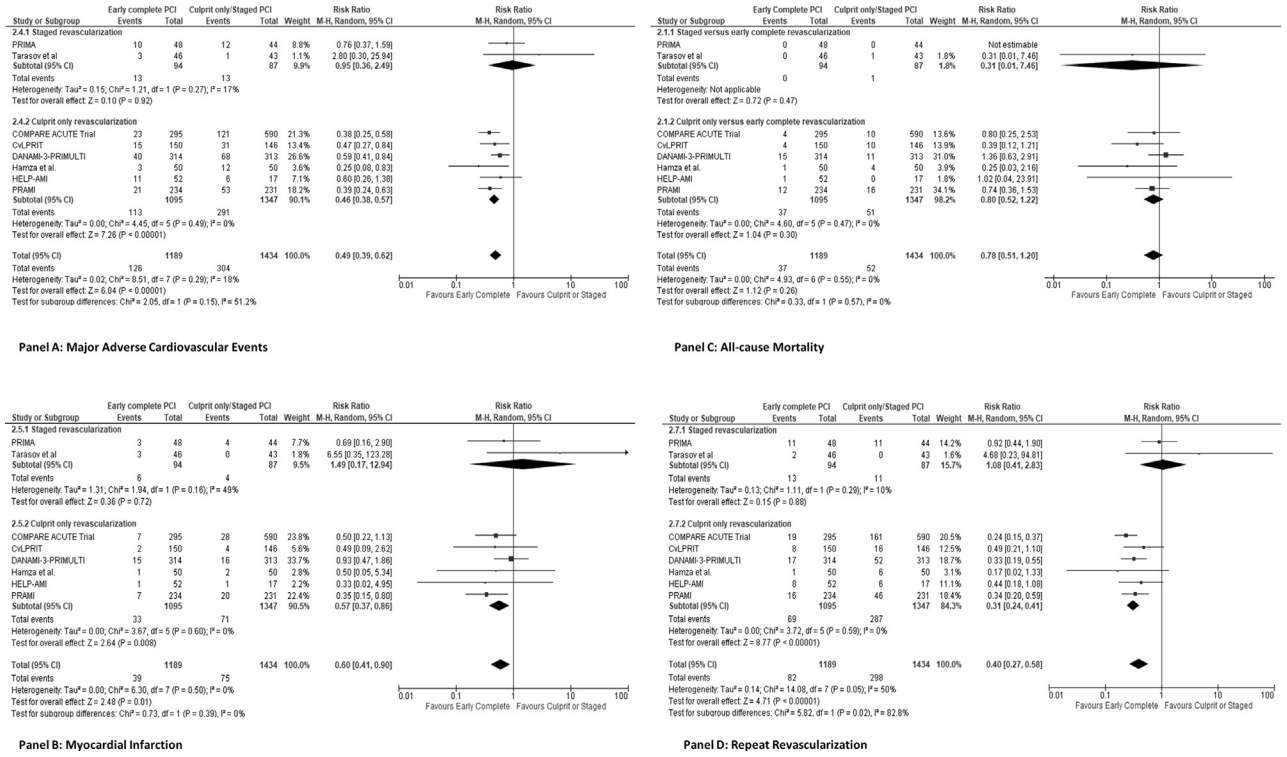


Figure 2. Efficacy end points; subgroup analysis on the efficacy end points according to the type of "other revascularization strategy" (staged revascularization vs culprit-only PCI) compared with early complete revascularization. The diamond indicates the point estimate, and the left and right end of the line indicate the 95% confidence interval. (**A**) Major adverse cardiovascular events; (**B**) myocardial infarction; (**C**) all-cause mortality; and (**D**) repeat revascularizartion. PCI, percutaneous coronary intervention.

