

BMJ Open Prognostic and diagnostic accuracy of intracoronary electrocardiogram recorded during percutaneous coronary intervention: a meta-analysis

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ABSTRACT

Objective Intracoronary ECG (IC-ECG) recording has been shown to be sensitive and reliable for detecting myocardial viability and local myocardial ischaemia in some studies. But IC-ECG is neither widely used during percutaneous coronary intervention (PCI) nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic and diagnostic accuracy of IC-ECG recorded during PCI.

Methods Relevant studies were identified by searches of MEDLINE until 19 June 2021. Observational and diagnostic studies which reported the prognostic or diagnostic accuracy of IC-ECG were included. Data were extracted independently by two authors. Summary estimates of clinical outcomes were obtained using a random effects model. Summary diagnostic accuracy was obtained by using a Bayesian bivariate random effects model.

Results Of the 12 included studies, 7 studies reported the clinical outcomes (821 patients) and 6 studies reported the diagnostic accuracy (485 patients) of IC-ECG. The pooled ORs with 95% CIs of ST-segment elevation recorded by IC-ECG were 4.65 (1.69 to 12.77), 5.08 (1.10 to 23.44), 4.53 (0.79 to 25.90) and 1.83 (0.93 to 3.62) for major adverse cardiac events, myocardial infarction, cardiac death and revascularisation, respectively. The weighted mean difference were 6.49 (95% CIs 3.84 to 9.14) for ejection fraction when ST-segment resolution was recorded, and 0.86 (95% CIs -8.55 to 10.26) when ST-segment elevation was recorded. The pooled sensitivity and specificity of ST-segment elevation were 0.78 (95% credibility intervals 0.64 to 0.89) and 0.87 (95% credibility intervals 0.75 to 0.94), respectively.

Conclusions These findings provide quantitative data supporting that IC-ECG had promising diagnostic ability for local myocardial injury, and could predict clinical outcomes.

INTRODUCTION

Percutaneous coronary intervention (PCI) is a well-established therapeutic strategy for patients with coronary artery disease (CAD). Except for coronary angiography, several invasive diagnostic tools, such as fractional flow reserve (FFR), intravascular ultrasound (IVUS) and optical coherence tomography are recommended for guiding PCI by the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ There were relatively large number of patients analysed.
- ⇒ We used Bayesian meta-analysis to reduce the bias when assessing the diagnostic accuracy.
- ⇒ Limited by the published studies, we could only perform meta-analysis of observational studies.
- ⇒ We did not perform sensitivity analysis for the timing when the intracoronary ECG (IC-ECG) was recorded, different types of coronary artery diseases, different definitions of significant ST-segment changes on IC-ECG or different guide wires used in the studies, limited by the number of studies.

guidelines.¹ But these tools are not always available. In some cases, catheters or pressure wires, may not pass through the lesions or may be damaged when crossing the stents or calcified lesions.²⁻⁵ Moreover, for some patients, the costs of these tools are important additional considerations.

Intracoronary ECG (IC-ECG) recording, with a guidewire functioning as a unipolar electrode, might be an alternative tool for guiding PCI. In some studies, the ST-segment elevation or resolution recorded by IC-ECG during or after PCI procedures have been shown to be sensitive and reliable for detecting myocardial viability, local myocardial ischaemia or microvascular obstruction.⁵⁻¹⁶ But IC-ECG is neither widely used during PCI nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic and diagnostic accuracy of IC-ECG recorded during PCI.

METHODS

The meta-analysis was conducted according to the checklist of the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement¹⁷ and the Meta-Analysis

of Observational Studies in Epidemiology group.¹⁸ We performed a systematic search of relevant studies published through 19 June 2021, in the MEDLINE database.

