Prehospital Administration of Aspirin and Nitroglycerin for Patients With Suspected Acute Coronary Syndrome
— A Systematic Review —

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Background: Recent guidelines for acute coronary syndrome (ACS) recommend prehospital administration of aspirin and nitroglycerin for ACS patients. However, there is no clear evidence to support this. We investigated the benefits and harms of prehospital administration of aspirin and nitroglycerin by non-physician healthcare professionals in patients with suspected ACS.

Methods and Results: We searched the PubMed database and used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence. Three retrospective studies for aspirin and 1 for nitroglycerin administered in the prehospital setting to patients with acute myocardial infarction were included. Prehospital aspirin administration was associated with significantly lower 30-day and 1-year mortality compared with aspirin administration after arrival at hospital, with odds ratios (OR) of 0.59 (95% confidence interval [CI] 0.35–0.99) and 0.47 (95% CI 0.36–0.62), respectively. Prehospital nitroglycerin administration was also associated with significantly lower 30-day and 1-year mortality compared with no prehospital administration (OR 0.34 [95% CI 0.24–0.50] and 0.38 [95% CI 0.29–0.50], respectively). The certainty of evidence was very low in both systematic reviews.

Conclusions: Our systematic reviews suggest that prehospital administration of aspirin and nitroglycerin by non-physician healthcare professionals is beneficial for patients with suspected ACS, although the certainty of evidence is very low. Further investigation is needed to determine the benefit of the prehospital administration of these agents.

Key Words: Acute coronary syndrome; Aspirin; Emergency medical service (EMS); Nitroglycerin; Prehospital

Aspirin and nitroglycerin have been recommended as initial drug therapy for acute coronary syndrome (ACS). Current guidelines for ACS recommend that aspirin is given as soon as possible to ACS patients without contraindications.1–3 Aspirin has been shown to reduce mortality in ACS.4 Furthermore, its effect has been shown to be greater when administered earlier after symptom onset.5 Nitroglycerin is similarly widely used for the effective treatment of the chest pain of angina or suspected ACS. Studies conducted before the era of reperfusion therapy reported the effectiveness of nitroglycerin in reducing infarct size and in-hospital mortality in patients with acute myocardial infarction (AMI) who were admit-
Methods

The JRC ACS Task Force for Guideline 2020 was established by the JCS, the Japanese Association of Acute Medicine, and the Japanese Society of Internal Medicine. The Task Force established 12 clinically relevant questions; in this paper we assess the following 2 clinical questions (CQ): should patients with suspected ACS be administered aspirin by non-physician healthcare professionals in the prehospital setting (CQ1); and should patients with suspected ACS be administered nitroglycerin by non-physician healthcare professionals in the prehospital setting (CQ2)?

After discussion between JRC ACS Task Force and the Guidelines Editorial Committee, the Population Intervention Comparator Outcome Study design and Time frame (PICOST) was to guide the systematic review search, as described below.

CQ1: Aspirin

P (patients): adult patients with suspected ACS in the prehospital setting
I (intervention): prehospital administration of aspirin by non-physician healthcare professionals
C (comparisons, controls): no prehospital administration of aspirin by non-physician healthcare professionals
O (outcomes): mortality, intracranial bleeding, reinfarction, revascularization, stroke, major hemorrhage, infarct size, and electrocardiogram (ECG) resolution ≥50%
S (study designs): randomized controlled trials (RCTs)
T (time frame): studies published before August 14, 2020.

CQ2: Nitroglycerin

P (patients): adult patients with suspected ACS in the prehospital setting
I (intervention): prehospital administration of nitroglycerin by non-physician healthcare professionals
C (comparisons, controls): no prehospital administration of nitroglycerin by non-physician healthcare professionals
O (outcomes): mortality
S (study designs): RCTs and non-randomized studies published in English
T (time frame): studies published before July 15, 2020.