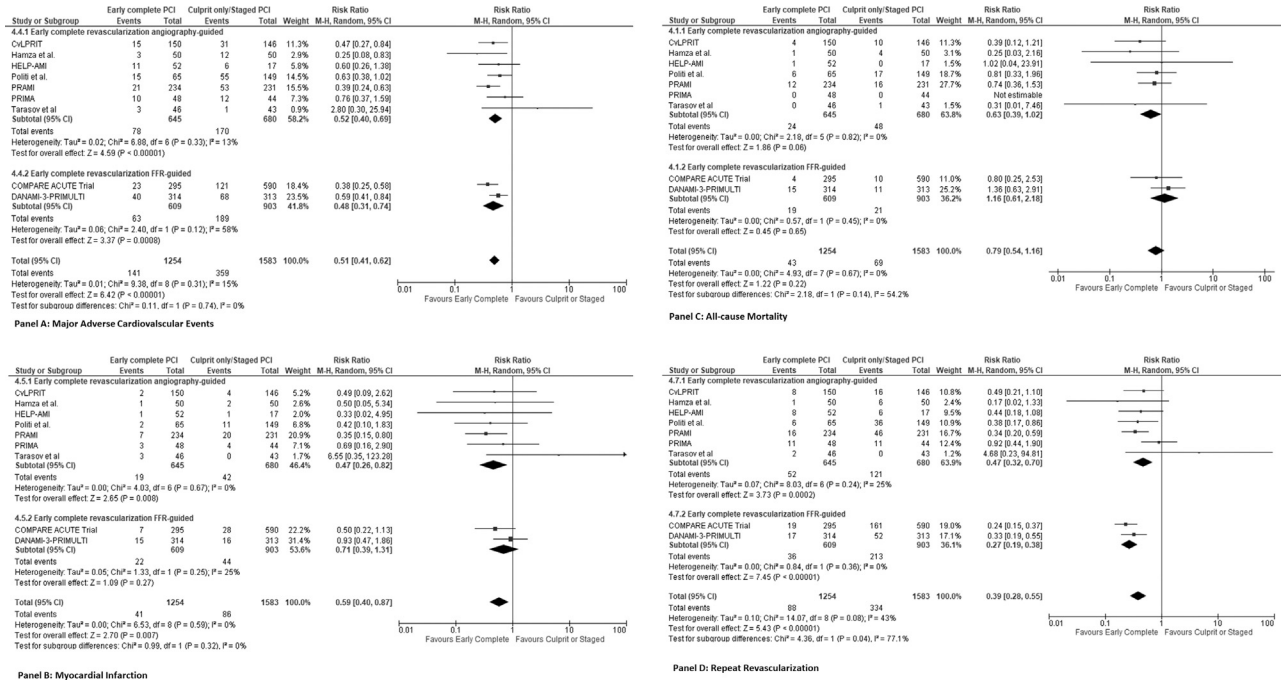


Figure 3. Efficacy end points; subgroup analysis on the efficacy end points according to the type of early complete revascularization (angiography-guided vs FFR-guided). The diamond indicates the point estimate, and the left and right end of the line indicate the 95% confidence interval. FFR, fractional flow reserve.

(1431 received culprit-only PCI and 152 staged complete revascularization; Supplemental Table S1). Among the patients who received early complete revascularization, in 39% of the cases complete revascularization was mandatory during the index procedure whereas in the remaining 61% the interventional cardiologist could decide between performing it during the same procedure or in a staged manner during the same hospitalization and within 72 hours. Early complete revascularization was angiography-guided in 51% of the cases whereas in the remaining 49% it was FFR-guided. Mean follow-up was 15.3 ± 9.4 months.

Table 2 shows the baseline characteristics for each study. The average age of patients was heterogeneous among trials (ranging from 54.3[7] to 65.9[21] years; median, 63.5 years); 78.5% were men; 61.7% were treated with DES, 31.3% had 3-vessel coronary disease, 36.8% had an anterior MI, 19.2% were diabetic, 36.5% had dyslipidemia and mean left ventricular ejection fraction ranged from 43.4%[20] to 51.5%.[22] Overall, participants who received an early complete revascularization and culprit-only or staged revascularization had similar baseline characteristics (Supplemental Table S1).

