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Review

Intravascular ultrasound-guided versus coronary angiography-guided percutaneous coronary intervention in patients with acute myocardial infarction: A systematic review and meta-analysis

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ABSTRACT

Background: Intravascular ultrasound (IVUS) can overcome the intrinsic limitations of coronary angiography for lesion assessment and stenting. IVUS improves outcomes of patients presenting with stable or complex coronary artery disease, but dedicated data on the impact of IVUS-guided percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) remains scarce.

Methods: We systematically searched Embase, MEDLINE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials and Google Scholar for studies that compared clinical outcomes for IVUS- versus angio-guided PCI in patients with AMI. The primary endpoint was all-cause mortality and the secondary endpoint major adverse cardiovascular events (MACE). Mantel-Haenszel random-effects model was used to calculate pooled risk ratios (RR) with 95% confidence intervals (CI).

Results: Nine studies (8 observational, 1 RCT) with a total of 838.902 patients (796.953 angio-guided PCI, 41.949 IVUS-guided PCI) were included. In patients with AMI, IVUS-guided PCI was associated with a significantly lower risk of all-cause mortality (pooled RR: 0.70; 95% CI, 0.59–0.82; $p < 0.01$), MACE (pooled RR: 0.86; 95% CI, 0.74–0.99; $p = 0.04$) and target vessel revascularization (TVR) (pooled RR: 0.83; 95% CI, 0.73–0.95; $p < 0.01$). In the subset of patients presenting with ST-segment elevation, IVUS-guided PCI remained associated with a reduced risk for both all-cause mortality (pooled RR: 0.79; 95% CI, 0.66–0.95, $p = 0.01$) and MACE (pooled RR: 0.86; 95% CI, 0.74–0.99, $p = 0.04$).

Conclusions: This is the first systematic review and meta-analysis comparing IVUS- versus angio-guided PCI in patients with AMI, showing a beneficial effect of IVUS-guided PCI on all-cause mortality, MACE and TVR. Results of ongoing dedicated prospective studies are needed to confirm these findings.

1. Introduction

espite its well-known limitations, coronary angiography remains the mainstream diagnostic modality to guide percutaneous coronary intervention (PCI). Coronary angiography is hampered by the inability to adequately assess lesion severity and visualize intracoronary plaque characteristics [1]. Moreover, key reasons for stent failure, including underexpansion, stenting-related complications (e.g. edge dissections) and geographic miss, often remain unrecognized by angiography alone [2,3].

Intravascular ultrasound (IVUS) is an intracoronary imaging technique that can overcome these limitations by allowing tailored lesion preparation, stent selection and stent optimization [3–6]. An increasing body of evidence, composed of both randomized and observational data, demonstrates that IVUS-guided PCI reduces major adverse cardiovascular events (MACE) and target vessel failure (TVF) as compared to

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angio-guided PCI in a broad spectrum of patients [7–11]. Nevertheless, patients with acute myocardial infarction (AMI) were vastly underrepresented in most studies. The latter is of particular interest given the fact that two dedicated studies comparing IVUS- versus angio-guided PCI in this subset of patients showed conflicting results for clinical outcomes [12,13]. The use of IVUS in the acute setting was linked to higher rates of spasm and dissection, and increased balloon dilatations that could hypothetically lead to higher rates of distal embolization [12,14].

Furthermore, it is unknown how the use of IVUS in patients with AMI impacts procedural characteristics, such as procedure time and contrast use.

As the role of IVUS-guided PCI in the setting of AMI remains unclear, we performed a systematic review and meta-analysis of studies comparing clinical outcomes between IVUS-guided and angio-guided PCI in patients with AMI.

2. Methods

The protocol of this systematic review and meta-analysis was registered in the PROSPERO international prospective register for systematic reviews (CRD42021252142). The study was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for searching and the 'PRISMA 2020 Checklist' was used (Supplementary Table 1) [15].

2.1. Data sources and search strategy

The systematic search strategy as performed by our hospital's medical library specialists was previously reported [16]. The following electronic databases were searched on May 5th, 2021: Embase, MEDLINE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials and Google Scholar. Key search terms included: "intravascular ultrasound" (and/or "intracoronary ultrasound") and "acute myocardial infarction" (and/or "acute heart infarction" and/or "ST(-segment) elevation myocardial infarction"). No language or publication date filters were applied. We searched for prospective and retrospective observational studies and randomized controlled trials (RCTs). A complete overview of the search strategy for each database is provided separately (Supplementary Table 2).

2.2. Study selection process

After removal of duplicates, two reviewers (FG and TN) independently screened all initial search records on title and abstract. Subsequently, independent full text evaluation for potentially eligible studies was performed. A study was included if the following entry criteria were met: 1) Comparison of clinical outcomes between IVUS-guided and angio-guided PCI in a study population with AMI, 2) Differentiation between IVUS-guided and optical coherence tomography (OCT)-guided PCI if both were compared to angio-guided PCI, 3) Full text availability and 4) No duplicate record (e.g. meeting abstract, studies with similar study populations). An AMI study population was defined as follows: all patients presented with myocardial infarction, including at least 50% of patients having ST-segment elevation myocardial infarction (STEMI) or undergoing primary PCI.