Search strategy

Accessing MEDLINE database, we performed a literature search for studies published until 19 June 2021 using the following search terms and key words: ((intracoronary) AND (electrocardiogram OR ECG OR EKG)) AND (st segment). The search strategy is shown in online supplemental table 1. We manually checked the reference lists of retrieved articles to identify any studies that were not identified from the preliminary literature searches.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: (1) Published in the English language; (2) Had an observational study design; (3) Enrolled patients with CAD who were undergoing PCI; (4) Reported the clinical outcomes during follow-ups, such as major adverse cardiac events (MACEs), cardiac death, myocardial infarction, ejection fraction (EF) and repeat revascularisation; (5) Reported the diagnostic accuracy of IC-ECG and (6) Presented estimates of ORs with 95% CIs or reported data necessary to calculate these. Animal, autopsy, duplicated and phantom studies were excluded. Moreover, studies would be excluded if IC-ECG was not one of the study objects.

Data extraction

From each retrieved article, two authors independently extracted the following data: name of the first author, year of publication, location where the study was performed, study design, number of cases, follow-up period, proportion of men, mean or median age, inclusion criteria, exclusion criteria, reference standard, ORs or event rates, EF during following-up and the diagnostic accuracy of IC-ECG. The true-positive, true-negative, false-positive and false-negative rates were also estimated, using the data we extracted from the studies.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

We directly extracted ORs from each study, or indirectly estimated ORs by calculating event rates. And then we pooled ORs using a random-effects meta-analysis method. For EF, we pooled unstandardised mean difference using a random-effects meta-analysis method. Summary sensitivity and specificity with their 95% credibility intervals of IC-ECG were obtained by using Bayesian bivariate random effects meta-analysis.^{19–21} Bayesian summary receiver operating characteristic (SROC) curves were constructed and the areas under the Bayesian SROC

curves (AUC) were performed to assess the diagnostic accuracy of IC-ECG.^{20 21}

To perform quality assessment, two authors independently assessed the prognostic studies' qualities by using the Newcastle-Ottawa Scale (NOS)²² and the diagnostic studies' qualities by using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) tool.²³ The NOS evaluated three parameters (selection, comparability and outcome) divided across eight items. Each item was scored from 0 to 1 star, except for comparability, which could be adapted to the specific topic of interest to score up to 2 stars. Thus, the maximum score for each study was 9. Studies with <3 stars were at a high risk of bias and would be excluded. The QUADAS tool contained 14 questions which could be used for assessing the qualities of diagnostic studies. Disagreements were resolved by consensus.

Statistical heterogeneities between prognostic studies were evaluated with the I^2 statistic,²⁴ which estimates the percentage of total variation across studies due to true between-study differences rather than chance, with I^2 values of 25, 50 and 75% representing low, medium and high heterogeneities, respectively. We performed conflict of evidence analysis for diagnostic studies by extending the random effects distribution, using a scale mixture of normal distributions per random effect.²⁰ P values that were less than 0.05 were considered statistically significant. Statistical analyses were carried out with STATA, V.16.0 (StataCorps), and R statistical software with 'bamdit' packages.²⁰

RESULTS

Literature search

The details of search steps are shown in figure 1. We identified and screen 480 articles from our preliminary search. After screening abstracts, 440 articles were excluded because the study objects were not IC-ECG. Sixteen articles were excluded because they were not clinical trials. Bigler's study compared deep learning with manually

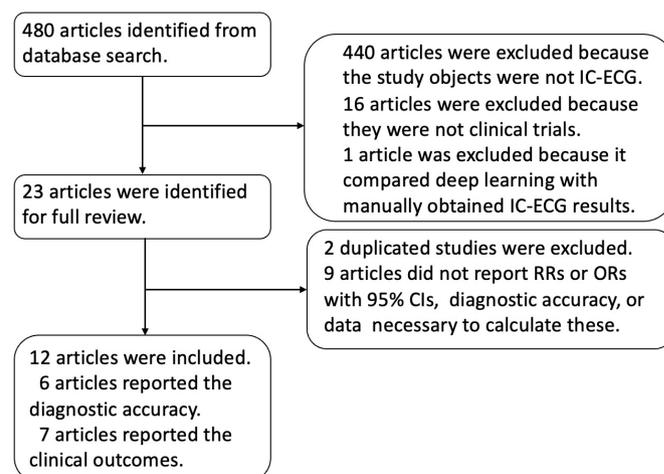


Figure 1 Selection of included studies. IC-ECG, intracoronary ECG; RR, risk ratio.