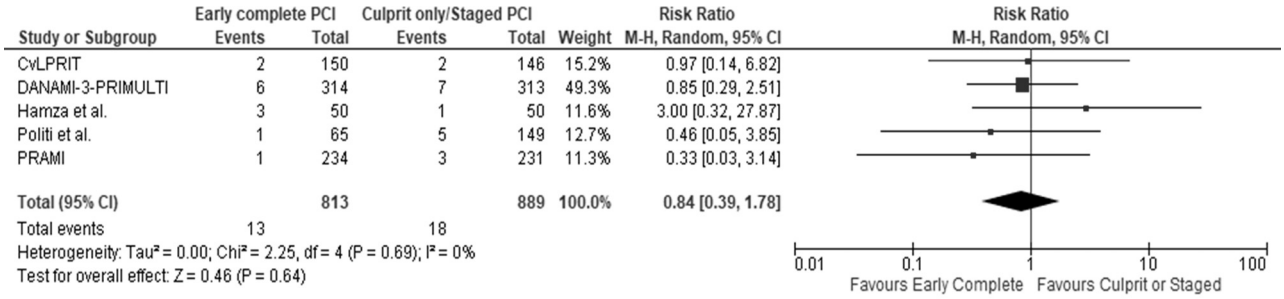
Efficacy end points

Figure 1A shows the comparative efficacy of early complete revascularization vs culprit-only or staged revascularization in preventing MACE. After a mean follow-up of 15.3 months, 500 MACE were recorded: 141 in 1254 patients treated with an early complete revascularization strategy (11.2%) and 359 in 1583 patients treated with culprit-only or staged revascularization (22.7%). Early complete revascularization was therefore associated with a lower risk of MACE compared with the other revascularization strategies (RR, 0.51; 95% CI, 0.41-0.62; $P < 0.00001$; Figure 1A) with a NNT of 8 and an ARR of 12%. Specifically, early complete revascularization reduced the risk of nonfatal MI (RR, 0.59; 95% CI, 0.40-0.87; $P = 0.007$; NNT = 45; Figure 1B) and repeat revascularization (RR, 0.39; 95% CI, 0.28-0.55; $P < 0.00001$; NNT = 7; Figure 1D) compared with the other revascularization strategies, whereas no significant difference was found in all-cause mortality (RR, 0.79; 95% CI, 0.54-1.16; $P = 0.22$; Figure 1C).

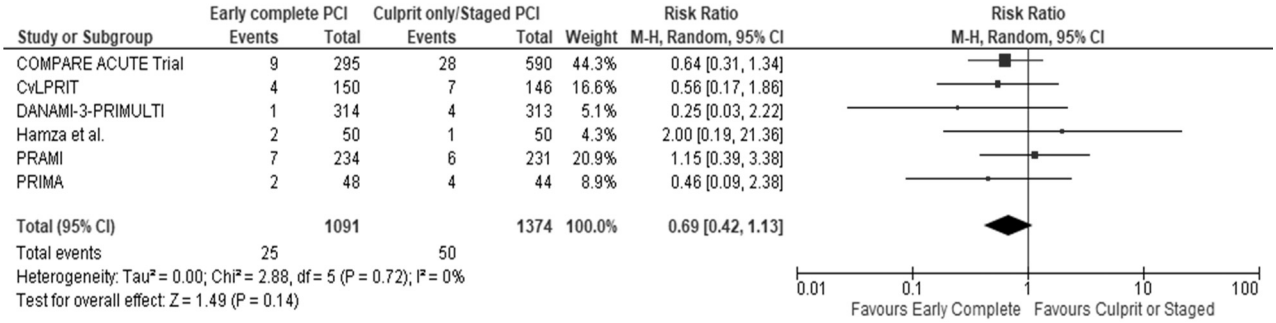
In the subgroup analyses, the superiority of early complete revascularization was consistent regardless of the type of revascularization strategy considered as comparator (culprit-only or staged revascularization) except for repeat revascularization, for which early complete revascularization was equivalent to staged revascularization (test for subgroup difference, $\chi^2 = 5.82$; $P = 0.02$; Fig. 2D). As shown in Supplemental Figure S2, the efficacy end points were consistent independently from the actual timing of early complete revascularization (mandatory during the same procedure vs the possibility to perform a staged procedure within 72 hours). On the contrary, early complete FFR-guided revascularization was superior to angiography-guided procedure in preventing further revascularizations (test for subgroup difference, $\chi^2 = 4.36$; $P = 0.04$; Figure 3D) whereas there was no difference in the other efficacy outcomes between the 2 strategies.

