ORIGINAL RESEARCH

Prognostic Implications of Door-to-Balloon Time and Onset-to-Door Time on Mortality in Patients With ST-Segment–Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention

Jonghanne Park, MD, PhD;* Ki Hong Choi, MD;* Joo Myung Lee, MD, MPH, PhD; Hyun Kuk Kim, MD, PhD; Doyeon Hwang, MD; Tae-Min Rhee, MD; Jihoon Kim, MD; Taek Kyu Park, MD; Jeong Hoon Yang, MD, PhD; Young Bin Song, MD, PhD; Jin-Ho Choi, MD, PhD; Joo-Yong Hahn, MD, PhD; Seung-Hyuk Choi, MD, PhD; Bon-Kwon Koo, MD, PhD; Shung Chull Chae, MD, PhD; Myeong Chan Cho, MD, PhD; Chong Jin Kim, MD, PhD; Ju Han Kim, MD, PhD; Myung Ho Jeong, MD, PhD; Hyeon-Cheol Gwon, MD, PhD; Hyo-Soo Kim, MD, PhD; The KAMIR-NIH (Korea Acute Myocardial Infarction Registry–National Institutes of Health) Investigators

***Background*—**In patients with ST-segment–elevation myocardial infarction, timely reperfusion therapy with door-to-balloon (D2B) time <90 minutes is recommended by the current guidelines. However, whether further shortening of symptom onset-to-door (O2D) time or D2B time would enhance survival of patients with ST-segment–elevation myocardial infarction remains unclear. Therefore, the current study aimed to evaluate the prognostic impact of O2D or D2B time in patients with ST-segment–elevation myocardial infarction who underwent primary percutaneous coronary intervention.

***Methods and Results*—**We analyzed 5243 patients with ST-segment–elevation myocardial infarction were treated at 20 tertiary hospitals capable of primary percutaneous coronary intervention in Korea. The association between O2D or D2B time with all-cause mortality at 1 year was evaluated. The median O2D time was 2.0 hours, and the median D2B time was 59 minutes. A total of 92.2% of the total population showed D2B time ≤90 minutes. In univariable analysis, 1-hour delay of D2B time was associated with a 55% increased 1-year mortality, whereas 1-hour delay of O2D time was associated with a 4% increased 1-year mortality. In multivariable analysis, D2B time showed an independent association with mortality (adjusted hazard ratio, 1.90; 95% CI, 1.51–2.39; $P<0.001$). Reducing D2B time within 45 minutes showed further decreased risk of mortality compared with D2B time >90 minutes (adjusted hazard ratio, 0.30; 95% CI, 0.19–0.42; $P<0.001$). Every reduction of D2B time by 30 minutes showed continuous reduction of 1-year mortality (90 to 60 minutes: absolute risk reduction, 2.4%; number needed to treat, 41.9; 60 to 30 minutes: absolute risk reduction, 2.0%; number needed to treat, 49.2).

***Conclusions*—**Shortening D2B time was significantly associated with survival benefit, and the survival benefit of shortening D2B time was consistently observed, even <60 to 90 minutes. **(*J Am Heart Assoc*. 2019;8:e012188. DOI: 10.1161/JAHA.119.012188.)**

Key Words: acute myocardial infarction • door-to-balloon time • outcome • percutaneous coronary intervention • prognosis

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy in patients with ST-segment–elevation myocardial infarction (STEMI). Treatment delays are important determinants of patient outcome and the most easily audited quality of care index. Treatment delay consists of patient delay, the time from symptom onset to

From the Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea (J.P., D.H., T.-M.R., B.-K.K., H.-S.K.); Department of Internal Medicine, Naju National Hospital, Jeollanam-do, Korea (J.P.); Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (K.H.C., J.M.L., J.K., T.K.P., J.H.Y., Y.B.S., J.-H.C., J.-Y.H., S.-H.C., H.-C.G.); Department of Internal Medicine and Cardiovascular Center, Chosun University Hospital, University of Chosun College of Medicine, Gwangju, Korea (H.K.K.); National Maritime Medical Center, Changwon, Korea (T.-M.R.); School of Medicine, Kyungpook National University, Daegu, Korea (S.C.C.); Cardiology Division, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Korea (M.C.C.); Department of Internal Medicine, Kyunghee University College of Medicine, Seoul, Korea (C.J.K.); and Department of Internal Medicine and Heart Center, Chonnam National University Hospital, Gwangju, Korea (J.H.K., M.H.J.).

