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Complete versus culprit-vessel only revascularization in STEMI: An updated meta-analysis of randomized control trials

1. Introduction

Around 50% of patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) have a multi-vessel disease [1]. Current options available for management of these "non-culprit" major epicardial vessels are (1) conservative management (2) complete revascularization of all major epicardial vessels during primary PCI (3) complete revascularization of all major epicardial vessels as a staged procedure during index hospitalization (4) complete revascularization of all major epicardial vessels as a staged procedure after discharge. Observational studies suggested an increased risk of adverse events with revascularization of the non-culprit vessels [2]. This was challenged by several randomized control trials (RCTs) and *meta*-analysis [3–5]. The recently published COMPLETE trial [6,7] is the largest among these trials and suggested significantly decreased risk of the composite outcome of cardiovascular (CV) mortality or myocardial infarction with no difference in safety outcomes. In light of this evidence, we performed an updated *meta*-analysis to evaluate the benefit of CV risk reduction in patients with multi-vessel disease undergoing PCI for STEMI.

2. Methods

We searched PubMed/MEDLINE®, Embase®, ClinicalTrials.gov and Cochrane CENTRAL for RCTs comparing revascularization strategies in patients with STEMI and multivessel disease from inception till November 31, 2019, using similar search terms as reported in a previous *meta*-analysis [5]. There were restrictions based on the language of publication or follow-up duration. If multiple publications were done for the same trial, the longest follow-up was included for the current analysis. Bias assessment was done using the Cochrane RoB 2.0 tool for trials comparing complete with incomplete revascularization. Early complete revascularization was defined as PCI of the non-culprit vessel either during index PCI or before hospital discharge. Delayed complete revascularization was defined as PCI of the non-culprit vessel after hospital discharge. The primary efficacy endpoint in this analysis was defined as a major adverse cardiovascular event (MACE) -a composite of all-cause mortality, revascularization, and re-infarction. The primary safety endpoint was defined as the composite of stent thrombosis, major bleeding, and stroke. CV-mortality and contrast-induced nephropathy were the other outcomes evaluated. Random effect *meta*-analysis was used to estimate the risk ratio (RR) and 95% confidence interval (CI) for complete revascularization over culprit-vessel only revascularization for each outcome. Only trials reporting all 3 components of MACE and safety events were considered for the analysis. Data were analyzed for heterogeneity using the I^2 statistic proposed by Higgins and Thompson [8]; 95% CI around the I^2 statistic was also estimated. Subgroup analyses were done to compare risk differences between early and delayed revascularization strategy for trials reporting these results. The pooled number needed to treat (NNT) to cause one MACE and number needed to harm (NNH) to cause one safety event was calculated using *meta*-analysis of risk differences. All analyses were performed using the STATA V15.0 (College Station, TX, USA) statistical software.

3. Results

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (e-component PRISMA Checklist). Our systematic search yielded 12 RCTs that met our inclusion criteria (e-component Fig. 1). These RCTs were published from 2004 to 2019 and sample size varied from 69 to 4,041. Trial follow-up varied from 6 to 36 months. The mean age in these studies varied from 52 to 73 years. The left anterior descending artery was the most common culprit-artery. No RCT enrolled patients with cardiogenic shock. The mean time to delayed revascularization varied from 9 to 57 days. Participant characteristics are given in Table 1. The risk of bias was deemed to be acceptable (e-component Figs. 2 and 3)

3.1. Complete revascularization vs. culprit-vessel only revascularization

Outcomes to compute MACE were provided in 9 RCTs (e-component Table). The overall risk of MACE was reduced by 49% with complete revascularization as compared to culprit-vessel only revascularization (12.6% vs. 23.0%, RR 0.51, 95% CI 0.42, 0.61, $p < 0.001$) (Fig. 1 Panel A). There was directional consistency in MACE reduction with complete revascularization with moderate heterogeneity across studies. Fractional flow reserve (FFR) was used to guide the PCI of non-culprit vessels in 4 studies. There was similar risk reduction irrespective of FFR (12.0% vs. 21.1%, RR 0.58, 95% CI 0.44, 0.76, $p < 0.001$ with FFR and 15.1% vs. 33.7%, RR 0.42, 95% CI 0.34, 0.53, $p < 0.001$ without FFR) (e-component Table).

