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REVIEW

Effects of Door-In to Door-Out Time on Mortality Among ST-Segment Elevation Myocardial Infarction Patients Transferred for Primary Percutaneous Coronary Intervention

— Systematic Review and Meta-Analysis —

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Background: Primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) is now widely accepted. Recent guidelines have focused on total ischemic time, because shorter total ischemic time is associated with a more favorable prognosis. The door-in to door-out (DIDO) time, defined as time from arrival at a non-PCI-capable hospital to leaving for a PCI-capable hospital, may affect STEMI patient prognosis. However, a relevant meta-analysis is lacking.

Methods and Results: We searched PubMed for clinical studies comparing short-term (30-day and in-hospital) mortality rates of STEMI patients undergoing primary PCI with DIDO times of ≤30 vs. >30 min. Two investigators independently screened the search results and extracted the data. Random effects estimators with weights calculated by the inverse variance method were used to determine pooled risk ratios. The search retrieved 1,260 studies; of these, 2 retrospective cohort studies (15,596 patients) were analyzed. In the DIDO time ≤30 and >30 min groups, the primary endpoint (i.e., in-hospital or 30-day mortality) occurred for 51 of 1,794 (2.8%) and 831 of 13,802 (6.0%) patients, respectively. The incidence of the primary endpoint was significantly lower in the DIDO time ≤30 min group (odds ratio 0.45; 95% confidence interval 0.34–0.60).

Conclusions: Our findings suggest that a DIDO time ≤30 min is associated with a lower short-term mortality rate. However, further larger systematic reviews and meta-analyses are needed to validate our findings.

Key Words: Door-in to door-out time; Primary percutaneous coronary intervention; Reperfusion; ST-elevation myocardial infarction

Primary percutaneous coronary intervention (PCI) for patients with ST-elevation myocardial infarction (STEMI) is now widely accepted as an acute treatment. The efficacy of timely PCI has also been established.[1] A recent analysis of 20,042 acute coronary syndrome (ACS) patients from a Japanese nationwide registry revealed that the overall 30-day all-cause mortality rate of STEMI (n=10,242) who undergoing primary PCI was 4%.[2] A previous guideline recommended a door-to-balloon time of <90 min when STEMI patients are admitted to PCI-capable hospitals.[3] However, the CREDO-Kyoto Acute Myocardial Infarction (AMI) Registry, a large-scale observational study of AMI in Japan, revealed that long-term clinical outcomes were not significantly different between

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(Footnote continued the next page.)

patients who had a door-to-balloon time <90 min and those who did not.[4] A door-to-device time <90 min is still the minimum acceptable time, but not the target time. The goal should be to make the time from the onset of STEMI to reperfusion as short as possible, considering that a shorter total ischemic time is associated with a more favorable prognosis. The ability of non-PCI-capable hospitals to rapidly identify patients with STEMI and transfer them to PCI-capable hospitals to shorten total ischemic time is critical. Several studies have already reported the importance of door-in to door-out (DIDO) time, defined as the time interval from arrival at a non-PCI-capable hospital to transfer to a PCI hospital.[5–7] Previous guidelines for STEMI recommended that the DIDO time should be ≤30 min,[8] and this has been widely adopted as an essential metric of the quality of STEMI care.[3] In addition, factors associated with DIDO times have been investigated.[6,7,9–12] However, a meta-analysis of recent relevant studies is lacking. Accordingly, this systematic review aimed to clarify the association between DIDO time and short-term mortality among STEMI patients transferred for primary PCI by analyzing the recent literature.

Methods

The Japan Resuscitation Council (JRC) ACS Task Force was established for the JRC guideline 2020 organized by the Japanese Circulation Society, the Japanese Association of Acute Medicine, and the Japanese Society of Internal Medicine. The JRC ACS Task Force set 12 clinically relevant questions against which this systematic review was conducted. Based on a discussion between the JRC ACS Task Force and the Guidelines Editorial Committee, the Population Intervention Comparator Outcome Study design and Time frame (PICOST) parameters to guide a systematic review search were set as follows:

P (population): STEMI patients who presented to non-PCI-capable hospitals and were transferred to a PCI-capable hospital
I (interventions): DIDO time ≤30 min
C (comparators, controls): DIDO time >30 min
O (outcomes): in-hospital or 30-day mortality
S (study design): observational trials (there were no randomized control trials [RCTs]) published in English, excluding review papers
T (time frame): all literature published up to April 15, 2020.