Accompanying Tables S1 through S6 and Figures S1 through S7 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012188

*Dr Jonghanne Park and Dr Ki Hong Choi contributed equally to this work.

Correspondence to: Joo Myung Lee, MD, MPH, PhD, Department of Internal Medicine and Cardiovascular Center, Heart Vascular Stroke Institute, Samsung Medical Center, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea. E-mails: drone80@hanmail.net; joomyung.lee@samsung.com

Received January 31, 2019; accepted April 2, 2019.

Clinical Perspective

What Is New?

- In patients with ST-segment–elevation myocardial infarction, timely reperfusion therapy with door-to-balloon (D2B) time <90 minutes is recommended by current guidelines.
- The current study showed that there was continuous association between shortening D2B time and reduced risk of 1-year mortality.
- The association between shorter D2B time and decreased risk of 1-year mortality was consistently observed, even in the range of D2B time <60 to 90 minutes.

What Are the Clinical Implications?

- Considering the continuous association between shorter D2B time and reduced risk of mortality, our results call for an "as soon as possible" recommendation for patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention, rather than accepting a specific cutoff of D2B time (ie, 90 or 60 minutes).

first medical contact; prehospital system delay, the time from first medical contact to arrival at a PCI-capable hospital; and in-hospital delay, the time from arrival at a PCI-capable hospital to balloon inflation (door-to-balloon [D2B] time).[1,2] The optimal approach to reduce each component of treatment delay may differ in terms of strategy and medical resources needed. Therefore, information pertaining to reducing each component of delay is important in allocation planning of limited healthcare resources and optimizing patient outcome. However, reports from previous studies are inconsistent about the effect of symptom onset-to-door (O2D) times and D2B times on long-term clinical outcomes in patients with STEMI undergoing primary PCI.[3–10]

The 2013 American College of Cardiology Foundation/American Heart Association guidelines for STEMI recommend that hospitals capable of primary PCI should treat patients within 90 minutes of contact with the medical system.[2] Currently, it is estimated that almost 90% of patients presenting to a PCI-capable hospital without a clinical reason for delay have a D2B time ≤90 minutes.[11] Several national and institutional programs have successfully achieved shorter D2B times.[12–14] In this regard, recent 2017 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for STEMI have changed their recommended D2B time to within 60 minutes after STEMI diagnosis for primary PCI-capable centers.[15] Despite substantial improvements in D2B times, evidence that these efforts have translated into reduced mortality rates is lacking; and the recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery recommendation for within 60 minutes from STEMI diagnosis to reperfusion time was solely based on expert opinion. Whether further shortening of O2D or D2B time would enhance survival of patients with STEMI remains unclear. Moreover, there are limited data representing contemporary practice for patients with STEMI, including reduced D2B times, modernized devices, improved PCI technique, and medical treatment.

Therefore, we sought to evaluate the prognostic impact of O2D or D2B time and to clarify the prognostic benefit of further shortening of O2D or D2B time in contemporary practice for patients with STEMI. As such, we analyzed data from KAMIR (Korea Acute Myocardial Infarction Registry)–National Institutes of Health (NIH), a nationwide multicenter prospective registry dedicated to patients with AMI.

Methods

Anonymized patient-level data will be made available by the corresponding author and executive committee of KAMIR-NIH on reasonable request.