Table 1 The characteristics of included studies

Studies	Study design	No of cases	Male (%)	Age (years old)	Follow-up (months)	Reference standards
Ikenaga <i>et al</i> 2018, Japan ¹⁰	Cohort study, single centre	84	36.8	67.4±9.9	12	N/A
Wong <i>et al</i> 2013, Australia ⁶	Cohort study, single centre	64	82.8	61.0±10.0	3	N/A
Hishikari <i>et al</i> 2016, Japan ⁷	Cohort study, single centre	111	73.9	68.8±12.6	35*	N/A
Uetani <i>et al</i> 2009 Japan ¹¹	Cohort study, single centre	339	66.4	69.7±8.6	In hospital	N/A
Balian <i>et al.</i> 2005, Italy ⁸	Cohort study, single centre	50	84.0	59.3±11.0	6	N/A
Yajima <i>et al</i> 2001, Japan ⁹	Cohort study, single centre	65	75.4	61.3±7.0	1	N/A
Balian <i>et al</i> 2006, Italy ¹²	Cohort study and diagnostic study, single centre	108	87.3	61.7±10.0	12±5	Troponin I
Balian <i>et al</i> 2011, Italy ¹³	Diagnostic study	48	52.0	65.0±9.0	N/A	FFR
Abaci <i>et al</i> 2003, Turkey ¹⁴	Diagnostic study	71	84.5	54.0±11.0	N/A	Low-dose dobutamine echocardiography
FIESTA. 2018, Bulgaria ⁵	Diagnostic study	37	69.0	65.0±10.0	N/A	FFR
Wang <i>et al</i> 2011, China ¹⁵	Diagnostic study	86	67.4	54.5±10.2	N/A	Troponin T
Vassilev <i>et al</i> 2016, Bulgaria ¹⁶	Diagnostic study	135	59.2	65.1±10.0	N/A	Troponin I

*The median followed-up period of this study was 35 months (28–40 months).
FFR, fractional flow reserve; N/A, not available.

obtained IC-ECG results,²⁵ and was excluded. Twenty-three articles were identified for full review. Among these articles, two duplicated studies were excluded. Nine articles were excluded because they did not report ORs, diagnostic accuracy or data necessary to calculate these. Finally, there were 12 studies included in our meta-analysis. Seven studies reported the clinical outcomes and six studies reported the diagnostic accuracy of IC-ECG.

Study characteristics

The characteristics of included studies are shown in [table 1](#) and online supplemental table 2. There were seven cohort studies and six diagnostic studies in our meta-analysis. There were 1198 cases included in our meta-analysis totally. Among these cases, 821 cases and 485 cases were included in the meta-analysis for prognostic and diagnostic accuracy of IC-ECG, respectively. The proportion of men was 68.8%. The inclusion criteria of the included articles were CAD patients, including stable or unstable angina pectoris, and myocardial infarction. The clinical outcomes reported in these studies were mainly MACEs, cardiac death, myocardial infarction, repeat revascularisation and EF. The difference of the definitions that significant ST-segment changes on IC-ECG in each study was not very great. The reference

standards reported in the diagnostic studies were varied, including FFR,^{5 13} echocardiogram¹⁴ and troponin.^{12 15 16}

The correlation between clinical outcomes and ST-segment elevation recorded by IC-ECG

Pooled OR for MACE is shown in [figure 2A](#). The inclusion criteria of these studies were patients with angina and stable conditions. MACEs were defined as cardiac death, myocardial infarction, revascularisation and hospitalisation for heart failure in Ikenaga's study.¹⁰ In Uetani's study¹¹ and Balian's study,¹² MACEs were defined as cardiac deaths and myocardial infarction. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE (OR 4.65, 95% CIs 1.69 to 12.77). There were mild heterogeneities among studies ($I^2=30.1%$, $p=0.239$).