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13,14]

Search Strategies

Published reports in the PubMed database were systematically searched to retrieve relevant articles for review. We searched for full-text papers describing interventions in humans published before April 2020. A combination of key terms was used to establish the search strategy (**Supplementary Figure 1**).

Study Selection and Inclusion Criteria

The study population consisted of adult patients with ACS in an emergency setting that included prehospital care. We did not restrict our analysis by country; however, we included only studies published in English. We sought to determine whether DIDO time affected short-term mortality rates among STEMI patients who underwent primary PCI. Outcomes were compared between DIDO times ≤30 and >30 min. The critical outcome for this study was short-term mortality, which included 30-day and in-hospital mortality.

Risk of Bias Assessment

The Cochrane Risk of Bias Tool (Review Manager 5.3; The Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) was used to appraise RCTs, non-RCTs, interrupted time series, and controlled before-and-after studies. Experienced pairs of reviewers (J.Y., T. Matoba) independently appraised the risk of bias in all the 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 was 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 (J.Y., T. Matoba) screened the abstracts and titles of the studies and subsequently reviewed the full texts. Disagreements were resolved by a third reviewer (H.N.).

Rating Evidence Certainty

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to rate the certainty of the evidence as to whether the DIDO time affected short-term mortality among STEMI patients transferred for primary PCI.[15–18] The confidence of the evidence was assessed as "high", "moderate", "low", or "very low" by evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Statistical Analysis

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) are used to express dichotomous outcomes. Heterogeneity between trials for each outcome was evaluated using the I^2 statistic to quantify inconsistency,[19] and the findings were considered significant if the reason for heterogeneity could not be explained and the I^2 value was ≥50%. A funnel plot was generated to investigate potential publication bias. The estimates for each outcome were pooled using a ran-

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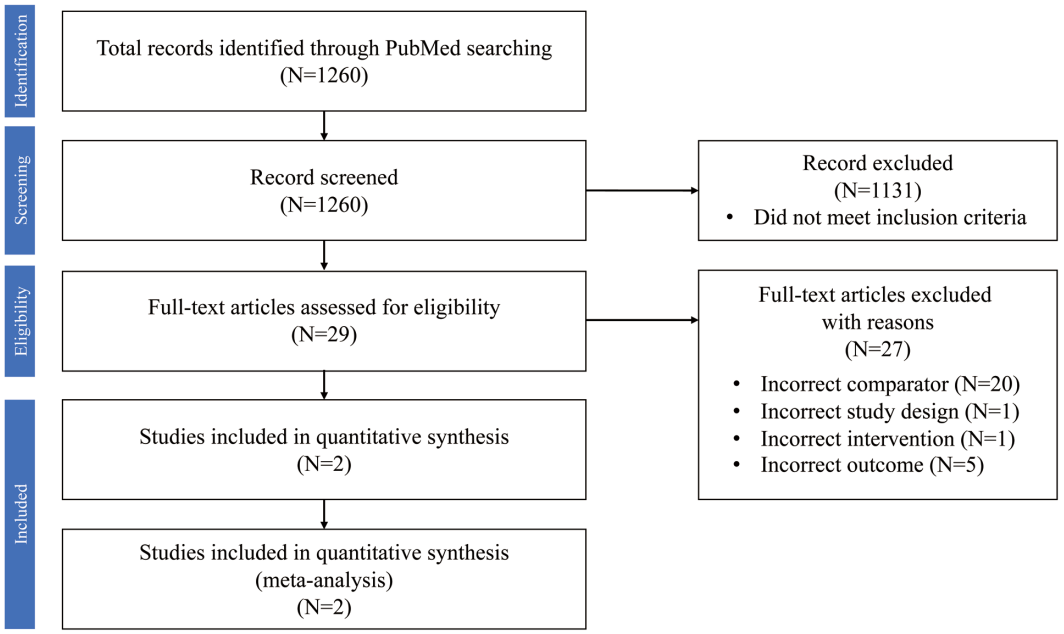

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of randomized and observational studies published between PubMed inception and April 15, 2020.

Table 1. Characteristics of the Included Trials

Study	Year	Study type	Patients	Comparison	Outcomes
Wang et al[6]	2011	Retrospective cohort study	14,821 patients with STEMI transferred to 298 STEMI receiving centers for primary PCI in the ACTION Registry–Get With the Guidelines[23] between January 2007 and March 2010 (USA)	DIDO ≤30 min (n=1,627) vs. DIDO >30 min (n=13,194)	Factors associated with a DIDO time >30 min, overall DTB times, and risk-adjusted in-hospital mortality
Shi et al[7]	2018	Retrospective cohort study	966 STEMI patients transferred for primary PCI in the Ontario portion of the Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System between January and December 2012 (Canada)	DIDO ≤30 min (n=194) vs. DIDO >30 min (n=722)	Independent predictors of timely DIDO as well as the association between DIDO times and 30-day mortality

DIDO, door-in door-out; DTB, door to balloon time; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

dom effects model, and the meta-analysis was performed based on all available published data. All analyses were performed using Review Manager software 5.3.