Setting and Design

The study population was derived from a nationwide multicenter prospective registry of patients with AMI. KAMIR-NIH consecutively enrolled a total of 13 104 patients with AMI from 20 tertiary university hospitals capable of primary PCI from November 2011 to December 2015. The detailed study protocol was published previously.[16,17] Briefly, AMI was diagnosed by detection of an increased level of cardiac biomarkers, preferably cardiac troponins, with at least one value >99th percentile of the upper reference limit, accompanied with at least one of the following: symptoms of myocardial ischemia, ECG (electrocardiogram) changes (ST elevation, left bundle branch block, and ST change without ST elevation), and imaging findings suggestive of MI (loss of viable myocardium or new regional wall motion abnormality).[1,2] There was no exclusion criterion for KAMIR-NIH other than patient refusal. The registry protocols of KAMIR-NIH were verified and approved by the institutional review board of each participating center, and the study was conducted according to the principals of the Declaration of Helsinki. Written informed consent was given by each patient or the health proxy when the patient was unavailable to give consent because of disease severity.

Patients and Procedures

Among the 13 104 patients enrolled in KAMIR-NIH, 5825 were diagnosed with STEMI and underwent primary PCI. STEMI was defined as new ST elevation in ≥2 contiguous

leads, measuring >0.2 mV in leads V1–3 or 0.1 mV in all other leads, or new left bundle branch block on 12-lead ECG with a concomitant increase in troponin-I or troponin-T.[17] Among the 5825 patients with STEMI who underwent primary PCI, patients who were treated after >24 hours after symptom onset or >6 hours after hospital admission were excluded from the analysis. Finally, a total 5243 patients with STEMI who underwent primary PCI within 24 hours of symptom onset and 6 hours of admission were included in the current analysis (Figure S1). The use of medications, stent selection, use of hemodynamic support devices, and other detailed PCI protocols were left to the discretion of the operators.

Symptom O2D Time and D2B Time

We defined onset time as the time of the symptom onset on the basis of patient interview. Door time was the time of patients presenting to the PCI-capable center. Balloon time was the time of first balloon inflation during PCI. In KAMIR-NIH, each time point was required to be entered in the unit of minutes. The time intervals, O2D time, D2B time, and symptom onset-to-balloon (O2B) time, were calculated from the corresponding time entries (Figure S2).

Data Collection, Follow Up of Patients, and Study End Points

For KAMIR-NIH, data were collected by independent clinical research coordinators via web-based case report forms in the internet-based Clinical Research and Trial management system, a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Korea (internet-based Clinical Research and Trial management system study No. C110016). Standardized definitions for all patient- and lesion-related variables, clinical diagnoses, and clinical events were used. After discharge, patients were followed up at 6 and 12 months by the attending physician. If the patient did not visit on the day of scheduled follow-up, the outcome data were assessed by telephone interview. For any clinical event, all relevant medical records were reviewed and adjudicated by an independent clinical event adjudication committee. The primary outcome of the study was all-cause mortality at 1 year after the index procedure. Complete 1-year follow-up information was available for all study patients.

Statistical Analysis

Dichotomous and categorical data are presented as percentages. Continuous variables are presented as medians with interquartile range (quartile 1–quartile 3). A χ^2 test was performed for evaluating nonrandom associations between categorical variables; and analysis of variance was performed for comparison of continuous variables among the groups, classified according to intervals of D2B times. We computed Kaplan-Meier cumulative mortality curves, stratified according to intervals of D2B times and O2D times, and made comparison between groups with log-rank statistics. Cox proportional hazard regression analysis, stratified by PCI centers, was used to examine the association between the covariates and mortality. The proportional hazard assumption was checked for each categorical variable by visual inspection of log minus log plot and with the scaled Schoenfeld residuals. For continuous variables, the linearity assumption was checked graphically using the Martingale residuals. The association between D2B time and the risk of 1-year mortality was graphically presented with penalized spline with *df* (degree of freedom)=4.[18]

Unadjusted and adjusted hazard ratios (HRs) with 95% CIs were calculated. Variables with Wald test $P<0.05$ in univariable Cox regression analyses were included in the multivariable Cox regression model. Missing values among covariates were replaced with multiple imputation by chained equations using a conditional distribution for each imputed variable. Covariates with collinearity, such as systolic blood pressure and diastolic blood pressure, were excluded from the multivariable Cox regression model.