Assessment of the Risk of Bias

The Cochrane Risk-of-Bias Tool (RevMan 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for appraising RCTs and non-RCTs. An experienced pair of reviewers (N.N. and T.Y.) independently appraised the risk of bias of all included studies. Studies were categorized as having a “low”, “unclear”, or “high” risk of bias in each domain. The risk of bias for each element was considered “high” when bias was present and likely to affect the outcomes and “low” when bias was not present or present but unlikely to affect the outcomes.

Data Extraction and Management

The following data were extracted: author(s), title, journal name, year of publication, website (URL), and abstract. Two independent reviewers (N.N., T.Y.) screened the abstracts and titles of the studies and subsequently reviewed the full-text articles. Disagreements were reconsidered and discussed until a consensus was reached. The full text of articles included in the final selection were independently reviewed by another 2 reviewers (Y.T., M.K.). Disagreements were resolved by a third reviewer (H.N.).
Prehospital Aspirin and Nitroglycerin for ACS

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to rate the certainty of the evidence as to whether patients with suspected ACS should be administered aspirin and nitroglycerin by non-physician healthcare professionals in the prehospital setting. The certainty of the evidence was assessed as “high,” “moderate,” “low”, or “very low” by evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

### Table 1. Study Characteristics and Findings

| Authors, Year | Patients   | Comparison                                                                 | No. patients | 30-day Mortality (%) | 1-year Mortality (%) | Reinfarction (%) | Stroke (%) | Major Hemorrhage (%) |
|---------------|------------|-----------------------------------------------------------------------------|--------------|----------------------|---------------------|------------------|------------|----------------------|
| **Aspirin**   |            |                                                                             |              |                      |                     |                  |            |                      |
| Zijlstra et al (2002) | 1,702 patients with STEMI | Administration of aspirin with heparin before transportation to hospital | 860          | 26 (3.0)             | 1 (0.1)             | 43 (5.0)         |            |                      |
|               |            | Administration of aspirin with heparin in the emergency room of the hospital | 842          | 24 (2.9)             | 3 (0.4)             | 59 (7.0)         |            |                      |
| Barbash et al (2002) | 922 patients with STEMI | Prehospital administration of aspirin (self-administration or administration in the mobile CCU) | 338          | 16 (4.9)             | 14 (4.1)            |                  |            |                      |
|               |            | In-hospital administration of aspirin (administration in the emergency room or CCU) | 584          | 64 (11.1)            | 17 (2.9)            |                  |            |                      |
| Strandmark et al (2015) | 1,726 patients with AMI | Prehospital administration of aspirin by EMS | 995          | 51 (5.1)             | 102 (9.4)           |                  |            |                      |
|               |            | No prehospital administration of aspirin by EMS | 731          | 72 (10.1)            | 143 (18.6)          |                  |            |                      |
| **Nitroglycerin** |            |                                                                             |              |                      |                     |                  |            |                      |
| Strandmark et al (2015) | 1,726 patients with AMI | Prehospital administration of nitroglycerin by EMS | 1,142        | 52 (4.6)             |                     |                  |            |                      |
|               |            | No prehospital administration of nitroglycerin by EMS | 584          | 71 (12.2)            |                     |                  |            |                      |

Unless indicated otherwise, data are given as n (%). AMI, acute myocardial infarction; CCU, cardiac care unit; EMS, emergency medical services; STEMI, ST-segment elevation myocardial infarction.

**Rating the Certainty of Evidence**

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to rate the certainty of the evidence as to whether patients with suspected ACS should be administered aspirin and nitroglycerin by non-physician healthcare professionals in the prehospital setting. The certainty of the evidence was assessed as “high,” “moderate”, “low”, or “very low” by evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias.
if the reason for heterogeneity could not be explained and if the $I^2$ value was $\geq 50\%$. We generated a funnel plot to investigate potential publication bias. The estimates for each outcome were pooled using a random effects model. The meta-analysis was performed based on all published data and data made available to us. All analyses were undertaken using Review Manager software (RevMan 5.3).