Results

Study Selection

We identified 1,260 studies in PubMed. Only 29 remained after the title and abstract review. The full-text review process eliminated another 27 studies because of an inappropriate comparator, study design, intervention, or outcome. This left 2 retrospective cohort studies[6,7] that were included in the present meta-analysis (**Figure 1**).

Study Characteristics

The characteristics of the included studies are summarized in **Table 1**. In all, 15,596 patients were included in the 2 retrospective cohort studies.[6,7] In both studies, patients who received fibrinolytic therapy at the non-PCI-capable hospital were excluded to enable examination of the performance related to the timeliness of primary PCI. There were 1,821 patients with a DIDO time ≤30 min and 13,916 patients with a DIDO time >30 min. The patients' characteristics are summarized in **Table 2**.[6,7]

Outcomes

A forest plot of the primary outcome is shown in **Figure 2**. The primary endpoint, in-hospital or 30-day mortality, was observed in 51 of 1,794 patients (2.8%) in the group with a DIDO time ≤30 min and in 831 of 13,802 patients (6.0%) with a DIDO time >30 min. The incidence of the primary endpoint was significantly lower in the group with a DIDO time ≤30 min than in the group with a DIDO time >30 min (OR 0.45 [95% CI 0.34–0.60]; 34 fewer per 1,000 [95% CI 41 fewer to 25 fewer]; **Table 3**).

Table 2. Patient Characteristics

Study	Year	DIDO time (min)	No. patients	Age	Males
Wang et al[6]	2011	≤30	1,627	58 [50–67][A]	1,269 (78.0)
		>30	13,194	61 [52–71][A]	9,151 (69.4)
Shi et al[7]	2018	≤30	194	18–55 years: 87 (44.8)	161 (83.0)
				56–65 years: 51 (26.3)	
				66–75 years: 36 (18.6)	
				≥75 years: 20 (10.3)	
		>30	722	18–55 years: 230 (29.8)	555 (74.9)
				56–65 years: 234 (30.3)	
				66–75 years: 154 (19.9)	
				≥75 years: 154 (19.9)	

Study	Hypertension	Diabetes	Previous MI	Previous stroke	After-hours presentation[B]	EMS transport to first hospital
Wang et al[6]	910 (55.9)	271 (16.7)	263 (16.2)	50 (3.1)	1,001 (61.5)	472 (29.0)
	8,277 (62.7)	3,246 (24.6)	2,333 (17.7)	723 (5.5)	8,720 (66.1)	3,589 (27.2)
Shi et al[7]	93 (47.9)	39 (20.1)	21 (10.8)	7 (3.6)	122 (62.9)	91 (47.0)
	390 (50.5)	167 (21.6)	99 (12.8)	30 (30.9)	508 (65.8)	262 (33.9)

Unless indicated otherwise, data are given as n (%). [A]Median [interquartile range] age in years. [B]After-hours presentation was defined as presentation to a hospital between 17:00 and 08:00 hours on weekdays and anytime on weekends (Wang et al[6]) or between 17:00 and 09:00 hours on weekdays and anytime on weekends (Shi et al[7]). DIDO, door-in door-out; EMS, emergency medical services; MI, myocardial infarction.