Absolute risk reductions and numbers needed to treat for 1-year mortality were obtained from a multivariable adjusted Cox regression model.[19,20] Using the estimated Cox proportional hazards regression model, each subject's probability of 1-year mortality at different D2B times (30, 60, 90, 120, 150, and 180 minutes) was determined. We then determined the marginal probabilities of all-cause mortality at 1 year at each 30-minute reduction of D2B time. The 95% CIs of the absolute measures of effect were obtained using nonparametric bootstrap with 1000 bootstrap samples each imputed for missing covariates, as above. All statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX) and R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics of the Study Population

A total of 5825 patients with STEMI were transferred or admitted directly to the 20 PCI-capable centers and underwent primary PCI. Patients were excluded if they had treatment delay of O2D time >24 hours (n=536) or D2B time >6 hours (n=45). Thus, the study cohort consisted of 5243 patients (Figure S1). Patients excluded from the analysis because of late presentation were more likely to be older, to be women, to have atypical symptoms, and to have more

Table 1. Baseline Characteristics of the Total Population

Characteristics	Value
No. of patients	5243
Demographics	
Age, y	62 (53–72)
Women	1081 (20.6)
Body mass index, kg/m^2	23.9 (22.1–26.0)
Calendar time	
First year (2012)	1392 (26.6)
Second year (2013)	1387 (26.5)
Third year (2014)	1450 (27.7)
Fourth year (2015)	1014 (19.3)
First medical contact	
Emergency medical service	1105 (21.1)
Transferred from another hospital	2669 (50.9)
Direct visit to emergency department	1469 (28.0)
Process-of-care index	
Symptom onset-to-balloon time, h	3.2 (2.1–5.3)
Symptom onset-to-door time, h	2.0 (1.0–4.2)
Door-to-balloon time, min	59 (46–72)
Symptom status	
Typical chest pain	4844 (92.4)
Dyspnea	965 (18.4)
Killip class	
1	4055 (77.4)
2	406 (7.8)
3	282 (5.4)
4	498 (9.5)
First 12-lead electrocardiography	
Anterior location	2713 (51.8)
Q wave	415 (7.9)
ST-segment depression	935 (17.8)
Left bundle branch block	38 (0.7)
Atrial fibrillation	281 (5.4)
Atrioventricular block (second degree or complete)	69 (1.3)
Wide QRS tachycardia	41 (0.8)
Medical history	
Hypertension	2422 (46.2)
Diabetes mellitus	1272 (24.3)
Treated with insulin	88 (1.7)
Dyslipidemia	558 (10.6)
Previous myocardial infarction	298 (5.7)
Previous angina pectoris	330 (6.3)
Heart failure	39 (0.7)
Previous symptomatic stroke	269 (5.1)
Current smoker	2374 (45.3)
Familial history of ischemic heart disease	326 (6.2)
Anemia (hemoglobin <11.0 g/dL)	319 (6.1)
Chronic kidney disease (eGFR <60 mL/min per 1.73 m^2)	1044 (19.9)
Initial hemodynamics	
Systolic BP, mm Hg	127 (110–144)
Diastolic BP, mm Hg	80 (66–90)
Heart rate, beats/min	76 (64–88)
Cardiogenic shock, %	386 (7.4)
LV ejection fraction, %	51 (45–57)
Culprit vessel	
Left anterior descending artery	2639 (50.3)
Left circumflex artery	494 (9.4)
Right coronary artery	2025 (38.6)
Left main coronary artery	85 (1.6)
Multivessel disease	2259 (43.1)
Procedural characteristics	
Transradial approach	1285 (24.5)
Glycoprotein IIb/IIIa inhibitor use	1165 (22.2)
Thrombus aspiration	2008 (38.3)
Culprit vessel treated with	
Bare metal stent	153 (2.9)
First-generation drug-eluting stent	69 (1.3)
Second-generation drug-eluting stent	4515 (86.1)
Balloon angioplasty	299 (5.7)
Use of IABP	264 (5.0)
Use of ECMO	88 (1.7)
Pre-PCI TIMI flow	
0–1	3981 (75.9)
2	539 (10.3)
3	723 (9.6)
Post-PCI TIMI flow	
0–1	50 (1.0)
2	188 (3.6)
3	5005 (95.5)
Discharge medications	
Dual-antiplatelet agent	5057 (96.5)
Aspirin	5103 (97.3)
Clopidogrel	3332 (63.6)