Disagreements were resolved in a consensus meeting, including the opinion of a third reviewer (JD).

2.3. Outcome measures

The primary endpoint was all-cause mortality and the secondary endpoint was MACE (or a similar composite endpoint related to cardiovascular disease). Other endpoints of interest included cardiac death, target vessel revascularization (TVR) and procedural characteristics (procedure time and contrast use).

2.4. Data extraction and quality assessment

Extraction of relevant study, baseline and procedural characteristics and outcome data was independently performed by both reviewers (FG and TN) with the use of a standardized data extraction form. Baseline characteristics of interest were age, sex, and clinical presentation with STEMI. Procedural characteristics of interest were procedure time and contrast use (endpoints) and the use of drug-eluting stents (DES).

Both reviewers (FG and TN) independently performed a systematic quality assessment of included studies. For observational studies the methodological quality was assessed with the preferred 'Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)' tool [17]. With help of this tool, risk of bias in 7 different domains (confounding, selection, intervention classification, deviation from intervention, missing data, measurement of outcome, selection of reported results) was classified as low, moderate, serious, or critical, resulting in an overall risk of bias judgement. For a randomized controlled trial (RCT) the preferred 'revised Cochrane risk-of-bias tool for randomized trials (RoB-2)' tool was used to assess methodological quality, scoring risk of bias in 5 different domains (randomization process, deviation from intended interventions, missing outcome data, measurements of outcomes, selection of reported results) as low, some concerns or high [18].

Disagreements were resolved in a consensus meeting, including the opinion of a third reviewer (JD).

2.5. Statistical analysis

For the categorical endpoints a pooled risk ratio (RR) with corresponding 95% confidence intervals (CI) was calculated using the Mantel-Haenszel random-effects model. For each study, outcome data at maximum follow-up time was used for the pooled analyses. If only event percentages were reported in an included study, the absolute number of patients with an event was calculated (rounded down). Funnel plots for the primary and secondary endpoint were obtained to assess the potential of publication bias [19]. Presence of study heterogeneity was quantified with the Q and I^2 statistic. To explore a potential cause for study heterogeneity, a subgroup analysis with only STEMI patients was performed. Moreover, to assess the assumption that studies with serious risk of bias did not impact the outcome in the main analysis, a sensitivity analysis was performed.

Review Manager (Rev-Man, version 5.4.1., the Nordic Cochrane Centre, The Cochrane Collaboration, 2020) was used for statistical analysis and to acquire forest plots. A p value <0.05 (two-sided) was considered statistically significant.

3. Results

3.1. Search results and study selection process

The initial search strategy resulted in 3183 records. After full-text evaluation of 39 potentially eligible records, 9 studies were included in the systematic review and meta-analysis (Fig. 1) [12,13,20–26]. One eligible record was excluded because the study population was also part of a larger included study by Ya'qoub et al. [25,27]

3.2. Main characteristics and quality assessment of included studies

An overview of included studies with main study, baseline and procedural characteristics is presented in Table 1 and Supplementary Table 3. Most studies were based on either prospective or retrospective observational data except for 1 RCT. Dedicated data on all-cause mortality was reported in 7 studies and a composite cardiovascular endpoint was used in 8 studies. Moreover, data on cardiac death was reported in 4 studies and data on TVR in 5 studies. Maximum follow-up time differed from in-hospital outcome up to 5 years.