Safety end points

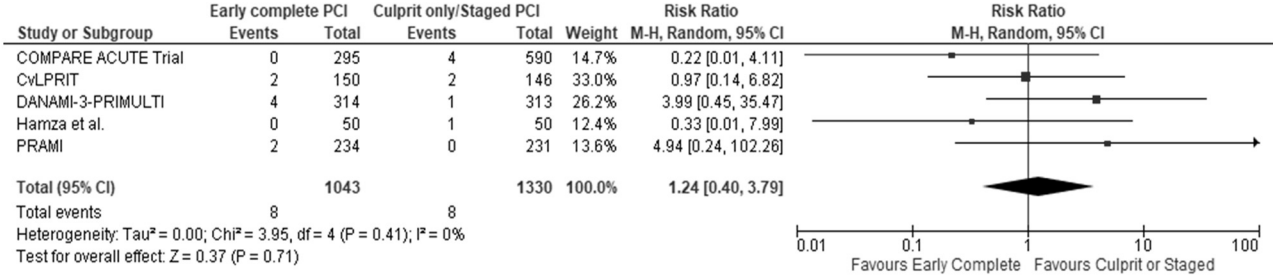
There was no difference in the safety end points between early complete vs culprit-only or staged revascularization. As shown in Figure 4, early complete revascularization did not increase the risk of CI-AKI (RR, 0.84; 95% CI, 0.39-1.78; $P = 0.64$), the risk of any bleeding event (RR, 0.69; 95%



Panel A: Contrast Induced Acute Kidney Injury



Panel B: All bleeding events



Panel C: Stroke

Figure 4. Safety end points. Forest plot reporting the relative risks with 95% confidence interval of contrast-induced acute kidney injury (**A**), all bleeding events (**B**), and stroke (**C**) in hemodynamically stable patients with acute coronary syndrome treated with early complete revascularization vs culprit-only or staged revascularization. The diamond indicates the point estimate, and the left and right end of the line indicate the 95% confidence interval.

CI, 0.42-1.13; $P = 0.14$), or the risk of stroke (RR, 1.24; 95% CI, 0.40-3.79; $P = 0.71$). As illustrated in Supplemental Figures S3-S5, these results were consistent regardless of the type of revascularization strategy considered as comparator (culprit-only or staged revascularization), and the type (angiography or FFR-guided), and the timing (during pPCI or within 72 hours) of early complete revascularization.

Metaregression

Among the patient and procedural characteristics taken into consideration, 4 factors had a significant moderator effect on the outcomes considered (Table 3). As illustrated in Figure 5, year of publication was associated with a significant decreasing trend in repeat revascularization (regression coefficient, −0.073; 95% CI, 0.125-0.020; $P = 0.007$). Aging was associated with an increased risk of repeat revascularization (regression coefficient, 0.155; 95% CI, 0.030-0.279; $P = 0.015$). The presence of dyslipidemia was related to an increased incidence of repeat revascularization (regression coefficient, 1.969; 95% CI, 0.504-3.433; $P = 0.008$). Finally, the use of a DES was associated with a decreased incidence of repeat revascularization (regression coefficient, 0.722; 95% CI, −1.323 to −0.121; $P = 0.019$).