Continued

Continued

Table 1. Continued

Characteristics	Value
Prasugrel	642 (12.2)
Ticagrelor	1098 (20.9)
β Blocker	4438 (84.7)
ACEI/ARB	4126 (78.7)
Statin	4797 (91.5)

Values are given as median (quartile 1–quartile 3) or number (percentage), unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LV, left ventricular; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

comorbidity (Table S1). Table 1 and Table S2 summarize the clinical presentation and baseline characteristics of the study cohort. Almost half of the patients were admitted to PCI-capable centers after triage by the emergency medical system (21.1%) or by themselves (28.0%). The other 50.9% of the patients were transferred from PCI noncapable centers for primary PCI. In the entire study population, the median O2B time was 3.2 hours (quartile 1–quartile 3, 2.1–5.3 hours) (Figure S3). The median O2D time was 2.0 hours (quartile 1–quartile 3, 1.0–4.2 hours), and the median D2B time was 59 minutes (quartile 1–quartile 3, 46–72 minutes). Among the total study population with STEMI, 92.2% had a D2B time within 90 minutes (Figure 1). Half of the patients presented with anterior STEMI. The success rate for PCI was 98.5%, with 50 suboptimal PCIs (1.0%) and 29 failures of PCI (0.6%). A total of 86.1% of the patients were treated with a second-generation drug-eluting stent with fair compliance to contemporary guidelines for medical treatment, including dual antiplatelet therapy (96.5%), β blockers (84.7%), renin-angiotensin-aldosterone system blockade (78.7%), and statins (91.5%) (Table 1).

Clinical Outcomes According to O2D Time and D2B Time

Figure 2 presents the association between O2D time and 1-year mortality, according to D2B time, or between D2B time and 1-year mortality, according to O2D time. Although the association of 1-year mortality and O2D time was not consistent between groups with a different D2B time, D2B time showed a significant association with 1-year mortality in all strata of O2D time (Figure 2). In univariable analysis, every 1-hour increase of D2B time was associated with a 55%