A total of 838.902 patients with AMI underwent PCI. Angio-guided

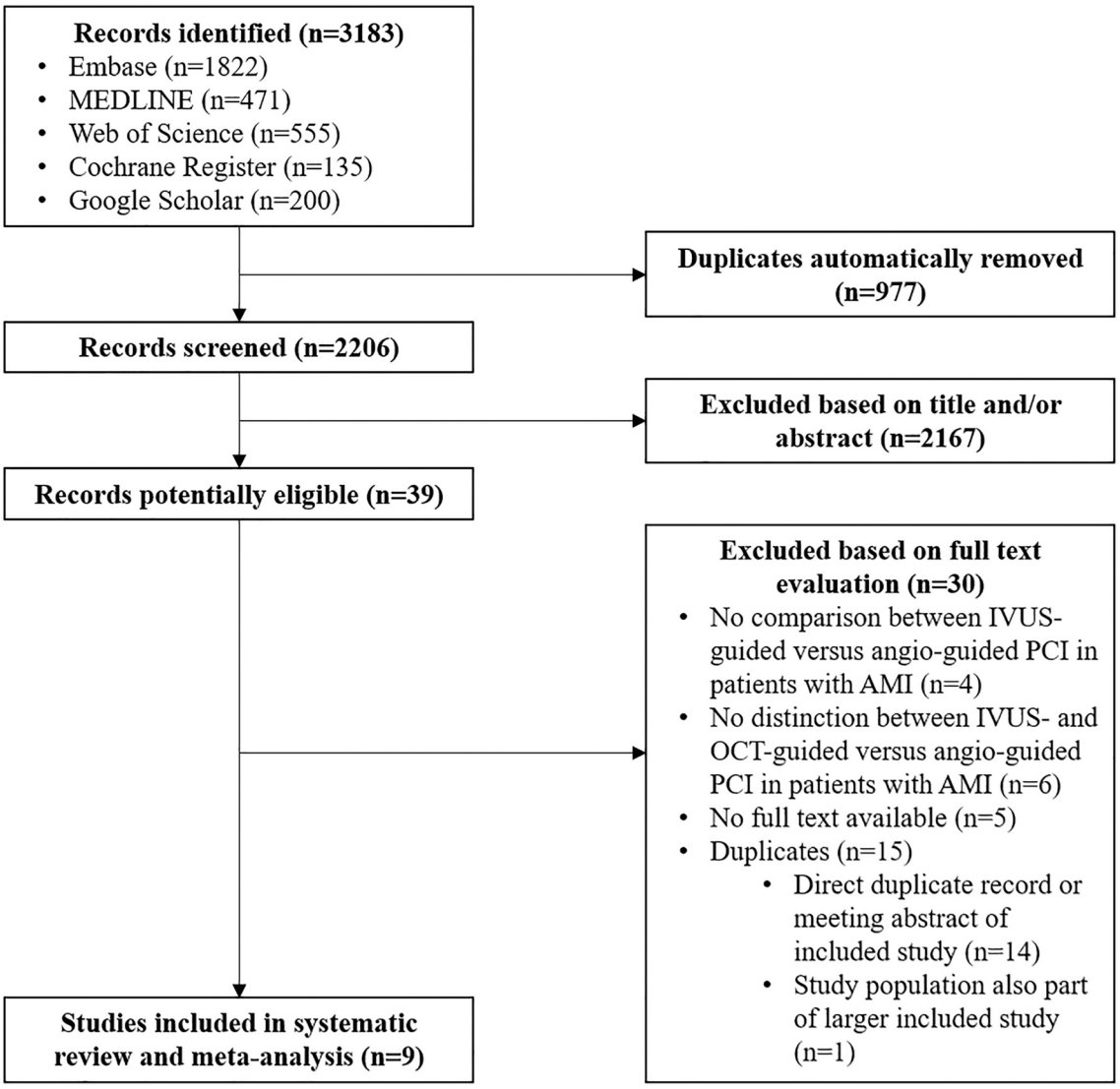


Fig. 1. Flowchart of the study selection process according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.
Legend: An overview of the study selection process.
AMI is acute myocardial infarction, IVUS is intravascular ultrasound, OCT is optical coherence tomography, PCI is percutaneous coronary intervention.

PCI was performed in 796.953 patients and IVUS-guided PCI in 41.949 patients (Table 1). Among studies, age differed from 53.7 to 70.0 years and patients were male in 60.5 to 75.6%. Six studies included only STEMI patients and in most studies drug-eluting stents (DES) were used in the majority of cases.

Quality assessment was performed using the ROBINS-I tool in 8 studies and the RoB-2 tool in one study (Supplementary Table 4). Overall risk of bias was scored as moderate in 7 observational studies. One observational study had serious risk of bias due to inappropriate adjustment for important confounding domains (shock and/or Killip Class) and an unclear intervention definition (the IVUS group was solely identified through ICD codes). The included RCT was considered to have some concerns regarding the overall risk of bias. No studies were classified to have a critical risk of bias.

3.3. Pooled analyses for clinical outcomes

In patients with AMI undergoing PCI, the use of IVUS significantly reduced the risk for all-cause mortality (pooled RR: 0.70; 95% CI, 0.59–0.82; $p < 0.01$; $I^2 = 62\%$) and MACE (pooled RR: 0.86; 95% CI, 0.74–0.99; $p = 0.04$; $I^2 = 61\%$) (Fig. 2). The risk of publication bias for all-cause mortality was considered as low (Supplementary Fig. 1). Conversely, the funnel plot for MACE was slightly asymmetric, as smaller studies with larger standard errors only reported lower RR in favor of IVUS.

With respect to the other clinical outcomes, IVUS-guided PCI in patients with AMI was associated with a significantly reduced risk for TVR (pooled RR: 0.83; 95% CI; 0.73–0.95; $p < 0.01$; $I^2 = 0\%$), but the beneficial effect of IVUS on cardiac death did not reach statistical significance (pooled RR: 0.62, 95% CI, 0.29–1.33; $p = 0.22$; $I^2 = 72\%$) (Fig. 2).

In addition to the pooled risk ratios, the unadjusted and adjusted clinical event rates as reported by the included studies are provided separately (Supplementary Table 5). After multivariate adjustment IVUS-guided PCI was associated with improved clinical outcomes in 3 studies, while in 3 other studies no significant associations were found. The three remaining studies provided no (un)adjusted effect measures.

3.4. Sensitivity and subgroup analyses for clinical outcomes

In the main analyses study heterogeneity was moderate to substantial ($I^2 > 50\%$) for all clinical outcomes, except for TVR (Fig. 2). For all-

Table 1
Main characteristics of the included studies.