Pooled ORs for cardiac death, myocardial infarction, and revascularisation are shown in [figure 2B–D](#). The inclusion criteria of these studies were patients with angina or non-ST-segment elevation myocardial infarction (NSTEMI). In the meta-analysis for cardiac death, Ikenaga's study¹⁰ was excluded because there were no events. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of myocardial infarction (OR 5.08, 95% CIs 1.10 to

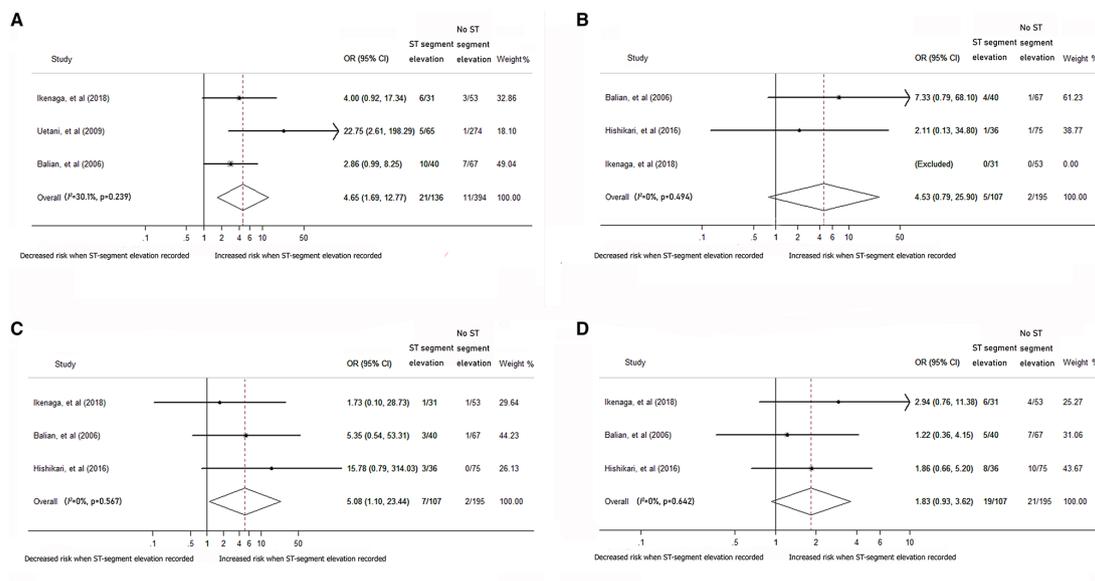


Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. The clinical outcomes were (A) MACE, (B) cardiac death, (C) myocardial infarction, and (D) revascularisation, respectively. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during follow-up, but was not significantly associated with cardiac death nor revascularisation. IC-ECG, intracoronary ECG; mace, major adverse cardiac event.

23.44), but not cardiac death (OR 4.53, 95% CIs 0.79 to 25.90) nor revascularisation (OR 1.83, 95% CIs 0.93 to 3.62). There were no heterogeneities among studies (cardiac death, $I^2=0\%$, $p=0.494$; myocardial infarction, $I^2=0\%$, $p=0.567$; revascularisation, $I^2=0\%$, $p=0.642$).

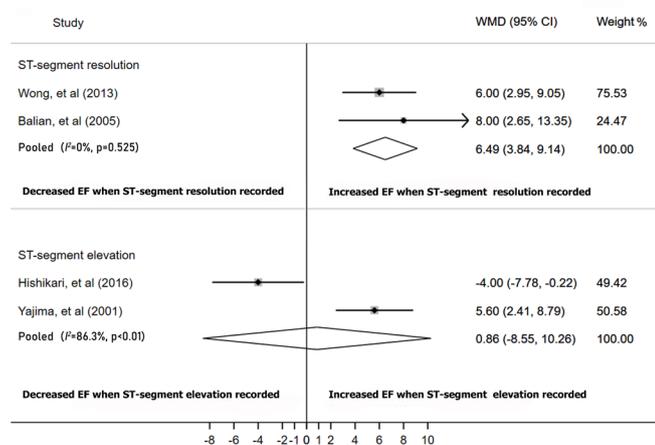


Figure 3 The differences in ejection fraction (EF) between different results recorded by IC-ECG during follow-up. We pooled unstandardised mean difference using a random-effects meta-analysis method. EF was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, while we could not find similar result when ST-segment elevation was recorded. IC-ECG, intracoronary ECG; WMD, weighted mean difference.