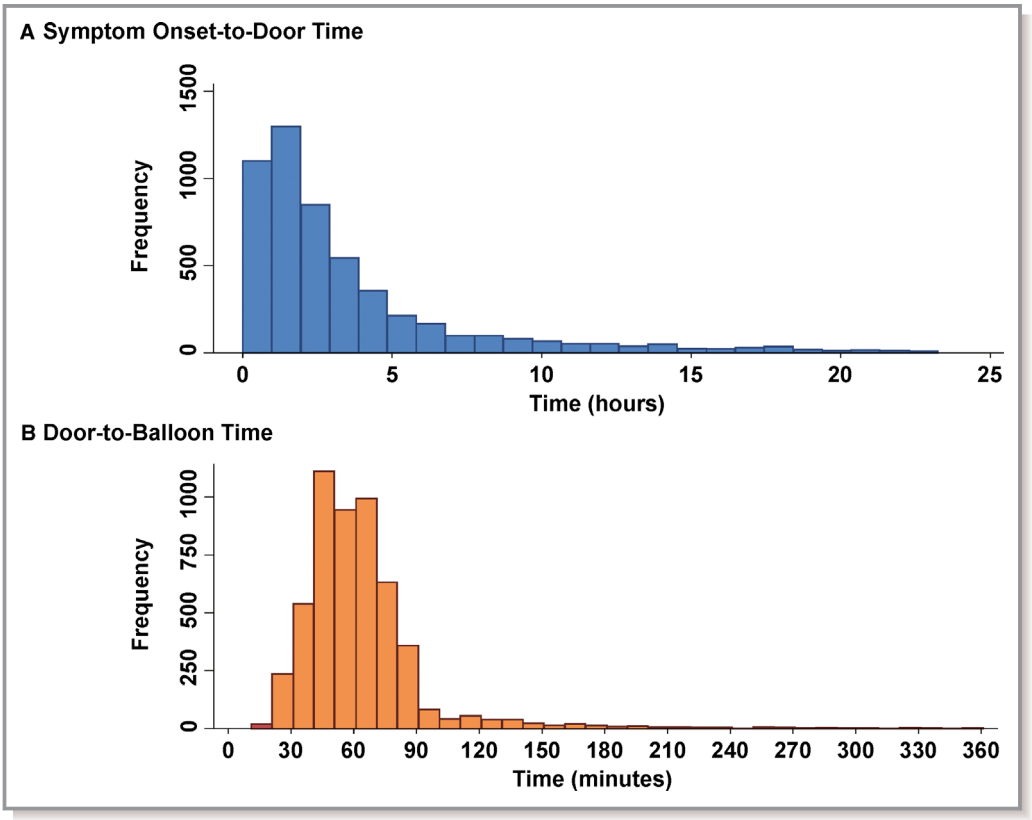


Figure 1. Distribution of symptom onset-to-door (**A**) and door-to-balloon (**B**) times of the study population.

