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REVIEW

Impact of Prehospital 12-Lead Electrocardiography and Destination Hospital Notification on Mortality in Patients With Chest Pain

— A Systematic Review —

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for the Japan Resuscitation Council (JRC) Acute Coronary Syndrome (ACS) Task Force and the Guideline Editorial Committee on behalf of the Japanese Circulation Society (JCS) Emergency and Critical Care Committee

Background: To achieve early reperfusion therapy for ST-elevation myocardial infarction (STEMI), proper and prompt patient transportation and activation of the catheterization laboratory are required. We investigated the efficacy of prehospital 12-lead electrocardiogram (ECG) acquisition and destination hospital notification in patients with STEMI.

Methods and Results: This is a systematic review of observational studies. We searched the PubMed database from inception to March 2020. Two reviewers independently performed literature selection. The critical outcome was short-term mortality. The important outcome was door-to-balloon (D2B) time. We used the GRADE approach to assess the certainty of the evidence. For the critical outcome, 14 studies with 29,365 patients were included in the meta-analysis. Short-term mortality was significantly lower in the group with prehospital 12-lead ECG acquisition and destination hospital notification than in the control group (odds ratio 0.72; 95% confidence interval [CI] 0.61–0.85; P<0.0001). For the important outcome, 10 studies with 2,947 patients were included in the meta-analysis. D2B time was significantly shorter in the group with prehospital 12-lead ECG acquisition and destination hospital notification than in the control group (mean difference −26.24; 95% CI −33.46, −19.02; P<0.0001).

Conclusions: Prehospital 12-lead ECG acquisition and destination hospital notification is associated with lower short-term mortality and shorter D2B time than no ECG acquisition or no notification among patients with suspected STEMI outside of a hospital.

Key Words: Door-to-balloon time; Short-term mortality; ST-elevation myocardial infarction (STEMI)

Acute coronary syndrome (ACS) is a significant public health problem in industrialized countries. The target duration from onset to reperfusion therapy in patients with ST-elevation myocardial infarction (STEMI) is ≤120 min, and ≤90 min from first medical contact to reperfusion therapy.[1–3] To achieve these targets, proper and prompt patient transportation and activation of the catheterization laboratory are required.

Several lines of evidence suggest that obtaining a prehospital 12-lead electrocardiogram (ECG) and notifying the

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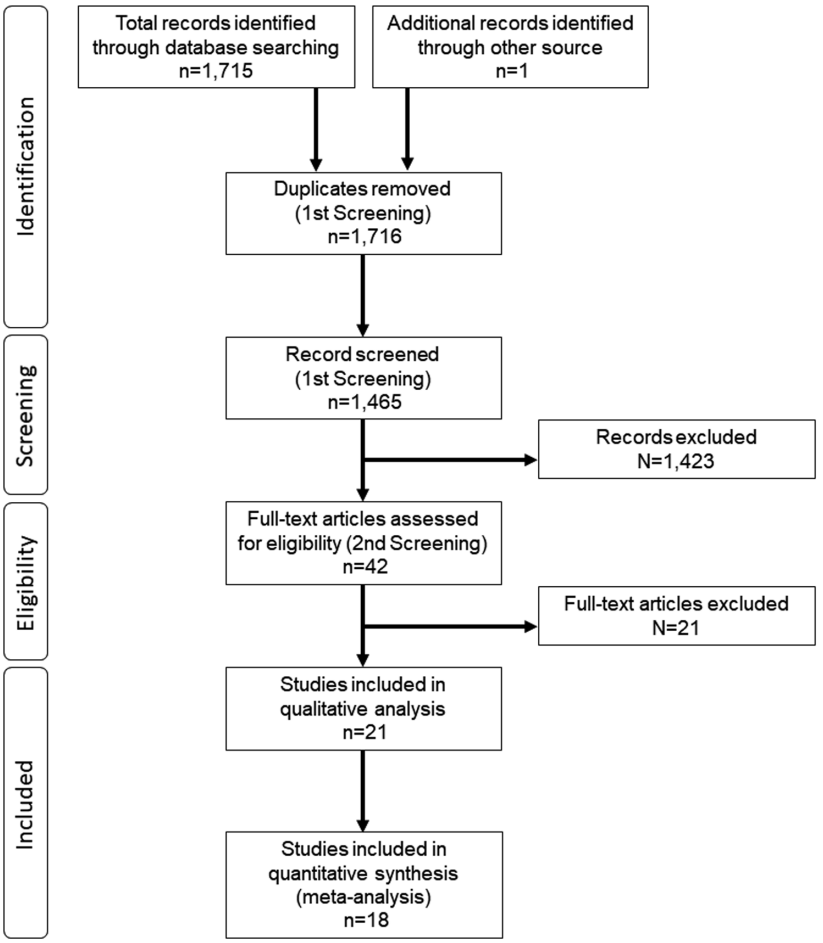