The decreased risk of MACE was driven by a lower risk of revascularization (4.2% vs. 12.3%, RR 0.37, 95% CI 0.25, 0.55, $p < 0.001$) and reinfarction (5.0% vs. 6.8%, RR 0.69, 95% CI 0.50, 0.95, $p = 0.022$) (Fig. 1 Panel A). Though there was directional consistency in the reduction of revascularization, there was substantial

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Table 1
Baseline characteristics of the included randomized control trials.

Study	Year	Mean Age (Years)	Subjects (n)	Women (%)	HTN (%)	DM (%)	Dyslipidemia (%)	Smoking (%)	Previous MI (%)	Anterior Infarction (%)	2-vessel disease (%)	3-vessel disease (%)	F/U (months)
HELP-AMI/ di Mario *et al.* [15]	2004	64/65	52/17	12/18	37/59	12/41	42/53	67/82	NR	52/59	69/53	31/47	12
PRIMA/Ochala *et al.* [16]	2004	65/67	48/44	27/25	52/48	31/34	81/91	38/43	29/23	46/45	NA	NA	6
Ghani *et al.* [17]*	2010	62/61	80/41	20/20	3/41	6/5	15/29	44/46	6/5	NA	75/80	25/20	6
Politi *et al.* [18]	2010	66/64	75/65	24/20	55/65	20/18	NA	NA	NA	45/58	NR	27/45	36
PRAMI/Wald *et al.* [4]	2013	62/62	234/231	24/19	40/40	15/21	NA	50/45	8/7	29/39	61/67	39/33	23
Tarasov *et al.* [19]	2014	59/59	46/43	30/42	96/86	26/21	NA	NA	11/5	NR	NR	43/47	6
CvLPRIT/Gershlick *et al.* [20]	2015	65/65	150/146	15/23	36/35	13/14	27/23	33/25	5/3	36/36	79/75	21/25	12
DANAMI-PRIMULTI/ Engstrom *et al.* [21]*	2015	64/64	314/313	20/28	41/47	9/13	NA	51/48	5/9	33/36	NA	NA	6
PRAGUE 13/ Hlinomaz *et al.* [22]	2015	NA	106/108	NA	NA	NA	NA	NA	NA	NA	NA	NA	38
Hamza *et al.* [23]	2016	50/52	50/50	18/14	26/36	100/100	48/42	72/78	10/6	48/46	72/66	28/34	20.5
COMPARE-Acute/ Smits *et al.* [3]*	2017	62/61	295/590	21/24	46/31	15/16	32/30	41/48	7/8	36/35	69/67	31/33	12
COMPLETE/Mehta *et al.* [6,7]*	2019	62/62	2016/2025	19/21	49/51	19/20	38/39	39/40	7/8	33/33	72/74	23/22	36

Percentage is given as (complete revascularization/ culprit-vessel only revascularization); COMPLETE, Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early Percutaneous Coronary Intervention [PCI] for STEMI; CvLPRIT, Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease; DANAMI3-PRIMULTI, The Third DANish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction PRImary PCI in MULTIvessel Disease; HELP-AMI, HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; MI, myocardial infarction; PRAMI, Randomized Trial of Preventive Angioplasty in Myocardial Infarction; PRIMA, Primary Percutaneous Intervention For Acute Myocardial Infarction; NA: Not Available; HTN: Hypertension; DM, Diabetes Mellitus; MI, Myocardial Infarction; F/U, Follow-up.

* Used FFR-guided PCI for non-culprit vessel revascularization.