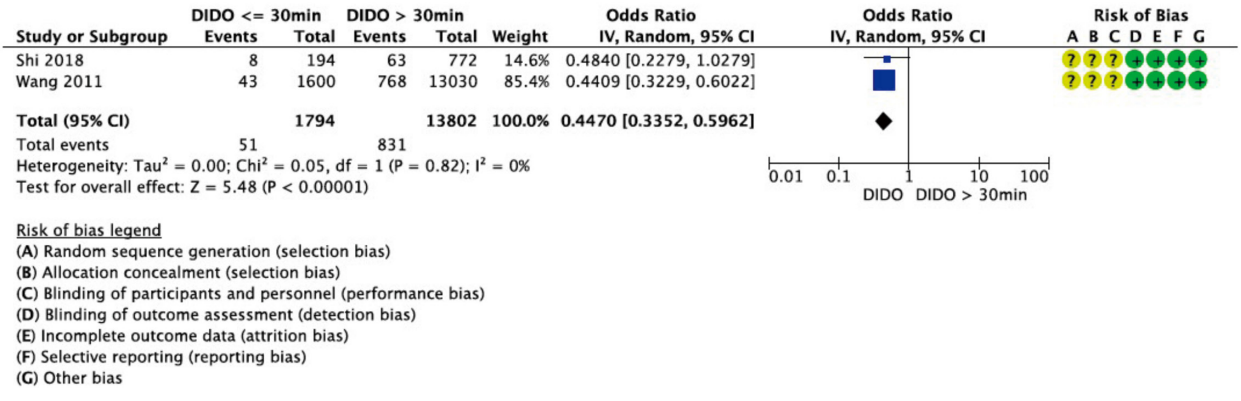

Figure 2. Forest plot of the incidence of in-hospital or 30-day mortality and a risk of bias summary for a door-in to door-out (DIDO) time of ≤30 min vs. >30 min. Risks of bias were categorized as follows: A, random sequence (selection bias); B, allocation concealment (selection bias; background factors of the 2 groups are unknown); C, performance bias (the intergroup difference in treatment strategy is unknown); D, detection bias (the primary outcome in the present analysis was only short-term mortality [low risk]); E, attrition bias (short-term prognosis with a high follow-up rate [low risk]); F, reporting bias (there seems to be no reporting bias because there are only 2 reports in this analysis [low risk]); G, other bias (not just reporting favorable outcomes [low risk]).

Publication Bias, Risk of Bias, and Quality of Evidence

The authors' judgment about each risk of bias item for each included study is shown in **Figure 2**. The presence of publication bias could not be analyzed because only 2 retrospective observational studies were included in this analysis. For reference, visual inspection of the funnel plot revealed no asymmetry for the primary endpoint (**Supplementary Figure 2**). The certainty of the evidence for each outcome was assessed and a summary is provided in the evidence profile in **Table 3**. Finally, we judged the level of evidence

Table 3. Evidence Profile

No. studies	Certainty assessment					
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
In-hospital or 30-day mortality						
2	Observational studies[A]	Serious	Not serious	Not serious	Serious[B]	None

No. studies	No. patients		Effect		Certainty	Importance
	DIDO ≤30 min	DIDO >30 min	Relative (95% CI)	Absolute (95% CI)		
In-hospital or 30-day mortality						
2	51/1,794 (2.8%)	831/13,030 (6.4%)	OR 0.45 (0.34–0.60)	34 fewer per 1,000 (from 41 fewer to 25 fewer)	Very low	Critical

[A]Retrospective cohort studies. [B]The reasons for the downgrade were the significant differences in the number of cases and background factors between the 2 retrospective cohort studies. CI, confidence interval; DIDO, door-in door-out; OR, odds ratio.

to be very low.

Discussion

This meta-analysis examined the effect of DIDO time on mortality among STEMI patients who underwent primary PCI. To the best of our knowledge, this study is the first to reveal that a DIDO time of ≤30 min was associated with lower short-term mortality rates.

The prognosis of patients with STEMI depends on the time from onset to reperfusion of the infarct-related culprit artery. Primary PCI for STEMI within 12 h of symptom onset is considered appropriate and has become standard of care.[20] A previous guideline recommended that primary PCI should be achieved within 90 min of the patient's arrival at the medical institution.[3] However, recent guidelines have focused on total ischemic time from the onset of STEMI,[20,21] and a door-to-balloon time of ≤90 min is no longer a target.

Even in the recent era, not all STEMI patients have reached PCI-capable hospitals in a timely manner for several reasons, such as coming from suburban or outer islands. A recent study reported that the COVID-19 pandemic and the outbreak response have had adverse effects on the efficiency of primary PCI services.[22] Accordingly, in the timeline for appropriate reperfusion of the infarct-related culprit artery, minimizing each component of the total ischemic time (i.e., symptom-to-door time, DIDO, door-out time to a PCI-capable hospital, and door-to-balloon time) is essential to improve the prognosis of STEMI patients.