Figure 1. Flow diagram summarizing the evidence search and study selection.

destination hospital help reduce mortality and door-to-balloon (D2B) time compared with no prehospital ECG in patients with STEMI.[4–9] However, a prehospital 12-lead ECG is not currently widely available in Japan. Recently, several small observational studies of prehospital 12-lead ECG acquisition in patients with ACS were conducted in Japan.[10–12] To promote acquisition of a prehospital 12-lead ECG in Japan, we believe that more high-quality evidence from Japan is required. Therefore, we performed a systematic review investigating the impact of prehospital 12-lead ECG acquisition and destination hospital notification on early mortality and D2B time in patients with suspected STEMI that included Japanese studies.

Methods

This systematic review was based on the Cochrane Handbook for Systematic Reviews of Intervention, version 5.1.011 (https://handbook-5-1.cochrane.org/). The results are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[13,14]

The systematic review team was organized by the Japan Resuscitation Council (JRC) Acute Coronary Syndrome (ACS) Task Force, which was established for the 2020 JRC guidelines. The Task Force were organized by the Japan Circulation Society, the Japanese Association of Acute Medicine, and the Japanese Society of Internal Medicine. The JRC ACS Task Force posed the clinically relevant question to be evaluated with this systematic review.

Search Strategy and Data Sources

To guide the systematic review, the research question was posed using the Population, Intervention, Comparator, Outcome, Study Design and Time frame (PICOST) format as follows: P (patients), adult patients with suspected STEMI that occurred outside of a hospital; I (intervention), prehospital 12-lead ECG acquisition and destination

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Table 1. Characteristics of Included Studies

Author	Year	Study design	Country	No. sites	No. patients	Age[A] (years)	% Male[A]	Mortality (%)		Mean D2B[A] (min)
								In-hospital	30 day	
Canto et al[4]	1997	Prospective	US	1,388	2,895	65 vs. 68	69 vs. 59	8.5		Median only
Dhruva et al[5]	2007	Prospective	US	1	49	54 vs. 56	75 vs. 66			80 vs. 146
Brown et al[6]	2008	Prospective	US	1	48	57 vs. 62	80 vs. 71	6.3		73 vs. 130
Diercks et al[7]	2009	Prospective	US	NCDR	7,098	61 vs. 62	68 vs. 65	8.7		Median only
Rao et al[8]	2010	Prospective	US	3	349	60 vs. 60	74 vs. 69	1.4		60 vs. 91
Martinoni et al[9]	2011	Prospective	Italia	Multicenter	1,529	62 vs. 63	77 vs. 75		7.0	Median only
Camp-Rogers et al[30]	2011	Prospective	US	1	53	58 vs. 55	62 vs. 71			49 vs. 67
Ong et al[24]	2013	Prospective	Singapore	6	283	55 vs. 56	94 vs. 89	3.2		
Horvath et al[21]	2012	Prospective	US	1	188	64 vs. 67	71 vs. 65	5.8	6.9	44 vs. 57
Cone et al[26]	2013	Prospective	US	1	85	61 vs. 67	68 vs. 62	0		37 vs. 87
Papai et al[19]	2014	Prospective	Hungary	1	775	60 vs. 62	67 vs. 67	6.3		43 vs. 64
Quinn et al[20]	2014	Prospective	UK	228	14,063	71 vs. 74	67 vs. 60	6.5	11.0	
Savage et al[22]	2014	Prospective	Australia	1	281	62 vs. 61	84 vs. 80		4.3	40 vs. 76
Squire et al[25]	2014	Retrospective	US	73	1,145	64 vs. 64	67 vs. 68	7.4		60 vs. 73
Marino et al[23]	2016	Prospective	Brazil	3	357	62 vs. 62	70 vs. 69	18.5		203 vs. 326
Kawakami et al[10]	2016	Prospective	Japan	1	162	37 vs. 68	84 vs. 97	1.2	0.6	Median only
Kobayashi et al[11]	2016	Retrospective	Japan	1	112	61 vs. 56	84 vs. 84	5.5		Median only
Yufu et al[12]	2019	Prospective	Japan	1	46	71 vs. 66	71 vs. 72			70 vs. 96