Study /first author	Year	Design	Primary endpoint	Composite endpoint	Maximum Follow-up	Patients (n)	Age (years)	Male (%)	STEMI (%)	DES (%)
						IVUS/ angio	IVUS/ angio	IVUS/ angio	IVUS/ angio	IVUS/ angio
Ahmed [20]	2011	Retrospective observational	[a]	MACE, composite of all-cause mortality, non-fatal MI, TVR	1 year	2127/ 8235	61.3/ 63.8	75.6/ 71.3	58.8/ 58.9	89.0/ 76.2
Kim [21]	2020	Prospective observational[b]	[a]	POCE, composite of all-cause mortality, any infarction, any revascularization	1 year	2333/ 9072	NR/ 64.0	NR/ 73.9	NR/ 53.6	NR/ 92.2
Maluenda [12]	2010	Prospective observational[b]	[a]	MACE, composite of all-cause mortality, Q-wave MI, TLR	1 year	382/523	63.6/ 61.1	66.2/ 68.6	100.0/ 100.0	79.9/ 72.3
Nakatsuma [22]	2016	Retrospective observational	TVR	MACE, composite of all-cause mortality, MI, TVR	5 years	932/2096	65.9/ 67.4	74.8/ 75.1	100.0/ 100.0	39.5/ 11.3
Okura [13]	2019	Prospective observational[b]	All-cause mortality	MACE, composite of all-cause mortality, cardiac failure, VF/ VT, bleeding	In-hospital	1947/689	69.0/ 70.0	77.0/ 75.0	74.4/ 77.5	66.0/ 49.0
Wang [23]	2015	RCT	[a]	MACE, composite of CD, MI, TVR, intractable myocardial ischemia	1 year	38/42	56.4/ 53.7	60.5/ 66.7	100.0/ 100.0	NR/NR
Witzenbichler [24]	2014	Prospective observational[b]	Definite or probable ST	MACE, composite of CD, definite/probable ST, MI	1 year	421/392	NR/NR	NR/NR	100.0/ 100.0	100.0/ 100.0
Ya'qoub [25]	2021	Retrospective observational	Readmission	NR	In-hospital	33,644/ 775,688	61.0/ 62.4	74.1/ 71.0	100.0/ 100.0	NR/NR
Youn [26]	2011	Prospective observational[b]	[a]	MACE, composite of all-cause mortality, MI, TVR, TLR	3 years	125/216	60.0/ 61.4	74.4/ 63.0	100.0/ 100.0	100.0/ 100.0

CD is cardiac death, DES is drug-eluting stent, IVUS is intravascular ultrasound, MACE is major adverse cardiovascular event, MI is myocardial infarction, NR is not reported, POCE is patient orientated composite endpoint, RCT is randomized controlled trial, ST is stent thrombosis, STEMI is ST-segment elevation myocardial infarction, TLR is target lesion revascularization, TVR is target vessel revascularization, VF is ventricular fibrillation, VT is ventricular tachycardia.

[a] Primary endpoint is similar to composite endpoint.

[b] Post-hoc analysis.

cause mortality, heterogeneity was mainly caused by conflicting data in the studies of Maluenda et al. and Okura et al. [12,13] The large registry of Ya'qoub et al. in favor of IVUS contributed most to the pooled analysis (29.4%) [25]. In a sensitivity analysis, in which this study with serious risk of bias was excluded, IVUS-guided PCI remained associated with a significantly lower risk for all-cause mortality (pooled RR: 0.68; 95% CI, 0.52–0.88; $p < 0.01$; $I^2 = 67\%$) (Supplementary Fig. 2). For MACE, study heterogeneity was mainly caused by the large study of Kim et al., favoring IVUS with a lower RR as compared to other studies [21].

In subgroup analyses including studies with only STEMI patients, the pooled RR for all-cause mortality was 0.79 (95% CI, 0.66–0.95; $p = 0.01$; $I^2 = 49\%$) whereas pooled RR for MACE was 0.86 (95% CI, 0.74–0.99; $p = 0.04$; $I^2 = 11\%$) (Fig. 3). Tests for subgroup differences between AMI patients presenting with- or without ST segment elevation did not reach statistical significance.

3.5. Procedural characteristics

Procedure time (1 study) and contrast use (0 studies) were largely unreported and therefore not compared between both techniques.

4. Discussion

This is the first systematic review and meta-analysis assessing the clinical impact of IVUS-guided PCI in patients with AMI. The main findings of this study can be summarized as follows: IVUS-guided PCI in patients with AMI is associated with a significantly lower risk for all-cause mortality (pooled RR 0.70) and MACE (pooled RR 0.86) as compared to angio-guided PCI. These findings were consistent for AMI patients with ST-segment elevation.

The results of the present study, specifically focusing on patients presenting with AMI, support the profound and growing body of evidence on the use of IVUS to improve PCI outcome in stable and more complex populations [7–11]. In the pooled analysis for all-cause mortality, IVUS-guided PCI was associated with a significant 30% relative risk reduction in all-cause mortality, while the reductions for MACE and TVR were 14% and 17% respectively. A similar numerical reduction was observed for cardiac death, although this pooled analysis did not reach statistical significance. The discrepancy between all-cause mortality and cardiac death could raise questions with respect to the plausibility of the results. However, the sample size of the pooled population was significantly lower for cardiac death, since this endpoint was investigated by only 4 studies, with 3 studies reporting event data for the pooled analysis (Fig. 3). This resulted in a lower statistical power. Furthermore, heterogeneity was more pronounced for cardiac death, which might be explained by the fact that clear definitions were not available for all studies and thus could have differed. Of note, determining the cause of death can be difficult and is more prone to bias in retrospective and observational studies. Obviously, these potential pitfalls are less applicable to all-cause mortality.