The correlation between EF and different results recorded by IC-ECG during follow-up

The correlation between EF and different results recorded by IC-ECG are shown in figure 3. We divided the included studies into two subgroups according to the different evaluation methods reported by the studies. One was ST-segment resolution, and the other one was ST-segment elevation. In the subgroup of ST-segment resolution, inclusion criteria were patients with STEMI. The pooled weighted mean difference (WMD) was 6.49, with 95% CIs 3.84 to 9.14. There were no heterogeneities ($I^2=0\%$, $p=0.525$). The inclusion criteria of ST-segment elevation subgroup were patients with NSTEMI (Hishikari *et al*⁷) or anterior myocardial infarction (Yajima *et al*⁸). The pooled WMD was 0.86, with 95% CIs -8.55 to 10.26. There were heterogeneities ($I^2=86.3\%$, $p<0.01$).

Diagnostic accuracy of ST-segment elevation recorded by IC-ECG

Abaci's study reported the diagnostic accuracy for myocardial viability,¹⁴ while the other five diagnostic studies reported the diagnostic accuracy for myocardial injury or ischaemia. Therefore, we excluded Abaci's study when we performed Bayesian meta-analysis for diagnostic studies. The inclusion criteria of included studies were angina patients with stable conditions. The pooled diagnostic accuracy and the predictive posterior rates are shown in online supplemental figure 1. The Bayesian SROC curve and the AUC are shown in figure 4. The pooled sensitivity and specificity were 0.78 (95% credibility intervals 0.64 to 0.89) and 0.87 (95% credibility intervals 0.75 to 0.94), respectively. The AUC of Bayesian SORC was 0.65 (95% credibility intervals 0.56 to 0.69). And there

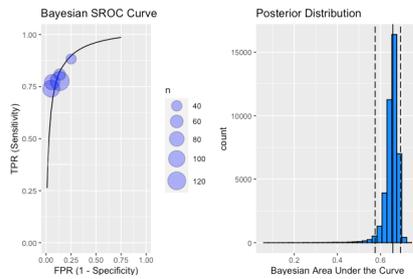


Figure 4 The Bayesian SROC curve of ST-segment elevation recorded by IC-ECG and the posterior distribution of AUC. Each circle identifies the true positive rate versus the false positive rate of each study. The AUC was 0.65 (95% credibility intervals 0.56–0.69). AUC, areas under the curve; FPR, false positive rate; IC-ECG, IC-ECG, intracoronary ECG; SROC, summary receiver-operating-characteristic; TPR, true positive rate.

were no heterogeneities. The posterior distributions of the component weights which were used for conflict of evidence analysis are shown in online supplemental figure 2.

Quality assessment

Results of quality assessment adapted from NOS are shown in online supplemental table 3. All the studies reached over three stars, but no study reached the maximum score. Considering all the studies included CAD patients, no study got scored in the fourth item of selection section. Only three studies^{6 7 11} reported the confounders and were scored 2 stars in the comparability section. Two studies^{9 11} reported the in-hospital outcomes and did not report the patients lost to follow-up, therefore, they were not scored in the second and third items of outcome section.

Results of quality assessment adapted from QUADAS tool are shown in online supplemental table 4. All the studies clearly described the methods. No studies described whether they blinded reviewers to the results of IC-ECGs, while three studies^{12–14} blinded reviewers to the results of reference standards. Only two studies^{12 14} reported the intermediate results, and two studies^{5 12} explained the withdrawals.

DISCUSSION

Our results from the meta-analysis of observational studies indicated that ST-segment elevation recorded by IC-ECG after PCI procedures for stable angina patients linked to worse MACE outcomes. For angina or NSTEMI patients, ST-segment elevation was significantly associated with higher risk of myocardial infarction during follow-up, but not cardiac death nor revascularisation. ST-segment resolution recorded by IC-ECG after PCI procedures for STEMI patients was significantly associated with increased EF during follow-up. But ST-segment elevation during PCI procedures did not significantly link to increased or decreased EF. After Bayesian meta-analysis, IC-ECG

showed promising diagnostic ability for myocardial injury or ischaemia.