Table 3. Meta-regression

Variable	Revascularization	MI	MACE	Stroke	CI-AKI	All-cause death	All bleeding events
Year of publication	0.007	0.743	0.106	0.576	0.284	0.902	0.853
Age	0.015	0.885	0.055	0.445	0.295	0.452	0.259
Male sex	0.254	0.652	0.709	0.158	0.145	0.742	0.888
Hypertension	0.204	0.158	0.053	0.441	0.360	0.701	0.425
Diabetes	0.638	0.742	0.551	0.657	0.286	0.235	0.387
Dyslipidemia	0.008	0.699	0.162	0.987	0.433	0.821	0.843
Smoker	0.398	0.903	0.879	0.667	0.864	0.581	0.376
Ejection fraction	0.096	0.246	0.867	0.413	0.907	0.152	0.755
Three-vessel disease	0.400	0.953	0.793	0.841	0.366	0.196	0.837
Drug-eluting stent	0.019	0.450	0.154	0.235	0.462	0.943	0.894
Previous PCI	0.193	0.860	0.183	0.977	0.284	0.423	0.800
Anterior MI	0.072	0.976	0.237	0.714	0.295	0.678	0.923
Renal impairment	0.501	0.834	0.166	—	—	0.539	—

P values for interaction are shown.
CI-AKI, contrast-induced acute kidney injury; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Influence analyses

As shown in Figure 6 the RR remained stable in the leave-one-out analyses on MACE, all-cause mortality, and repeat revascularization. In comparison, the results on nonfatal MI became marginally nonsignificant after removing PRAMI (**Pr**eventive **A**ngioplasty in Acute **M**yocardial **I**nfarction)[20] (RR, 0.68; 95% CI, 0.440-1.045; Fig. 6B) and the superiority of early complete revascularization in preventing nonfatal MI compared with the other revascularization strategy was more evident after removing DANAMI-3-PRIMULTI (Third **Dan**ish Study of Optimal **A**cute Treatment of Patients With STE**MI**: **Pri**mary PCI in **Multi**vessel Disease)[6] (RR, 0.477; 95% CI, 0.300-0.759).

Risk of bias assessment

All studies were randomized; 5 studies used an electronic device to allocate participants into the intervention groups,[5,6,8,19,20] whereas the remaining studies did not describe how the allocation sequence was generated.[7,18,21,22] Several trials were either at high risk for performance bias[5,6,20,22] or blinding of personnel and participants was not mentioned in the article. For the studies that did not report the number of withdrawals the attrition bias was considered unclear,[18,19,21,22] otherwise the number of dropouts per group was similar and trials were considered at low risk. For trials that were not registered in any clinical trial database or did not have a published protocol the reporting bias was assessed as high,[7,18,19,21] whereas most of the studies were at low risk for selective reporting (Supplemental Table S3).

Visual inspection of funnel plots and Egger regression tests showed no evidence of publication bias for the efficacy and safety outcomes (Supplemental Fig. S6).

Discussion

Our findings

In the current analysis including 9 RCTs on hemodynamically stable patients with STEMI we found a 12% ARR