[A]Values are shown for the intervention group vs. control group. All studies were observational. D2B time, door-to-balloon time; NCDR, National Cardiovascular Data Registry.

hospital notification; C (Comparator), no ECG acquisition or no notification; O (outcomes), critical outcome, defined as short-term mortality (30-day mortality or in-hospital mortality) from any cause, and important outcome, defined as D2B time; S (study design), randomized control trials (RCTs) or observational studies; T (time frame), all studies published before March 31, 2020.

A systematic search was conducted of the PubMed database for reports published from inception to March 31, 2020. A manual search was also performed to identify additional literature. We searched for full-text manuscripts of human studies published before March 31, 2020. We used a combination of key terms and established a full search strategy (**Supplementary Appendix**).

Study Selection

Two reviewers (T.N. and K.H.) independently screened titles and abstracts (first screening). Next, the same 2 reviewers independently assessed the full-text reports of potentially eligible studies for inclusion (second screening). The 2 reviewers achieved consensus on literature selection. Disagreements were resolved by a third reviewer (H.N.). Studies were included if they met the following criteria: (1) prehospital ECG acquisition and destination hospital notification was used as an intervention; (2) comparison to no prehospital ECG acquisition or no notification was performed; and (3) outcomes were defined as mortality or D2B time. Pilot or single-arm studies and studies with irretrievable full-text reports were excluded. We did not restrict our analysis by country. However, we only included studies involving human subjects.

Assessment of the Risk of Bias

Two experienced reviewers (T.N. and K.H.) independently assessed the risk of bias of all included studies according to the Risk of Bias Assessment tool of Review Manager, version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Studies were categorized as having a low, unclear, or high risk of bias in each element. The risk of bias for each element was considered high when bias was present and likely to affect outcomes and low when bias was not present or present but unlikely to affect outcomes.

Data Synthesis, Analysis

The meta-analysis was performed using Review Manager, version 5.3. For each outcome, we calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using a random-effects model. Statistical heterogeneity was determined based on I^2 values, which were interpreted as follows: 0–40%, may not be important; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity.[15] A funnel plot was constructed to assess the potential for publication bias.[16]

Assessment of Certainty of the Evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of the available evidence.[17,18] The certainty of the evidence was assessed as high, moderate, low, or very low after evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias. We generated an evidence profile table generated using GRADEpro GDT (Evidence Prime, Hamilton, ON, Canada).