**Statistical Analysis**

The results were summarized using a random effects model to facilitate the pooling of estimates of the treatment effects. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for dichotomous outcomes. Heterogeneity between trials for each outcome was evaluated using the $I^2$ statistic to quantify inconsistency, and was considered significant if the $I^2$ value was $\geq 50\%$. We generated a funnel plot to investigate potential publication bias. The estimates for each outcome were pooled using a random effects model. The meta-analysis was performed based on all published data and data made available to us. All analyses were undertaken using Review Manager software (RevMan 5.3).

### Figure 2

Forest plot for each outcome following prehospital aspirin administration: (A) 30-day mortality, (B) 1-year mortality, (C) reinfarction, (D) stroke, and (E) major hemorrhage.
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Results

**CQ1: Aspirin**

**Literature Search** The study flow diagram is presented in Figure 1. We identified 329 citations through the database search. Twelve studies were assessed for eligibility based on the titles and abstracts. After full-text assessment, 3 citations were included in the meta-analysis.15–17

**Study Characteristics** No RCTs were identified, and all 3 identified citations were non-RCTs.15–17 Details of the individual studies are presented in Table 1. Analysis of the observational study reported by Strandmark et al17 became possible by asking the authors for detailed data not described in the original paper.

**Critical Outcomes** Forest plots of the critical outcomes with the risk of bias are shown in Figure 2. For the critical outcome of 30-day mortality, 3 observational studies were identified.15–17 Among 4,350 patients, 93 of 2,193 patients (4.2%) in the prehospital administration group and 160 of 2,157 patients (7.4%) in the control group died within 30 days. For the critical outcome of 1-year mortality, 1 observational study was identified.17 In that study, among 1,726 patients, 102 of 995 patients (10.3%) in the prehospital administration group and 143 of 731 patients (19.6%) in the control group died within 1 year. The prehospital administration group had significantly lower 30-day and 1-year mortality than the control group (OR 0.59 [95% CI: 0.35–0.99; P<0.01] and 0.47 [95% CI: 0.36–0.62; P<0.01], respectively). For the critical outcome of reinfarction, 1 observational study was identified.16 Among the 922 patients in that study, reinfarction was observed in 14 of 338 patients (4.1%) in the prehospital administration group and 17 of 584 patients (2.9%) in the control group. For the critical outcome of stroke, 1 observational study was identified.15 Among the 1,702 patients in that study, stroke was observed in 1 of 860 patients (0.1%) in the prehospital administration group and 3 of 842 patients (0.4%) in the control group. The prehospital administration group had significantly lower stroke (OR 0.33 [95% CI: 0.03 to 3.13]; P<0.01) than the control group. For the critical outcome of major hemorrhage, 1 observational study was identified.15 Among the 1,702 patients in that study, major hemorrhage was observed in 43 of 860 patients (5.0%) in the prehospital administration group and 59 of 842 patients (7.0%) in the control group. The prehospital administration group had significantly lower major hemorrhage (OR 0.71 [95% CI: 0.49 to 1.04]; P<0.01) than the control group.

**Table 1. Evidence Profile Table for Aspirin**

| No. studies | Certainty assessment |
|-------------|----------------------|
| Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 30-day mortality15–17 | 3 Observational studies | Very seriousA | SeriousB | Very seriousC,D | SeriousE | None |
| 1-year mortality17 | 1 Observational study | Very seriousA | Not serious | Very seriousC,D | SeriousE | None |
| Reinfarction16 | 1 Observational study | Very seriousA | Not serious | Very seriousC,D | SeriousE,F | None |
| Stroke15 | 1 Observational study | Very seriousA | Not serious | Very seriousC,D | SeriousE,F | None |
| Major hemorrhage15 | 1 Observational study | Very seriousA | Not serious | Very seriousC,D | SeriousE | None |