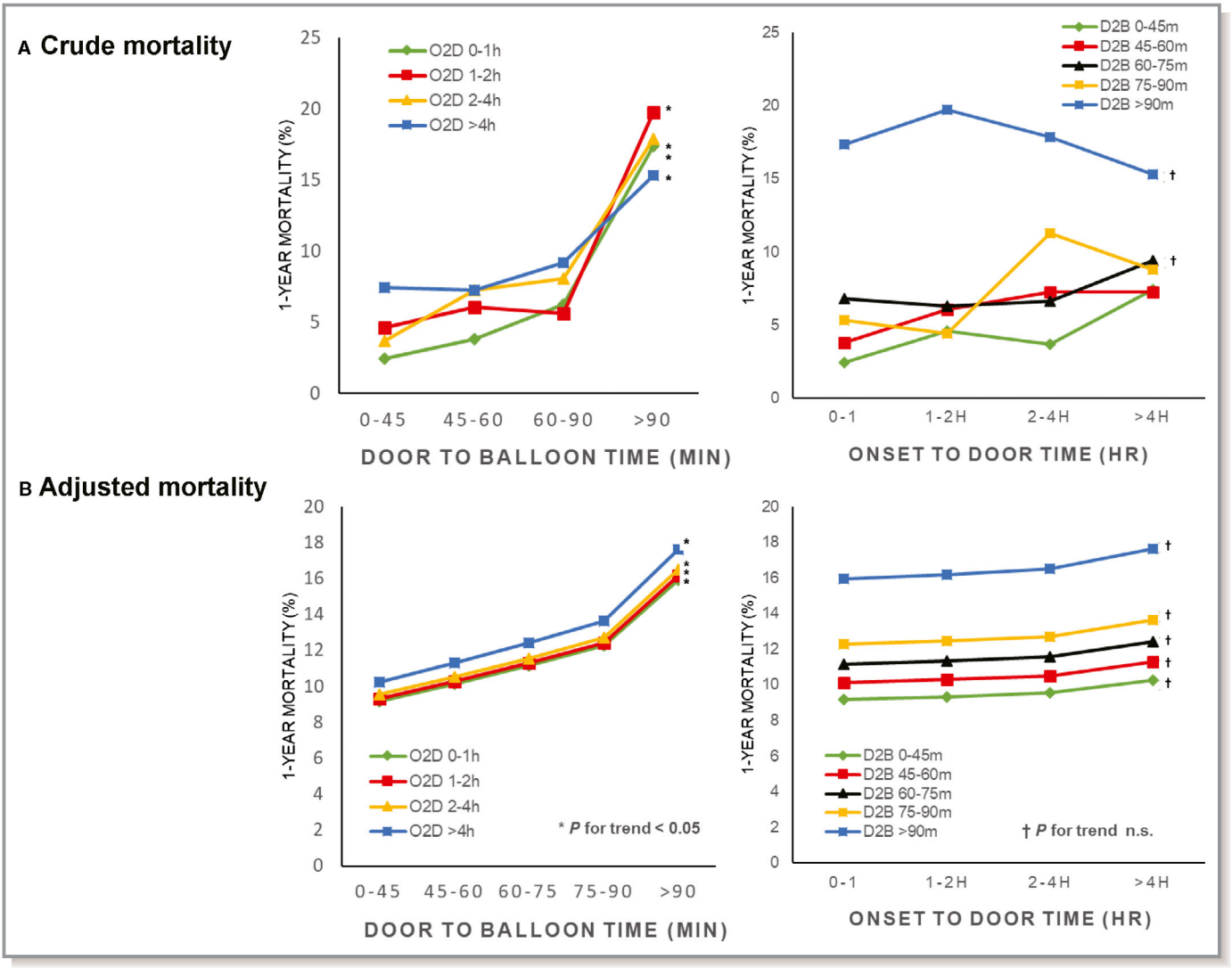


Figure 2. One-year mortality, according to symptom onset-to-door (O2D) and door-to-balloon (D2B) times. **A**, The rate of crude 1-year all-cause mortality was compared among classification of D2B time (*x* axis) in strata of O2D time (blue lines, **left**) or was compared among classification of O2D time (*x* axis) in strata of D2B time (red lines, **right**). **B**, Multivariable adjusted all-cause mortality at 1 year was compared among classification of D2B time (*x* axis) in strata of O2D time (blue lines, **left**) or was compared among classification of O2D time (*x* axis) in strata of D2B time (red lines, **right**). n.s. Indicates not significant.

increase of 1-year mortality (HR, 1.55; 95% CI, 1.40–1.72; *P*<0.001), whereas every 1-hour increase of O2D time was associated with a 4% increase of 1-year mortality (HR, 1.04; 95% CI, 1.02–1.06; *P*<0.001) (Table 2).

When stratifying according to D2B time, 1-year cumulative mortality was 4.6% (53/1194) in patients with D2B time 0 through 45 minutes, 6.3% (103/1655) in those with D2B time 46 through 60 minutes, 7.5% (147/1984) in those with D2B time 61 through 90 minutes, and 17.5% (71/410) in those with D2B time 90 through 360 minutes (overall log-rank *P*<0.001, Figure 3). In a sensitivity analysis, differences in cumulative incidence of mortality, according to D2B time, were similarly observed using 30-day mortality (Figure S4). When stratifying according to O2D time, 1-year cumulative mortality was 5.8% (75/1302) in patients with O2D time 0 to 1 hour, 6.6% (75/1153) in those with O2D time 1 to 2 hours, 7.4% (101/1387) in those with O2D time 2 to 4 hours, and 8.9% (123/1401) in those with O2D time >4 hours (overall log-rank *P*=0.018, Figure S5).

In the multivariable Cox regression analysis, the D2B time remained significant, with every 1-hour increase of D2B time being associated with a 64% increased risk of 1-year mortality (HR, 1.90; 95% CI, 1.51–2.39; *P*<0.001) (Table 3). In a stratified analysis in the 4 O2D groups, the reduction of risk associated with short D2B time was consistently observed in every O2D time subgroup (O2D 0–1 hour: HR, 0.47; 95% CI, 0.37–0.62; *P*<0.001; O2D 1–2 hours: HR, 0.60; 95% CI, 0.42–0.85; *P*=0.004; O2D 2–4 hours: HR, 0.51; 95% CI, 0.42–0.85;