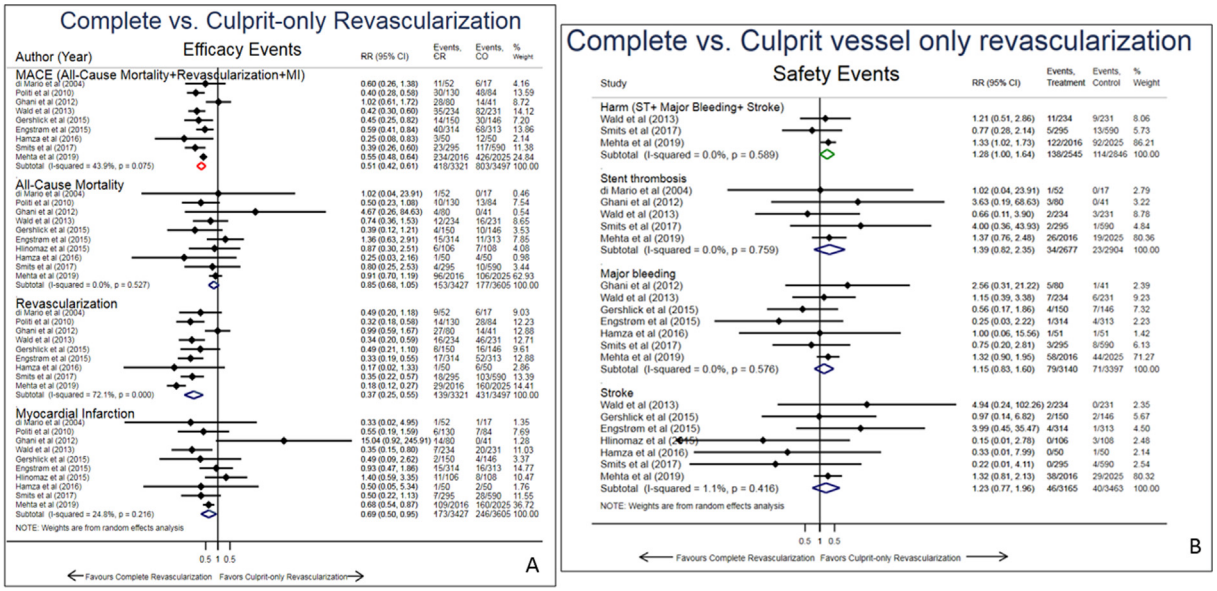

Fig. 1. Panel A: Forest Plot comparing efficacy [major adverse cardiovascular events) in complete revascutarizatlon with culprit-artery onfy revascularization. Black solid diamonds markers and associated solid lines represent the summary risk ratio (RR) and 95% confidence interval (CI) of each trial listed in the left column. The numerical estimates in the right columns are RRs with 95% *C*| and number of events and denominators of each trial listed in the left column. The hollow red diamond is summary RRand 95% CI for MACE. The hollow blue diamond is summary RR for components of major adverse cardiovascular events. Panel B: Forest Plot comparing safety events in complete revascularization with culprit-artery only revascularization. Black solid diamonds markers and associated solid lines represent the summary risk ratio (RR) and 95% confidence interval (CI) of each trial listed in the left column. The numerical estimates in the right columns are RRs with 95% CI and number of events and denominators of each trial listed in the left column. The hollow green diamond is summary RR and 95% CI for safety events. The hollow blue diamond is summary RRfor components of safety events.

heterogeneity across studies. Although risk of all-cause mortality did not decrease, a significant decrease in CV mortality (2.5% vs. 3.1%, RR 0.71, 95% CI 0.51, 1.00, p = 0.047) was seen with complete revascularization in 7 trials with 6,597 patients reporting the CV mortality (e-component Table). NNT to prevent one MACE event and NNH to cause one safety event were 9 and 71, respectively.

Outcomes for harm were reported in 3 RCTs (Fig. 1 Panel B). There was a 28% increased risk of harm (5.4% vs. 4.0%, RR 1.28, 95% CI 1.00, 1.64, p = 0.048) with complete revascularization. There was no difference in the individual components of harm or contrast-induced nephropathy between the 2 strategies (e-component Table).

3.2. Early complete revascularization vs. culprit-vessel only revascularization

The risk of MACE was reduced by 50% (12.0% vs. 23.2%, RR 0.50, 95% CI 0.41, 0.60, p < 0.001) in 9 RCTs with early complete revascularization (e-component Table). This was driven by a reduced risk of revascularization and reinfarction with no difference in all-cause or CV mortality.

There was a 39% higher risk of harm with early complete revascularization (5.4% vs. 3.6%, RR 1.39, 95% CI 1.04, 1.87, p = 0.027) (e-component Table). There was no difference in the individual components of harm between the 2 strategies.

3.3. Delayed complete revascularization vs. culprit-vessel only revascularization

The risk of MACE in 2 RCTs was significantly lower with delayed revascularization (14.6% vs. 25.9%, RR 0.55, 95% CI 0.39, 0.76, p < 0.001), which was driven by a lower risk of revascularization with no difference in other outcomes (e-component Table). There was no difference in safety events.