**Table 2. Evidence Profile Table for Aspirin**

| No. studies | No. patients (%) | Effect | Certainty | Importance |
|-------------|-----------------|--------|-----------|------------|
| Prehospital | In-hospital | Relative (95% CI) | Absolute (95% CI) |
| 30-day mortality15–17 | 3 | 93/2,193 (4.2) | 160/2,157 (7.4) | OR 0.61 (0.38 to 0.98) | 28 fewer per 1,000 (from 45 fewer to 1 fewer) | ⊕⊕⊕⊕ | Very low | Critical |
| 1-year mortality17 | 1 | 102/995 (10.3) | 143/731 (19.6) | OR 0.52 (0.41 to 0.66) | 83 fewer per 1,000 (from 105 fewer to 57 fewer) | ⊕⊕⊕ | Very low | Critical |
| Reinfarction16 | 1 | 14/338 (4.1) | 17/584 (2.9) | OR 1.42 (0.71 to 2.85) | 12 more per 1,000 (from 8 fewer to 50 more) | ⊕⊕⊕ | Very low | Critical |
| Stroke15 | 1 | 1/860 (0.1) | 3/842 (0.4) | OR 0.33 (0.03 to 3.13) | 2 fewer per 1,000 (from 3 fewer to 8 more) | ⊕⊕⊕ | Very low | Critical |
| Major hemorrhage15 | 1 | 43/860 (5.0) | 59/842 (7.0) | OR 0.71 (0.49 to 1.04) | 19 fewer per 1,000 (from 34 fewer to 3 more) | ⊕⊕⊕ | Very low | Important |
administration group and 3 of 842 patients (0.4%) in the control group. For the important outcome of major hemorrhage, 1 observational study was identified. In that study, among 1,702 patients, major hemorrhage was observed in 43 of 860 patients (5.0%) in the prehospital administration group and 59 of 842 patients (7.0%) in the control group. For the critical outcome of reinfarction and stroke, and for the important outcome of major hemorrhage, there were no significant differences between the prehospital administration and control groups. There were no clinical papers assessing the outcome of intracranial bleeding, revascularization, infarct size, or ECG resolution ≥50%.
We judged the level of evidence to be very low because: the study population was limited to cases finally diagnosed with AMI; the prehospital administration of aspirin was not performed by a healthcare professional other than a physician; the number of cases was small; and the 95% CI crosses the threshold of significant benefits and significant harm.

Certainty of Evidence We assessed the certainty of evidence for each outcome and present a summary in Table 2. We judged the level of evidence to be very low because: patient backgrounds differed between the 2 groups; $F>50\%$ and variation in point estimation; the study population was limited to cases finally diagnosed with AMI; the prehospital administration of aspirin was not performed by a healthcare professional other than a physician; the number of cases was small; and the 95% CI crosses the threshold of significant benefits and significant harm.

Certainty of Evidence We assessed the certainty of evidence for each outcome and present a summary in Table 3. We judged the level of evidence to be very low because patient backgrounds differed between the 2 groups, the study population was limited to patients finally diagnosed with AMI, and there was only a small number of cases.

CQ2: Nitroglycerin

Certainty of Evidence We assessed the certainty of evidence for each outcome and present a summary in Table 3. We judged the level of evidence to be very low because patient backgrounds differed between the 2 groups, the study population was limited to patients finally diagnosed with AMI, and there was only a small number of cases.

Discussion

The present systematic reviews showed that prehospital administration of aspirin to patients with AMI by non-physician healthcare professionals significantly decreased 30-day and 1-year mortality compared with no prehospital aspirin administration, as did prehospital nitroglycerin administration. The present study suggests that prehospital administration of aspirin and nitroglycerin by non-physician healthcare professionals is beneficial in patients with suspected ACS, although the certainty of evidence was very low for both drugs because of the included risk of bias. In the GRADE approach for guideline development, the evidence-to-decision framework clarifies the reasons for determining recommendations, taking into account the favorable and unfavorable effects of an intervention, its costs, and its value for patients. The present systematic reviews provide pieces of evidence that fill the knowledge gaps in the current clinical guidelines.