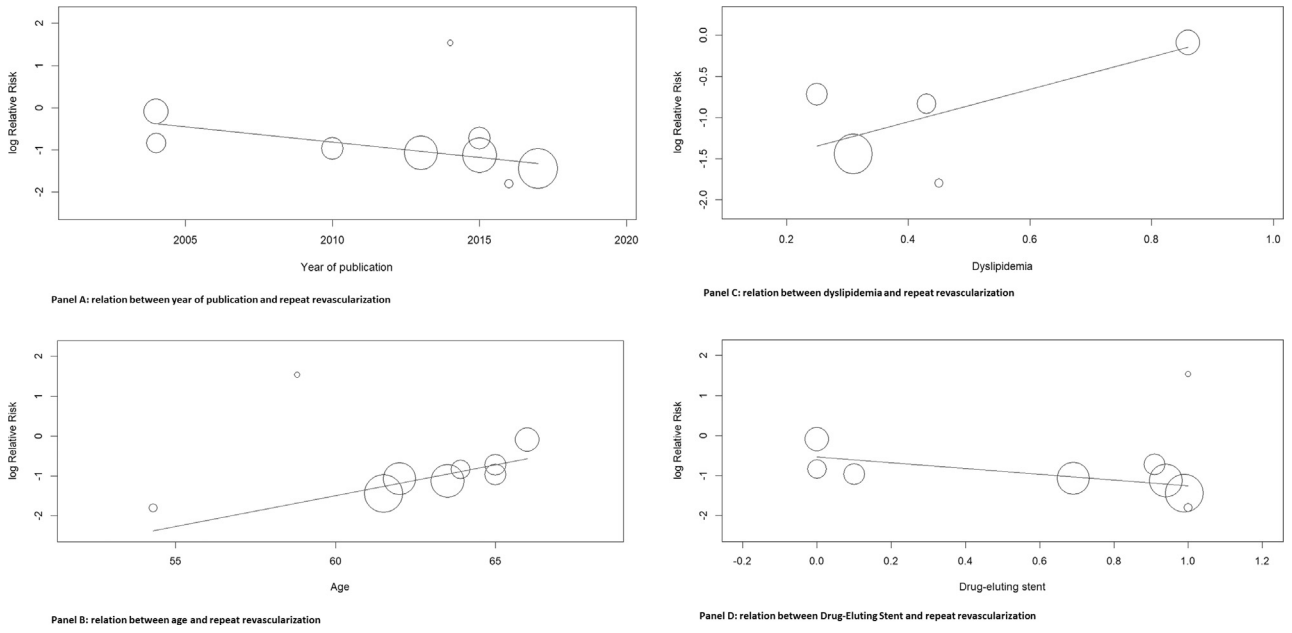


Figure 5. Univariate metaregression for unadjusted log relative risk showing the moderator effect of year of publication (**A**), age (**B**), dyslipidemia (**C**), and use of drug-eluting stent (**D**) on repeat revascularization.