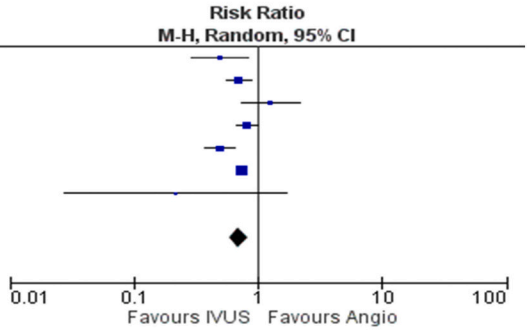
In addition to the present systematic review and meta-analysis, 3 recent observational studies (large registries) compared the use of intravascular imaging with angio-guided PCI in patients with AMI and showed similar results [28–30]. Intravascular imaging guidance was associated with a reduction in all-cause mortality and a composite of cardiac death, non-fatal myocardial infarction and stent thrombosis. Although IVUS was the most frequently used intravascular imaging modality, these studies were not included in the present study, because no distinction was made between IVUS and OCT.

Based on the present findings, it seems reasonable to conclude that the beneficial effect of IVUS-guided PCI also applies to patients with AMI. This can be explained by both the general advantages of IVUS, as well as the specific potential benefits of IVUS in the acute setting. First, pre-intervention IVUS allows accurate sizing of lesion length and lumen and vessel diameter, which enables selection of correct stent and balloon sizes [1,4,5]. As a result, geographic miss and procedural complications due to malsizing can be prevented. Second, IVUS can be used to assess different plaque types and disease extent which might improve procedural planning and treatment strategies [1,4,5]. Third, post-intervention IVUS can be used to guide optimization strategies for relevant post-PCI findings, such as underexpansion, malapposition and stenting-related complications (e.g. edge dissections), as well as residual focal lesions

1) All-cause mortality

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahmed 2011	16	1635	121	6075	7.5%	0.49 [0.29, 0.83]
Kim 2020*	81	1658	398	5679	18.9%	0.70 [0.55, 0.88]
Maluenda 2010	24	382	26	523	7.1%	1.26 [0.74, 2.17]
Nakatsuma 2016	112	932	311	2096	20.8%	0.81 [0.66, 0.99]
Okura 2019	100	1947	72	689	15.6%	0.49 [0.37, 0.66]
Ya'qoub 2021	1312	33644	41111	775688	29.4%	0.74 [0.70, 0.78]
Youn 2011	1	125	8	216	0.6%	0.22 [0.03, 1.71]
Total (95% CI)		**40323**		**790966**	**100.0%**	**0.70 [0.59, 0.82]**
Total events	1646		42047			

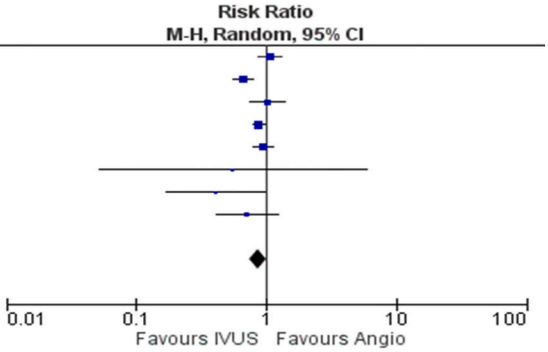
Heterogeneity: Tau² = 0.02; Chi² = 15.95, df = 6 (P = 0.01); I² = 62%
Test for overall effect: Z = 4.29 (P < 0.0001)
*Data on all-cause mortality was only available from the matched cohort



2) Major adverse cardiovascular events

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahmed 2011	108	1635	374	6075	17.5%	1.07 [0.87, 1.32]
Kim 2020	132	2333	774	9072	19.2%	0.66 [0.55, 0.79]
Maluenda 2010	55	382	74	523	11.8%	1.02 [0.74, 1.41]
Nakatsuma 2016	313	932	813	2096	23.5%	0.87 [0.78, 0.96]
Okura 2019	354	1947	133	689	19.2%	0.94 [0.79, 1.13]
Wang 2015	1	38	2	42	0.4%	0.55 [0.05, 5.85]
Witzenbichler 2014	7	421	16	392	2.6%	0.41 [0.17, 0.98]
Youn 2011	16	125	39	216	5.9%	0.71 [0.41, 1.21]
Total (95% CI)		**7813**		**19105**	**100.0%**	**0.86 [0.74, 0.99]**
Total events	986		2225			

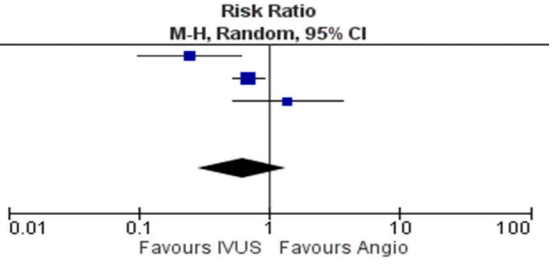
Heterogeneity: Tau² = 0.02; Chi² = 18.08, df = 7 (P = 0.01); I² = 61%
Test for overall effect: Z = 2.06 (P = 0.04)