In the present meta-analysis, we focused on DIDO time. No previous study has examined the frequency of adverse events, such as cardiac arrest, cardiac rupture, and reinfarction during transfer from non-PCI-capable hospitals to PCI-capable hospitals. Thus, the risk of maintaining a DIDO time within 30 min is not clear. The American College of Cardiology/American Heart Association guidelines previously recommended that the DIDO time be <30 min in the timeline for transport from non-PCI-capable hospitals to PCI-capable hospitals.[3,8]

Wang et al[6] reported that the median DIDO time from non-PCI-capable hospitals to PCI-capable hospitals was 120 min (interquartile range [IQR] 96–159 min) from the first arrival at the initial hospital, and a door-to-balloon time of 90 min was achieved for only 19% of all transferred patients. Furthermore, a reported 60% of patients transferred to a hospital with a DIDO time of ≤30 min achieved a door-to-balloon time of ≤90 min, compared with only 13% of patients transferred to a hospital with a DIDO time of >30 min (**Supplementary Table**).

Shi et al[7] reported that the median DIDO time was 55 min (IQR 35–112 min), almost half of that reported by Wang et al,[6] but only 194 patients (20.1%) achieved a DIDO benchmark of ≤30 min. A significantly higher proportion of those who met the DIDO benchmark also had timely first medical contact-to-balloon times, with rates almost 3-fold higher (78.7% vs. 27.4%; P<0.0001; **Supplementary Table**). Shi et al[7] also reported that after-hours presentation was one of the independent predictors of a delay in the DIDO time, suggesting it would be one of the risk factors for higher mortality in STEMI patients.

A national retrospective cohort study in the US revealed that hospital characteristics affected the DIDO time for the referral hospitals.[5] Patient-level characteristics such as age, sex, heart rate, diabetes, signs of heart failure, and a history of cerebral infarction were also suggested as factors related to DIDO time.[6] Other common reasons for the delay in DIDO times were awaiting transport and emergency department delays, diagnostic dilemmas, and non-diagnostic initial electrocardiography (ECG; median 81 min; IQR 64–110.5 min),[9] and difficulties interpreting the ECG.[10] Hospital practices to improve systems to minimize transfer time in STEMI patients are also essential. Expert consensus identified and verified 18 critical factors, including the use of emergency medical services transport, prehospital ECG, and protocols for transferring STEMI patients, among others, to minimize transfer time to PCI-capable hospitals.[11,12] However, it seemed still difficult to achieve the 30-min DIDO goal and the there is a need for continued focus on strategies for reducing DIDO time, including system-wide quality improvement programs. Moreover, there are some factors for which no consensus has been reached; we propose to investigate and examine these factors in clinical practice in Japan.

Considering the geographical and medical conditions,

the effect of DIDO time on outcomes cannot be ignored in the US and other countries. Conversely, in Japan, especially in urban areas, there are many facilities located within a short distance that can provide primary PCI for STEMI. It is necessary to note that the effect of DIDO time on outcomes may differ in Japan from that in other countries. In addition: (1) a unique system has not been constructed to verify, in Japan, whether 30 min is appropriate as the time to make a diagnosis, stabilize the condition, or confirm transfer to another hospital at a non-PCI-capable hospital; (2) the significance of shortening DIDO time is not sufficiently recognized by practicing clinicians; and (3) concrete methods for shortening door-to-ECG time are insufficient, meaning that many issues remain to be overcome.

Study Limitations

The results of this analysis should be interpreted in light of some significant limitations. First, this analysis consisted of only 2 retrospective cohort studies identified from a search of PubMed. One of these studies had a small sample size,[7] meaning that the point estimate of this paper may be affected by another study with relatively large sample size. Information about time intervals and patient characteristics was ascertained through a retrospective chart review, and these records could not be independently validated. Moreover, the role of confounding variables in our analysis is unknown. Second, the primary endpoint was short-term (30-day and in-hospital) mortality. We could not examine the number of patients who survived for more than 30 days or died during the index hospitalization. Third, critical factors that would affect clinical outcomes and STEMI severity (e.g., age, past medical history, Killip class, vital signs, including blood pressure on admission, and detailed PCI strategy) were not assessed in detail in the present analysis. The group with a DIDO time >30 min was older, had a higher proportion of females, and had a higher frequency of hypertension and previous stroke than those the group with a DIDO time ≤30 min. These differences could have influenced the present results. Finally, detailed information about the non-PCI-capable hospitals is lacking, but could have affected the diagnosis of STEMI and decisions regarding transfer.

Conclusions

This meta-analysis suggests that a DIDO time ≤30 min is associated with lower short-term mortality rates. However, further systematic reviews and meta-analyses that include more studies are needed to validate our findings.

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Disclosures

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

IRB Information

None.

Authors Contribution

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

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Supplementary Files

Please find supplementary file(s);
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