Results

Literature Search

The study flow diagram is presented in **Figure 1**. In all, 1,716 citations were identified through the database and manual searches. There were no RCTs. After title and abstract assessment (first screening), 145 citations were eligible. After excluding 21 studies based on full-text

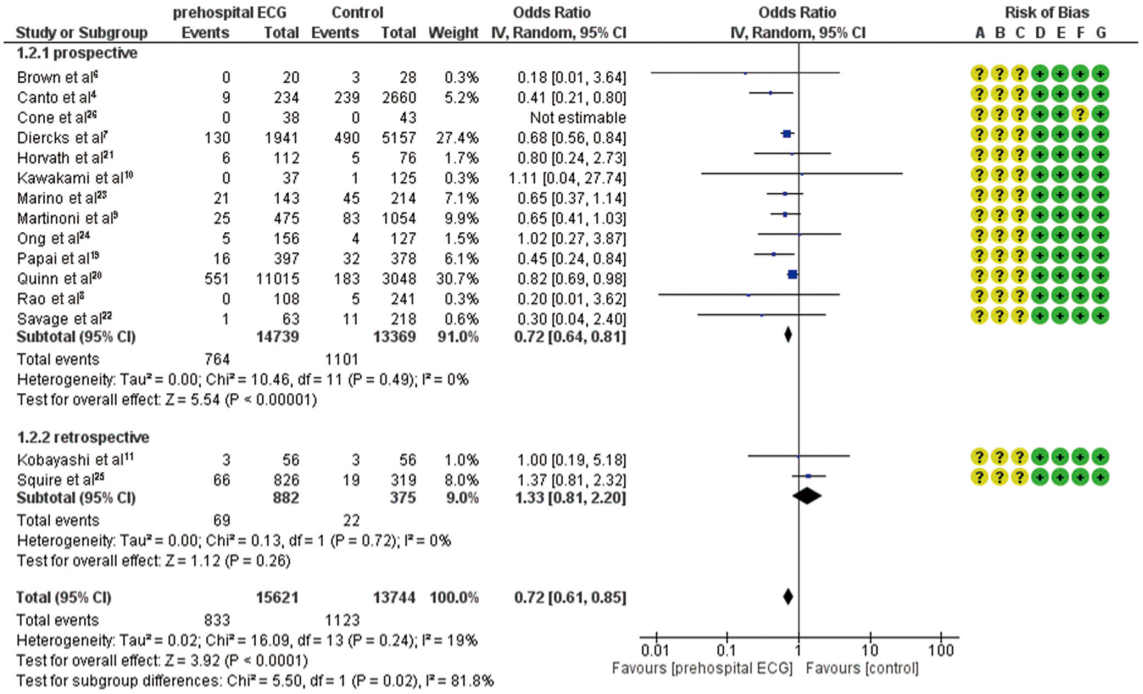

Figure 2. Forest plot comparing the odds ratios for the critical outcome of short-term mortality in patients with prehospital 12-lead electrocardiogram (ECG) acquisition and hospital notification vs. controls. The risk of bias is listed as follows: A, random sequence generation (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of outcome assessment (detection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); and G, other bias. Studies were categorized as having a low (green), unclear (yellow), or high (red) risk of bias in each element. CI, confidence interval; ECG, electrocardiogram; IV, interval variable.