3) Cardiac death

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahmed 2011	5	1635	76	6075	28.5%	0.24 [0.10, 0.60]
Kim 2020*	59	1658	294	5679	44.6%	0.69 [0.52, 0.90]
Maluenda 2010	8	382	8	523	26.9%	1.37 [0.52, 3.62]
Wang 2015	0	38	0	42		Not estimable
Total (95% CI)		**3713**		**12319**	**100.0%**	**0.62 [0.29, 1.33]**
Total events	72		378			

Heterogeneity: Tau² = 0.32; Chi² = 7.05, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 1.24 (P = 0.22)
*Data on cardiac death was only available from the matched cohort



4) Target vessel revascularization

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahmed 2011	7	1635	41	6075	2.7%	0.63 [0.29, 1.41]
Maluenda 2010	44	382	56	523	12.5%	1.08 [0.74, 1.56]
Nakatsuma 2016	188	932	524	2096	79.5%	0.81 [0.70, 0.94]
Wang 2015	0	38	2	42	0.2%	0.22 [0.01, 4.45]
Youn 2011	15	125	29	216	5.1%	0.89 [0.50, 1.60]
Total (95% CI)		**3112**		**8952**	**100.0%**	**0.83 [0.73, 0.95]**
Total events	254		652			

Heterogeneity: Tau² = 0.00; Chi² = 3.25, df = 4 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.72 (P = 0.007)

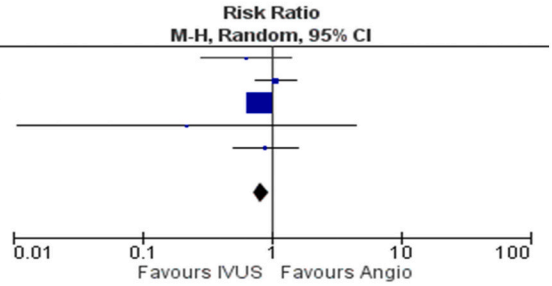
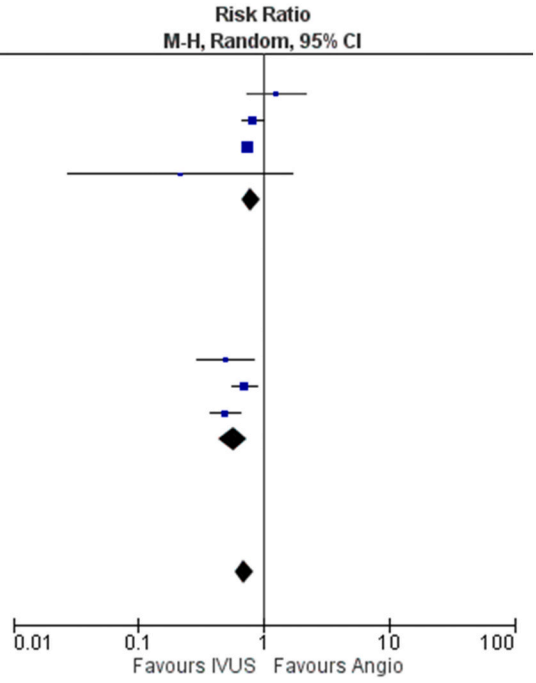


Fig. 2. Studies comparing intravascular ultrasound-guided versus angio-guided percutaneous coronary intervention in patients with acute myocardial infarction – Main pooled analyses for clinical outcomes.
Legend: Pooled analyses for all-cause mortality, major adverse cardiovascular events, cardiac death and target vessel revascularization. Risk ratios are provided, including statistical tests for heterogeneity and overall effect. The horizontal line is the 95% confidence interval.
CI is confidence interval, IVUS is intravascular ultrasound, M-H is Mantel-Haenszel.

or high plaque burden at stent edges [1–3,5,7]. More specifically for patients presenting with AMI, IVUS can be used to visualize specific culprit lesion plaque characteristics, such as plaque ruptures and attenuation, which are associated with no-reflow [31–33]. Moreover, IVUS allows the assessment of thrombus (burden), thrombus protrusion and vulnerable attenuated plaque, which might impact treatment strategies (e.g. aspiration thrombectomy, atherectomy and filter protection) and hypothetically also the administration of peri-procedural pharmacotherapy (e.g. glycoprotein IIb/IIIa receptor antagonist) [33,34]. Conversely, IVUS-guided optimization could lead to increased balloon dilatations with more distal embolization, specifically in case of high thrombus burden. However, this does not seem to negatively impact clinical outcomes. Two included studies reported a higher percentage of post-dilatation in the IVUS-guided PCI group, but differences in