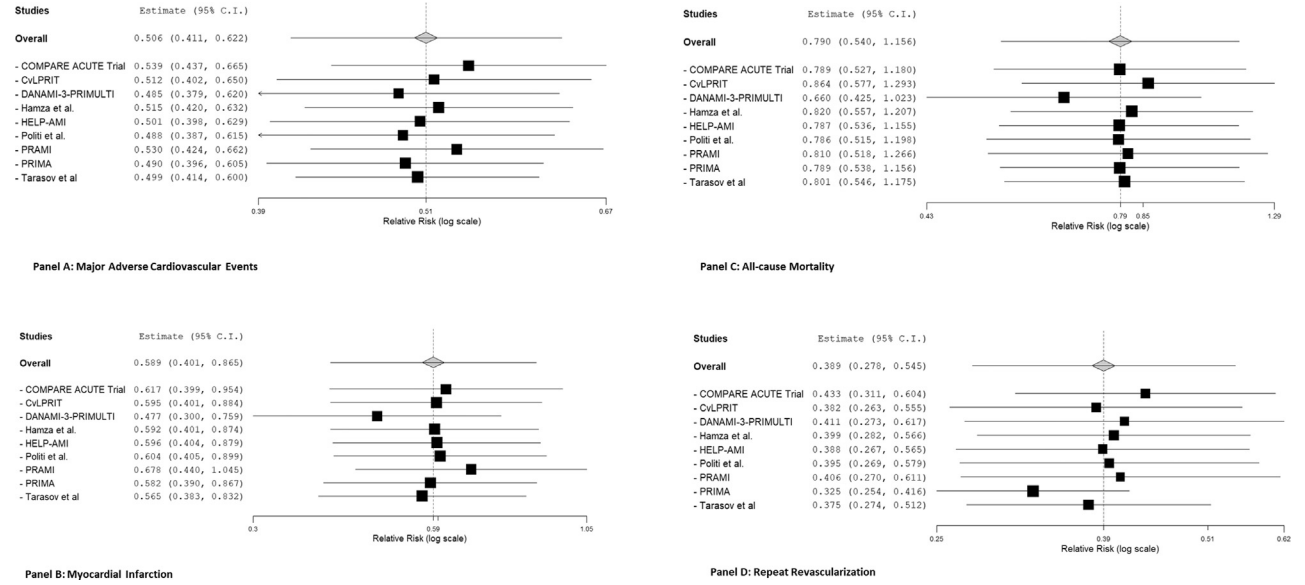


Figure 6. Leave one out analysis on efficacy outcomes. Forest plot reporting the relative risks (RR) with 95% confidence interval (CI) of the leave one out analysis on major adverse cardiovascular events (**A**), myocardial infarction (**B**), all-cause mortality (**C**), and repeat revascularization (**D**). The first column of every panel shows the omitted study. The horizontal axis of the graph illustrate the RR. Every diamond indicates the pooled RR when the left study is omitted in this meta-analysis. The 2 ends of every broken line represent the respective 95% CI.

of MACE in the early complete revascularization compared with the culprit-only or staged revascularization arm; in comparison, we found no difference in the safety end points between the groups. In particular, early complete revascularization was associated with 14.1% ARR of repeat revascularization and 2.2% ARR in MI. In addition, FFR-guided early complete revascularization was superior to the angiography-guided procedure in reducing repeat revascularization, supporting the functional vs the anatomical approach to guide revascularization in the setting of pPCI. Importantly, in the COMPARE ACUTE (**Compa**rison Between FFR Guided **Re**vascularization Versus Conventional Strategy in **Acute** STEMI Patients With MVD) trial[8] 83.4% of FFR-guided procedure were performed during the index PCI, which highlights the safety and efficacy profile of adenosine-induced hyperemia during pPCI, however, novel nonhyperemic indexes such as the instantaneous wave-free ratio might overcome this potential barrier also in hemodynamically unstable patients, expanding deliverability the in acute setting.

The reduction in repeat revascularization is probably influenced by the fact that most of the RCTs were not blinded and the knowledge that patients treated with a culprit-only strategy have significant coronary stenosis left untreated might by itself trigger indication for new revascularizations. However, early complete revascularization reduced also the incidence of the hard individual component of MACE such as nonfatal MI, and this highlights the robustness and clinical importance of our results. Moreover, the knowledge that in patients with STEMI the risk for adverse events (such as MI recurrence) is higher in the first days and weeks and then decreases after the first month,[23] is in agreement with the suggestion to proceed with an early complete treatment of significant nonculprit lesions during pPCI or within 72 hours.

Our results should be interpreted in light of the inclusion criteria of the RCTs that we considered (Supplemental Table S2). All RCTs included only hemodynamically stable patients and specifically excluded patients in cardiogenic shock. Moreover, patients with high-risk features such as left main disease or who required complex PCI such as chronic total occlusion (CTO) revascularization were specifically excluded from all RCTs. In addition, frail patients who are notably more at risk to develop complications (such as CI-AKI) are usually excluded from RCTs and for them an accurate monitoring of clinical and laboratory parameters after pPCI might be indicated, and a staged procedure, potentially within 72 hours, might be advisable.