ST-segment shift pattern recorded by ECG during acute myocardial infarction was reported 100 years ago.²⁶ And ST-segment deviation recorded by surface ECG was a part of the universal definition of myocardial infarction.²⁷ However, surface ECG was not reliable for detecting local myocardial ischaemia during PCI procedures in real time.²⁸ In this case, IC-ECG was more reliable and sensitive for detecting local ischaemia.²⁹ Although IC-ECG was more sensitive than surface ECG when assessing left ascending artery and circumflex territory, It should be noted that IC-ECG was less sensitive when assessing right coronary artery territory.^{30 31} On the other hand, impaired microvascular perfusion during PCI might lead to periprocedural myocardial infarction, indicating worse outcomes. IC-ECG could detect local ischaemia, which was found to be well associated with impaired microvascular perfusion.¹⁰ For instance, in Sato's study, the prolongation of ST-segment elevation time recorded by IC-ECG was associated with higher max-lipid core burden index 4 mm detected by near-infrared spectroscopy with IVUS in stable angina patients, which might indicate distal embolisation and microvascular disease.³²

The results from this meta-analysis indicated that ST-segment elevation recorded by IC-ECG after PCI procedure was significantly associated with worse MACE outcomes and higher risk of myocardial infarction in angina or NSTEMI patients, but not significantly associated with cardiac death nor revascularisation. Although there were trends that the risks of cardiac death and revascularisation were higher when ST-segment elevation was observed, more cases might be needed to prove this hypothesis. ST-segment elevation recorded by IC-ECG might be observed when higher pressure or longer duration balloon inflation was performed, indicating local ischaemia. Local myocardial ischaemia could be confirmed by testing myocardial biomarkers. Vassilev's study found that the maximal ST-segment elevation during inflation significantly correlated with final absolute ST-segment elevation and creatine kinase-MB isoenzyme increase post PCI, but not with troponin.¹⁶ Interestingly, IVUS guided stent overexpansion was associated with higher periprocedural creatine kinase-MB isoenzyme level too, but lower risk of target lesion revascularisation and mortality at 1 year.³³ Therefore, IC-ECG might provide useful information for guiding stent expansion.¹⁰ Moreover, Ikenaga and Sato found more plaque rupture, vulnerable plaque or higher lipid core burden when ST-segment elevation was observed, even persisted on IC-ECG.^{10 32} IC-ECG could help to distinguish the plaque, optimising medical therapies or PCI strategies. For instance, we could use vasodilators, loading dose of statin or embolic protection devices to reduce distal embolisation.³² And, Vassilev's studies found that IC-ECG had good correlation with FFR, which might be used in guiding bifurcation PCI procedures.^{5 16}

According to our meta-analysis, EF was significantly higher during follow-up when ST-segment resolution



was observed on IC-ECG in STEMI patients. ST-segment resolution on surface ECG which was observed 90 min after the initial therapy was found to be significantly associated with smaller infarct size and fewer deaths.³⁴ But surface ECG could not explore some small infarct zone sometimes.⁸ Furthermore, restoration of coronary flow didn't mean normal myocardial perfusion nor better outcomes.³⁵ IC-ECG could provide real time ST-segment information, and was found to be well associated with microvascular obstruction and infarct size.⁶ In our meta-analysis, ST-segment resolution recorded by IC-ECG was significantly associated with higher EF, meaning better recovery of heart function. This finding was similar to previous studies. In the subgroup of ST-segment elevation, there were heterogeneities between two studies. In Hishikari's study,⁷ ST-segment elevation recorded by IC-ECG was associated with lower EF during follow-up in NSTEMI patients, while in Yajima's study,⁹ the result was different in anterior myocardial infarction patients. The possible explanation might be the timing of recording IC-ECG. In Hishikari's study, IC-ECG was performed after the PCI procedure while in Yajima's study, IC-ECG was performed after the balloon inflation. On IC-ECG, ST-segment elevation after PCI procedure might indicate prolonged local myocardial ischaemia and worse outcome, as we described above. The result of Hishikari's study that lower EF was observed in ST-segment elevation group, was one of these evidences. On the other hand, there might be myocardium stun after acute myocardial infarction.³⁶ The results of Yajima's study showed that ST-segment elevation recorded by IC-ECG after balloon inflation could predict myocardial viability and better outcomes.⁹ These findings showed that IC-ECG might help to optimise PCI procedure by providing real time information, which could predict clinical outcomes.