3.4. Early vs. Delayed complete revascularization

Four RCTs compared early vs. delayed revascularization strategy. The risk of MACE was similar (11.3% vs. 14.3% for early and delayed revascularization, respectively, RR 0.82, 95% CI 0.66, 1.01, p = 0.067) (e-component Table). The power of this analysis to detect a significant difference in MACE or safety events was 60% and 9% respectively. We estimate that a future *meta*-analysis with 3,892 and 35,740 patients for MACE and safety events, respectively is required to detect the observed effect estimates at 80% power, and 5% significance.

4. Discussion

In this updated *meta*-analysis of RCTs comparing revascularization strategies in patients with STEMI, we found that complete revascularization resulted in a lower risk of MACE. The lower risk was driven by decreased revascularization and reinfarction. Absolute rates of safety outcomes were low in general for complete revascularization strategies, however, there was an expected slightly higher risk of harm. There were no differences in individual components of major bleeding, stroke or stent thrombosis. We estimate for every 72 patients treated with complete revascularization we would expect to prevent 8 MACE while causing 1 safety event as compared to culprit-vessel only revascularization. There was similar risk reduction irrespective of early or delayed revascularization.

Current ESC guidelines give Class IIa recommendation (should be considered) before hospital discharge [1]. The guideline statement is not specific about the exact timing of revascularization (during primary PCI vs. staged) given the lack of high-quality data. In light of current trials, we believe there is a signal towards more benefit than harm with complete revascularization but the timing still remains unclear and is dependent on patient profile and physician expertise.

Around 50% of patients with STEMI have a multivessel disease [1]. Literature from observational studies [9,10] suggested a higher risk of short-term mortality with complete revascularization. There is a theoretical risk of intra-operative and peri-operative complications like major bleeding due to a higher anticoagulant use, stent thrombosis due to prothrombotic state, and stroke due to the manipulation of atherosclerotic vessels [11]. Conversely, complete revascularization helps salvage remote myocardium in non-culprit vessel territory and restore optimal systolic function while reducing the need for repeat procedures [11].

A previous *meta*-analysis by Elgendy *et al.* [5] used trial-defined MACE as the primary outcome and reported a significant reduction with complete revascularization, driven by reduced revascularizations only. Our previous *meta*-analysis [12] comparing complete versus culprit artery revascularization suggested reduced MACE (defined as a composite of all-cause mortality, revascularization, and myocardial infarction), which were driven by reduced revascularization only. Compare-Acute [3] and COMPLETE trial [6] have been subsequently published and have more than doubled the patient population being studied. Our updated *meta*-analysis, which has higher precision, suggests that reduced MACE with complete revascularization is driven by a reduction in revascularization as well as reinfarction. In addition, there is a significant reduction in CV mortality. As reported previously [12], there is no difference if revascularization is performed during index hospitalization (early) or after discharge (delayed). FFR as a strategy to guide revascularization of non-culprit vessels was similar to a non-FFR guide strategy in MACE risk reduction.

Currently, hospitalization for the management of MI is one of the most expensive diagnoses [13]. 45% of this cost is related to catheterization laboratory and 79% procedures are for a single vessel [14]. One-year follow-up costs in patients discharged after MI include $4,776 for angioplasty without stent placement and $3,083 for bare-metal stent placement [14]. Complete revascularization before hospital discharge has the potential to reduce the cost of repeat hospitalization and angioplasty. The current *meta*-analysis is underpowered to estimate the risk difference between early or delayed revascularization. A longer follow-up of the current RCTs and future trials like FULL REVASC (NCT02862119) will help clarify the risk and benefits.

Our *meta*-analysis has several limitations. The trials varied in terms of patient demographics, inclusion and exclusion criteria, procedural details, adjunct medical management, and duration of follow-up. This may have contributed to the heterogeneity in the reported reduction in MACE. The lower risk of MACE in recent trials in both arms could be due to better adjunct medical management. The risk and benefits of complete revascularization also vary according to previous procedures like PCI or coronary artery bypass grafting, co-morbidities like diabetes mellitus and coronary anatomy- bifurcation lesions and chronic total occlusion.

5. Conclusion

In patients with STEMI and multivessel disease undergoing PCI, complete revascularization, either during the index hospitalization or staged after discharge results in a significant reduction in MACE, driven by reduced revascularization and myocardial infarction. There was no difference in risk of mortality, stent thrombosis, major bleeding or stroke.

Declaration of Competing Interest

The authors report no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100481.

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