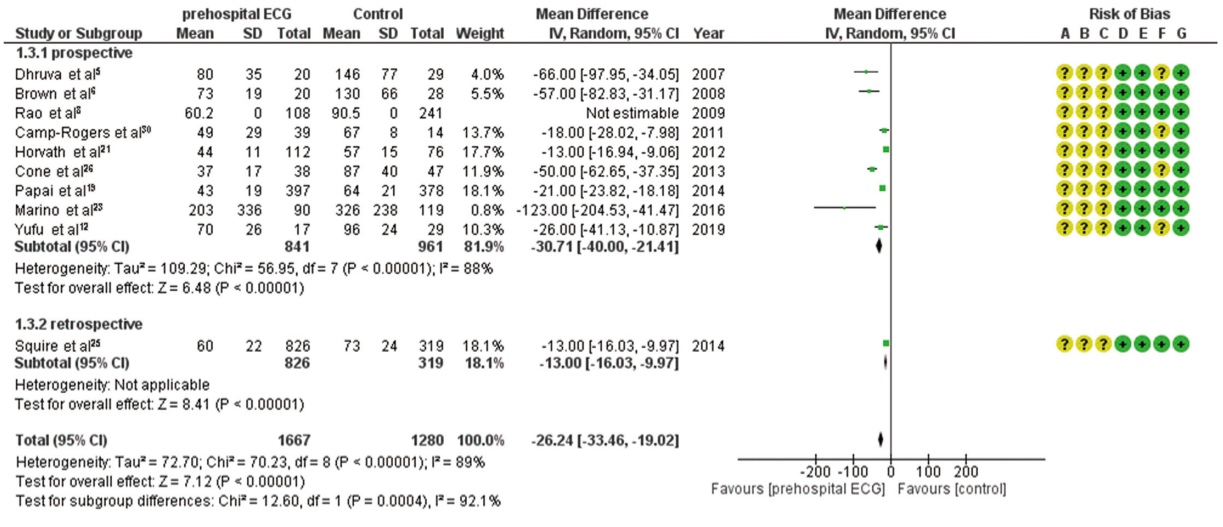

Figure 3. Forest plot comparing the odds ratios for the important outcome of door-to-balloon time in patients with prehospital 12-lead electrocardiogram (ECG) acquisition and hospital notification vs. controls. The risk of bias is listed as follows: A, random sequence generation (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of outcome assessment (detection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); and G, other bias. Studies were categorized as having a low (green), unclear (yellow), or high (red) risk of bias in each element. CI, confidence interval; ECG, electrocardiogram; IV, interval variable; SD, standard deviation.

Table 2. Evidence Profile

No. studies	Study design	Certainty assessment				Other considerations
		Risk of bias	Inconsistency	Indirectness	Imprecision	
In-hospital outcome						
15	Observational studies	Serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect
D2B time (mean)						
10	Observational studies	Serious	Not serious	Not serious	Not serious	Publication bias strongly suspected All plausible residual confounding would reduce the demonstrated effect

No. studies	No. patients		Effect		Certainty	Importance
	Prehospital ECG	No prehospital ECG	Relative (95% CI)	Absolute (95% CI)		
In-hospital outcome						
15	833/15,621 (5.3%)	1,123/13,744 (8.2%)	OR 0.72 (0.61 to 0.85)	22 fewer per 1,000 (from 30 to 11 fewer per 1,000)	⊕⊕◯◯ (Low)	Critical
D2B time (mean)						
10	1,667	1,280	–	26.24 lower (from 33.46 to 19.02 lower)	⊕◯◯◯ (Very low)	Important

CI, confidence interval; D2B time, door-to-balloon time; ECG, electrocardiogram; OR, odds ratio.

assessment (second screening), 21 were included in qualitative analysis. Finally, 18 studies were included in the meta-analysis. Detailed characteristics of each study included are presented in **Table 1**.

Critical Outcomes

For the critical outcome of short-term mortality from any cause, 15 observational studies with 29,365 patients were identified. The forest plot of the critical outcome with the risk of bias is shown in **Figure 2**. Among 29,365 patients, 833 of 15,621 patients (5.3%) in the group with prehospital 12-lead ECG acquisition and hospital notification died, compared with 1,123 of 13,744 patients (8.2%) in the control group. Short-term mortality was significantly lower in the group with prehospital 12-lead ECG acquisition and destination hospital notification than in the control group (OR 0.72; 95% CI 0.61–0.85; P<0.0001). There was no evidence of heterogeneity (I^2=19%). This set of 15 observational studies had low likelihood of publication bias; the funnel plot had a symmetric distribution (**Supplementary Figure 1**).

Important Outcomes

For the important outcome of D2B time, 16 observational studies were identified. However, 6 studies were excluded because D2B time was presented as a median and interquartile range. Ultimately, 10 studies with 2,947 patients were included in the meta-analysis. The forest plot of the important outcome with the risk of bias is shown in **Figure 3**. The group with prehospital 12-lead ECG acquisition and destination hospital notification had significantly shorter D2B time than the control group (mean difference −26.24; 95% CI −33.46, −19.02; P<0.0001). Heterogeneity was suspected because I^2 was high (89%). This set of 10 observational studies had publication bias; the funnel plot had an asymmetric distribution (**Supplementary Figure 2**).