1) All-cause mortality

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Studies with only STEMI patients						
Maluenda 2010	24	382	26	523	7.1%	1.26 [0.74, 2.17]
Nakatsuma 2016	112	932	311	2096	20.8%	0.81 [0.66, 0.99]
Ya'qoub 2021	1312	33644	41111	775688	29.4%	0.74 [0.70, 0.78]
Youn 2011	1	125	8	216	0.6%	0.22 [0.03, 1.71]
Subtotal (95% CI)		**35083**		**778523**	**58.0%**	**0.79 [0.66, 0.95]**
Total events	1449		41456			
Heterogeneity: Tau² = 0.01; Chi² = 5.94, df = 3 (P = 0.11); I² = 49%						
Test for overall effect: Z = 2.52 (P = 0.01)						
1.1.2 Studies with both STEMI and NSTEMI patients						
Ahmed 2011	16	1635	121	6075	7.5%	0.49 [0.29, 0.83]
Kim 2020*	81	1658	398	5679	18.9%	0.70 [0.55, 0.88]
Okura 2019	100	1947	72	689	15.6%	0.49 [0.37, 0.66]
Subtotal (95% CI)		**5240**		**12443**	**42.0%**	**0.57 [0.44, 0.75]**
Total events	197		591			
Heterogeneity: Tau² = 0.03; Chi² = 3.99, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 4.14 (P < 0.0001)						
Total (95% CI)		**40323**		**790966**	**100.0%**	**0.70 [0.59, 0.82]**
Total events	1646		42047			
Heterogeneity: Tau² = 0.02; Chi² = 15.95, df = 6 (P = 0.01); I² = 62%						
Test for overall effect: Z = 4.29 (P < 0.0001)						
Test for subgroup differences: Chi² = 3.94, df = 1 (P = 0.05), I² = 74.7%						



*Data on all-cause mortality was only available from the matched cohort

2) Major adverse cardiovascular events

Study or Subgroup	IVUS Events	IVUS Total	Angio Events	Angio Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Studies with only STEMI patients						
Maluenda 2010	55	382	74	523	11.8%	1.02 [0.74, 1.41]
Nakatsuma 2016	313	932	813	2096	23.5%	0.87 [0.78, 0.96]
Wang 2015	1	38	2	42	0.4%	0.55 [0.05, 5.85]
Witzenbichler 2014	7	421	16	392	2.6%	0.41 [0.17, 0.98]
Youn 2011	16	125	39	216	5.9%	0.71 [0.41, 1.21]
Subtotal (95% CI)		**1898**		**3269**	**44.1%**	**0.86 [0.74, 0.99]**
Total events	392		944			
Heterogeneity: Tau² = 0.00; Chi² = 4.47, df = 4 (P = 0.35); I² = 11%						
Test for overall effect: Z = 2.04 (P = 0.04)						
2.1.2 Studies with both STEMI and NSTEMI patients						
Ahmed 2011	108	1635	374	6075	17.5%	1.07 [0.87, 1.32]
Kim 2020	132	2333	774	9072	19.2%	0.66 [0.55, 0.79]
Okura 2019	354	1947	133	689	19.2%	0.94 [0.79, 1.13]
Subtotal (95% CI)		**5915**		**15836**	**55.9%**	**0.87 [0.66, 1.16]**
Total events	594		1281			
Heterogeneity: Tau² = 0.05; Chi² = 13.62, df = 2 (P = 0.001); I² = 85%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)		**7813**		**19105**	**100.0%**	**0.86 [0.74, 0.99]**
Total events	986		2225			
Heterogeneity: Tau² = 0.02; Chi² = 18.08, df = 7 (P = 0.01); I² = 61%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

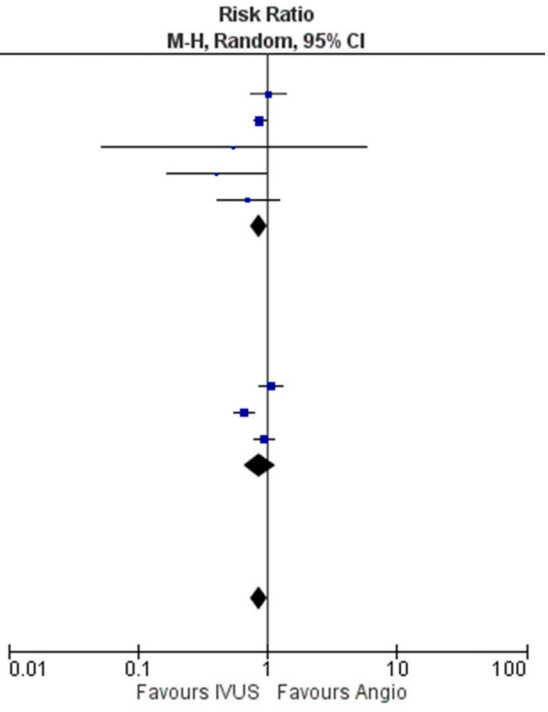


Fig. 3. Studies comparing intravascular ultrasound-guided versus angio-guided percutaneous coronary intervention in patients with acute myocardial infarction – Subgroup analyses for all-cause mortality and major adverse cardiovascular events.

Legend: Subgroup analysis for all-cause mortality and major adverse cardiovascular events, comparing studies with only STEMI patients to studies with both STEMI and NSTEMI patients. Risk ratios are provided, including statistical tests for the overall effect within the subgroup and difference between subgroups. The horizontal line is the 95% confidence interval.