The meta-regression interestingly illustrated a significant trend toward a decreased need for further revascularization according to the year of trial publication and the use of DESs. This might overall reflect an increased control of cardiovascular risk factors thanks to lifestyle improvement and medical therapy, and it might be related to the several advancements in interventional cardiology regarding materials (ie, DESs) and techniques throughout the years. Furthermore, it illustrated an increased risk of repeat revascularization with aging and with the increase in the prevalence of dyslipidemia. Aging can be a marker of comorbidities and multiple ischemic and thrombotic risk factors that might increase the need for further revascularization.[24] The data about dyslipidemia might emphasize the importance of medical therapy, and in particular of lipid-lowering agents after an acute coronary syndrome to prevent coronary atherosclerotic plaque progression and, thus, the need for further revascularization.[25]

Although our study was not sufficiently powered to detect a difference in safety end points, there was no apparent difference in CI-AKI, stroke, and all bleeding events; the latter being, albeit in a marginally nonsignificant manner, rather less frequent in the early complete revascularization arm than in staged or culprit-only revascularization.

Previous meta-analyses

Some analyses tried to address the issue regarding the optimal revascularization strategy in patients with STEMI.[26-31] Differently from our analysis, they were all focused on the outcome differences between complete (including early complete or staged, but, at any time) and culprit-only revascularization, none of them specifically focused on the timing and the test to achieve complete revascularization and had some limitations. The first meta-analysis, published in 2015,[26] included only 5 studies with a total of 1165 patients; the second[27] included RCTs and observational studies, most of which were retrospective. The most recent analyses[28-31] all included studies that are not yet published as full-length articles in international peer-reviewed journals published in the English language.[32-34] Moreover, Hideo-Kajita et al.[31] included also a retrospective study in their analysis[35]; and Bajraktari et al.[30] included an RCT about revascularization of CTO after STEMI,[36] which are usually complex procedures and patients with CTO were specifically excluded from all of the other RCTs on the topic.

The present meta-analysis has further strength points, besides the inclusion of the latest available evidence on the topic: (1) the inclusion only of randomized data and the rigourous assessment of study quality; and (2) the subgroup analyses to assess the best timing and guiding (angiography-guided vs FFR-guided) of early complete revascularization.

Limitations

We must acknowledge some limitations. First, baseline characteristics were heterogeneous among the studies. A meta-regression on the efficacy and safety outcomes was performed to explore the potential moderator effect of the available patients and procedural features. However, only dyslipidemia, year of publication, aging, and use of DESs resulted to have a significant moderator effect on repeat revascularization. Second, there was a difference in the definition of MACE between RCTs (Table 1). However, we analyzed also individual components of MACE and it was found that repeat revascularization was the factor that mainly drove the observed outcome difference. Moreover, also repeat revascularization and bleeding events were defined in a heterogeneous way among the studies (Table 1). To overcome this issue, we decided to consider any of these events (ie, any bleeding events and any myocardial revascularization).

The definition of significant coronary stenosis was different across the RCTs. However, to better understand the influence of the various studies on the efficacy outcomes we performed a leave-one-out analysis that showed consistent results for most of the end points.

Finally, although we collected all of the available evidence to properly assess this issue, our study was not adequately powered to detect a difference in all-cause mortality and safety outcomes between the 2 groups. Ongoing, larger RCTs have the same aim of our analysis and they will provide additional data to better explore this debate. In particular, the COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial[37] will compare complete early staged with culprit-only revascularization, whereas, the FULL REVASC (**F**FR-G**u**idance for Comp**l**ete Non-Cu**l**prit **Revasc**ularization) trial[38] will compare immediate complete vs staged FFR-guided PCI.

Conclusions

Early complete revascularization reduces the incidence of MACE, nonfatal MI, and repeat revascularization without any apparent risk compared with culprit-only or staged revascularization, therefore, it should be considered in hemodynamically stable patients with STEMI and multivessel disease deemed suitable for percutaneous interventions. Moreover, FFR-guided complete revascularization might be preferred over an angiography-guided procedure because it might reduce the need for further interventions

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.03.006.