Certainty of the Evidence

We assessed the certainty of the evidence for each outcome. We summarized our findings in the evidence profile table (**Table 2**). For the critical outcome, namely in-hospital mortality, the certainty of the evidence for the effect of prehospital 12-lead ECG acquisition and destination hospital notification was rated as low because of the serious risk of bias. For the important outcome of D2B time, the certainty of the evidence for the effect of prehospital 12-lead ECG acquisition and destination hospital notification was rated as very low because of the serious risk of bias and strong publication bias.

Discussion

This systematic review, which included studies from Japan, demonstrated that a prehospital 12-lead ECG acquisition and destination hospital notification strategy is associated with significantly lower short-term mortality than no ECG acquisition or no notification among adult patients with suspected STEMI outside of a hospital. In addition, the prehospital 12-lead ECG strategy was associated with a significantly shorter D2B time.

To date, several small observational studies have reported that prehospital 12-lead ECG acquisition and destination hospital notification may be associated with lower mortality,[4,7,19,20] but this was not supported by other studies.[6,8–11,21–26] There have been no RCTs evaluating this issue. The 2017 European Society of Cardiology (ESC) guidelines[27] for STEMI included a Class IB recommendation to obtain a 12-lead ECG at the point of first medical contact based on only 2 studies.[28,29] Our systematic review of 15 observational studies, which included studies conducted in Japan, showed that the group with prehospital 12-lead ECG acquisition and destination hospital notification had significantly lower odds of short-term outcomes than the control group. Our results are consistent with the

recommendation in the ESC guidelines.[27]

For patients with STEMI, the JCS and ESC guidelines recommended primary percutaneous coronary intervention within 120 min of symptom onset and 90 min of first contact with medical personnel.[1,27] All studies in this systematic review, including Japanese studies, reported a trend towards shorter D2B time in the group with prehospital 12-lead ECG acquisition and destination hospital notification than in the control group.[5,6,8,12,19,21,23,25,26,30] Our systematic review showed that the group with prehospital 12-lead ECG acquisition and destination hospital notification had significantly shorter D2B time than the control group, by 26 min. Rapid initial response of the cardiac catheterization team and laboratory via hospital notification may have led to shorter D2B time, and possibly even lower mortality. Although prehospital 12-lead ECG acquisition is not sufficiently widespread in Japan, dissemination of the prehospital 12-lead ECG acquisition and destination hospital notification strategy should be considered based on our systematic review, which included studies conducted in Japan.

This study has several limitations. First, this systematic review only included observational studies, so the certainty of the evidence was low. However, we consider that our results should be taken seriously because short-term mortality is a critical outcome for patients with ACS. For D2B time, the studies that were included in the analysis had considerable heterogeneity. However, even in the studies that were excluded from the systematic review because only median D2B time was available, there was a trend towards shorter D2B time in the group with prehospital 12-lead ECG acquisition and destination hospital notification (**Supplementary Table**). RCTs are needed to validate these findings in the future. Second, we extracted citations only from the PubMed database. Finally, there was nearly 20 years between the first (1997) and most recent (2019) studies, which may have resulted in differences in healthcare systems. Further RCTs are required to support our findings.

Conclusions

Prehospital 12-lead ECG acquisition and destination hospital notification are associated with lower short-term mortality than no ECG acquisition or no notification among patients with suspected STEMI outside of a hospital. In addition, the prehospital 12-lead ECG and destination hospital notification was associated with shorter D2B time.

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Disclosures

T. Matoba is a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest with regard to this article.

Contributors

T.N. contributed to the screening of articles, the data analysis, interpretation of the results, and preparation of the final report. K.H. contributed to the screening of articles and interpretation of the results. Y.T., M.K. and H.N. contributed to the formulation of the concept of the JRC ACS guidelines. Other members contributed to the final report. All authors approved the final version.

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Supplementary Files

Please find supplementary file(s);
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