Early treatment with aspirin has been shown to be beneficial in ACS patients, and the administration of aspirin to ACS patients after their arrival at hospital can result in treatment delay. No studies have examined whether prehospital administration of aspirin or nitroglycerin to patients with suspected ACS improves clinical outcomes.
compared with no administration. In the present study, we were able to conduct a systematic review in retrospective observational studies of patients with a confirmed diagnosis of AMI, in place of those with suspected prehospital ACS. The nitroglycerin analysis was made possible by contacting the authors of a single-center, retrospective observational study reported in 2015.17 identified during the course of searching for evidence for aspirin, and asking for detailed data. The 2010 and 2015 JRC guidelines state that insufficient evidence exists to support or refute the routine administration of aspirin and/or nitroglycerin to patients with suspected ACS in the prehospital setting.8,9 We believe that the present study is the first to provide important evidence to fill the knowledge gaps in these recent guidelines.

There have been concerns about adverse events following prehospital administration of aspirin and nitroglycerin. However, the incidence of stroke and major hemorrhage did not differ significantly between the prehospital and in-hospital administration groups in this systematic review. Furthermore, previous studies reported that aspirin was rarely associated with adverse events when administered by prehospital personnel for patients with suspected ACS.18 With regard to nitroglycerin, prehospital administration to patients with suspected ST-segment elevation myocardial infarction did not result in a clinically significant decrease in blood pressure compared with patients who did not receive nitroglycerin.19 Thus, there is little risk of adverse events following a single dose of aspirin and nitroglycerin, and prehospital administration is likely safe. Therefore, early administration in selected patients without contraindications is certainly reasonable.

The prehospital administration of aspirin and nitroglycerin has already been implemented in many countries, with both agents having the advantages of being inexpensive and easy to administer by emergency medical service (EMS) personnel to patients with suspected ACS, but prehospital administration has not been approved in Japan. In the future, EMS personnel should be able to administer aspirin and nitroglycerin in the prehospital setting in Japan as well. The 2018 JCS guideline for ACS states that further investigation is needed to confirm the benefit of prehospital administration of aspirin and nitroglycerin by EMS personnel. As pointed out earlier, there is a knowledge gap in previous guidelines, and it is useful to accumulate evidence regarding the prehospital administration of aspirin and nitroglycerin to confirm the safety of these drugs in the prehospital setting before the implementation of prehospital administration by EMS personnel in Japan. We propose the collection of data from patients with and without prehospital administration of aspirin and nitroglycerin by physicians attending by rapid response (road and air) medical vehicles. These data may strengthen the certainty of evidence and recommendations in future guidelines. In addition, it would be invaluable for the Medical Control Council to establish an appropriate protocol for prehospital treatment of ACS patients, including a prehospital 12-lead ECG for the appropriate diagnosis of ACS.20

Unfortunately, the present study has several limitations, with the chief limitation being that the certainty of evidence is very low. First our systematic reviews contained no RCTs, and only 3 observational studies for aspirin15–17 and one observational study for nitroglycerin.19 This may be due, in part, to the fact that we only searched the PubMed database and restricted the language to English because of limited resources for this study. Second, the study populations of all included papers consisted of patients who were finally diagnosed with AMI. Third, there were differences in patient characteristics in each observational study, including the frequency of prehospital administration of drugs other than aspirin and nitroglycerin. For these reasons (i.e., the risk of bias, imprecision, and indirectness), the certainty of evidence was downgraded to very low. Although these systematic reviews of studies of the prehospital administration of aspirin and nitroglycerin, which had not been previously evaluated, do provide small evidence that will constitute an advancement for the guidelines.

In conclusion, prehospital administration of aspirin and nitroglycerin by non-physician healthcare professionals is suggested to be beneficial for patients with suspected ACS, although the certainty of evidence is very low. Further studies are needed to confirm the benefit of prehospital administration of aspirin and nitroglycerin.

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Disclosures

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

Author Contributions

All authors were involved in the study design. N.N. and T.Y. identified the studies included in the meta-analysis and analyzed the data. N.N. and T.Y. drafted the manuscript, Y.T., M.K., T. Matoba, and H.N. reviewed the manuscript. All authors were involved in data interpretation and discussion. All authors had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the analysis. All authors read and approved the final manuscript.

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**Supplementary Files**

Please find supplementary file(s);

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