The diagnostic studies included in our study reported three reference standards. After excluding Abaci's study, there were still two reference standards. And the reference standards (FFR and troponin) for diagnosing myocardial ischaemia or injury were not perfect. Also, there were too few studies included in our meta-analysis. Considering these situations, we used Bayesian meta-analysis to assess the pooled diagnostic accuracy of IC-ECG. There were already several papers illustrated this method to reduce the bias which came from the different or imperfect reference standards.^{20 21 37 38} The results of our Bayesian meta-analysis showed the promising diagnostic ability of IC-ECG for diagnosing myocardial ischaemia or injury. Furthermore, comparing to other invasive diagnostic tools, IC-ECG could be easily performed and produce real-time information. But some details might affect the diagnostic accuracy when performing IC-ECG. One of the details was the type of guide wire used. Vassilev *et al* found out that the exact size of recording electrode is the last 3 cm of every workhorse guidewire.¹⁶ And Uetani found that the waveforms of IC-ECG were different in the same position between conventional uninsulated guidewires and polymer-covered wires.¹¹ However, we could

not perform sensitivity analysis for different guide wires, limited by the included studies, to verify the hypothesis that different types of guide wires would affect the diagnostic accuracy of IC-ECG. The other one detail was the position of the wire tip. The convenient way of performing IC-ECG was putting the wire tip in the distal position of the target vessel, just like what the most included studies did. In most situation, IC-ECG could detect local ischaemia in the pertinent area of target vessels by using this method. But Vassilev found that when they pulled back the guidewire, the elevated ST-segment would suddenly normalise if the wire tip exited the border of ischaemic territory.¹⁶ And they explored a method to detect and define the ischaemic territory. Further researches should consider how these details affect the diagnostic accuracy of IC-ECG in order to guide the PCI procedures better. Although Abaci's study was excluded when performing the meta-analysis, this study still provided important results. Like Yajima's study which was mentioned above, Abaci's study recorded IC-ECG after balloon inflation, not PCI procedures. Both of these two studies found a good correlation between ST-segment elevation and myocardial viability. In short, IC-ECG had potential value for guiding PCI.

The strengths of our study were the relatively large number of patients analysed. And we used Bayesian meta-analysis to reduce the bias when assessing the diagnostic accuracy. However, there were limitations to our study. First, limited by the published studies, we could only perform meta-analysis of observational studies. And the wide CIs of ORs were the results of low event rates reported in the studies, especially in the no ST-segment elevation group. Second, not all the included studies performed adjustments for confounders, or reports of patients lost to follow-up. Thus, the results of quality assessment were not so satisfactory. Third, there were varied and imperfect reference standards reported in the diagnostic studies. Therefore, we chose Bayesian meta-analysis to assess the pooled diagnostic accuracy, reducing the bias. Fourth, we did not perform sensitivity analysis for the timing when the IC-ECG was recorded, different types of CADs, different definitions of significant ST-segment changes on IC-ECG or different guide wires used in the studies, limited by the number of studies. But in the meta-analysis of clinical outcomes, there were no heterogeneities. These results indicated that these subgroups might have little influence on the ORs. And we found that recording IC-ECG in different phases of PCI procedures might produce different information which might help decision making. Further researches should consider whether the correlation between IC-ECG measures and clinical outcomes depend on the timing of the IC-ECG. Fifth, we did not report publication bias, because given the small numbers of included studies, it was not possible to meaningfully assess publication bias.

CONCLUSIONS

IC-ECG had promising diagnostic ability for local myocardial injury, and could predict clinical outcomes, which could be easily performed and produce real-time information during and after PCI procedures. IC-ECG could be an alternative tool for guiding PCI when other invasive tools are not available.

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