CI is confidence interval, IVUS is intravascular ultrasound, M-H is Mantel-Haenszel, NSTEMI is non-ST-segment elevation myocardial infarction, STEMI is ST-segment elevation myocardial infarction.

composite cardiovascular endpoints, as compared to the angio-guided PCI group, were not observed [12,26].

When interpreting the results of the pooled analyses, it is noteworthy that intravascular imaging is widely utilized in modern Asian countries, whereas its usage in the United States and Europe still lags behind [35]. As a result, the majority of the included studies was derived within Asian populations. Differences in underlying epidemiology (incidence, risk factors) of cardiovascular disease and patient demographics, along with differences in plaque and lesion phenotype between Asian and Western populations, should therefore be considered [36–38]. Intracoronary imaging studies have shown differences in plaque morphology between both ethnicities, with Western patients having higher lipid indexes, higher plaque burden, more calcification and longer lesion lengths as compared to Asian populations [39,40]. Moreover, cultural differences in operator and patient preference with respect to either the frequency of IVUS use and preference for PCI over surgery, might preclude the generalizability of our findings.

Dedicated ongoing prospective studies, including the SPECTRUM study (NCT05007535), the iSTEMI trial (NCT04775914), the IMPROVE trial (NCT04221815) and the IVUS-CHIP trial (NCT04854070), will provide more insight in the potential beneficial effect of IVUS-guided PCI in Western populations. Whereas the IMPROVE and IVUS-CHIP trial will focus on IVUS guidance for complex high-risk indicated procedures (including high-risk lesions in patients with non-STEMI), the SPECTRUM study and iSTEMI trial investigate the use of IVUS during primary PCI.

In the present meta-analysis, IVUS-guided PCI was also associated with improved clinical outcomes in STEMI subgroup analyses. Although the forest plot for all-cause mortality indicated a less beneficial effect in STEMI patients, subgroup differences were not statistically significant. The SPECTRUM study, iSTEMI trial and a small RCT from China (NCT04929158) will specifically assess the impact of IVUS guidance in STEMI. Moreover, these studies will provide more insight in relevant procedural characteristics such as procedure time and contrast use, which were underreported in the included studies of this meta-analysis. We hypothesize that if IVUS-guided PCI is performed by an experienced team with a contemporary IVUS system, procedure times will not be significantly longer. Of note, IVUS guidance can reduce contrast use, although data in STEMI patients is lacking [41].

Finally, a comparison between IVUS guidance in the acute setting versus other invasive imaging techniques or coronary physiology, was beyond the scope of the present study. A recent meta-regression analysis showed a trend towards lower rates of subsequent myocardial infarction with IVUS as compared to fractional flow reserve, in patients with acute coronary syndrome [42]. Dedicated studies are needed to further address the respective value of invasive imaging versus physiological tools in acute patients.

4.1. Limitations

First, mainly retrospective and prospective observational studies based on large AMI registries were included in this systematic review and meta-analysis. In general, data derived from registries is more prone to bias and might affect results. Quality assessment was performed to provide a complete overview of each study's risk of bias per domain. Moreover, risk of publication bias was assessed by visual inspection of funnel plots. The funnel plot for MACE showed a slightly asymmetric pattern, indicating that publication bias in favor of IVUS could not be completely excluded. However, visual inspection of funnel plots has been found a subjective tool for the assessment of publication bias [43]. The aforementioned dedicated prospective studies are needed to confirm the potential positive impact of IVUS-guided PCI in patients with AMI. Second, follow-up time differed among studies (in-hospital up to 5 years), although maximum follow-up in most included studies was one year. Third, inherent to using a composite endpoint in a meta-analysis is that definitions differ among included studies. In the present meta-analysis definitions for MACE were largely comparable. Fourth, differences in DES use, DES type (generation), and lesion complexity between studies and study groups, could potentially have impacted clinical outcomes. Meta-regression was not performed, since less than 10 studies were included and data of the described variables was largely missing, significantly decreasing the potential reliability of adjusted results [19]. Finally, study heterogeneity was moderate to substantial for all clinical outcomes. However, Mantel-Haenszel random-effects model was used to account for this and subgroup analyses were performed to explore possible sources of study heterogeneity.

5. Conclusions

This is the first systematic review and meta-analysis comparing IVUS- versus angio-guided PCI in patients with AMI, showing a beneficial effect of IVUS-guided PCI on all-cause mortality, MACE and TVR. Results of ongoing dedicated prospective studies are needed to confirm these findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.01.021.

Data availability statement

Data in this systematic review and meta-analysis was extracted from the included studies (full text, tables, figures, and supplementary files). The data extraction forms are available upon reasonable request.

Declaration of Competing Interest

Joost Daemen received institutional grant / research support from Abbott Vascular, ACIST Medical, Astra Zeneca, Boston Scientific, Medtronic, Microport, Pie Medical, and ReCor Medical. Nicolas Van Mieghem received institutional research grant support from Abbott Vascular, Abiomed, Boston Scientific, Daiichi-Sankyo, Edward Lifesciences, Medtronic, and PulseCath. The remaining authors report to have no disclosures.

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