Table 2. Univariable Cox Regression Analysis for 1-Year All-Cause Mortality in Patients With STEMI Treated With Primary PCI

Covariables	Valid Cases	Deaths*	HR (95% CI)	Wald Test	*P* Value
Demographics					
Age, per 10-y increase	5243	. . .	2.01 (1.82–2.22)	192	<0.001
Women	5243	132	2.17 (1.75–2.67)	51.5	<0.001
Comorbid conditions					
Hypertension	5243	220	1.70 (1.38–2.08)	25.4	<0.001
Diabetes mellitus	5243	133	1.76 (1.42–2.17)	27.4	<0.001
Previous myocardial infarction	5243	26	1.24 (0.84–1.85)	7.73	0.276
Previous angina pectoris	5243	36	1.62 (1.15–2.29)	6.71	0.006
Previous congestive heart failure	5243	9	3.43 (1.82–6.48)	14.5	<0.001
Dyslipidemia	5243	26	0.61 (0.41–0.91)	5.86	0.015
Active or previous smoker	5243	185	0.50 (0.41–0.61)	45.7	<0.001
Delay to treatment, per 1-h increase					
Symptom onset-to-door time	5243		1.04 (1.02–1.06)	13.16	<0.001
Door-to-balloon time	5243		1.55 (1.40–1.72)	68.25	<0.001
First medical contact	5243	. . .	. . .	. . .	. . .
Direct visit to PCI center	1469	68	1 (Reference)	18.8	. . .
Emergency medical service (911)	1105	85	1.70 (1.23–2.33)	10.5	0.001
Transport from another hospital	2669	221	1.81 (1.38–2.38)	18.5	<0.001
Clinical characteristics					
Typical chest pain	5243	80	0.28 (0.22–0.36)	103	<0.001
Body mass index, per 1-unit increase	5063	. . .	0.85 (0.82–0.89)	54.2	<0.001
Systolic blood pressure, per 10 mm Hg	5227	. . .	0.82 (0.80–0.84)	248	<0.001
Diastolic blood pressure, per 10 mm Hg	5227	. . .	0.76 (0.73–0.79)	211	<0.001
Heart rate, per 10-min increase	5227	. . .	1.19 (1.11–1.27)	25.0	<0.001
Killip class	5241	374	. . .	. . .	. . .
I	4055	137	1 (Reference)	417	. . .
II	406	37	2.78 (1.94–3.99)	30.8	<0.001
III	282	53	6.08 (4.44–8.33)	127	<0.001
IV	498	147	10.5 (8.31–13.2)	397	<0.001
Cardiogenic shock	5243	129	8.3 (6.7–10.3)	19.43	<0.001
Anterior infarct location	5243	221	1.36 (1.11–1.67)	8.7	0.003
Left bundle branch block	5243	10	4.30 (2.26–8.19)	19.8	<0.001
Atrial fibrillation	5243	42	2.33 (1.69–3.20)	27.0	<0.001
Culprit vessel left main	5243	46	4.25 (3.12–5.80)	83.9	<0.001
Multivessel disease	5243	192	1.41 (1.15–1.73)	11.1	0.001

HR indicates hazard ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.
*Total number of deaths=374.

P<0.001; O2D >4 hours: HR, 0.62; 95% CI, 0.42–0.92; *P*=0.017) without significant interaction (interaction *P*=0.38) (Figure S6A). The association between shorter D2B time and lower mortality was also consistently observed, according to different types of hospital visits (direct visit: HR, 0.54; 95% CI, 0.42–0.68; *P*<0.001; emergency medical system: HR, 0.54; 95% CI, 0.42–0.68; *P*<0.001; transferred from another hospital: HR, 0.81; 95% CI, 0.65–1.00; *P*=0.048), with significant interaction between route of visit with D2B time on mortality (interaction *P*=0.013) (Figure S6B). In addition, the continuous association between D2B time and the risk of mortality at 1 year was similarly observed in both patients

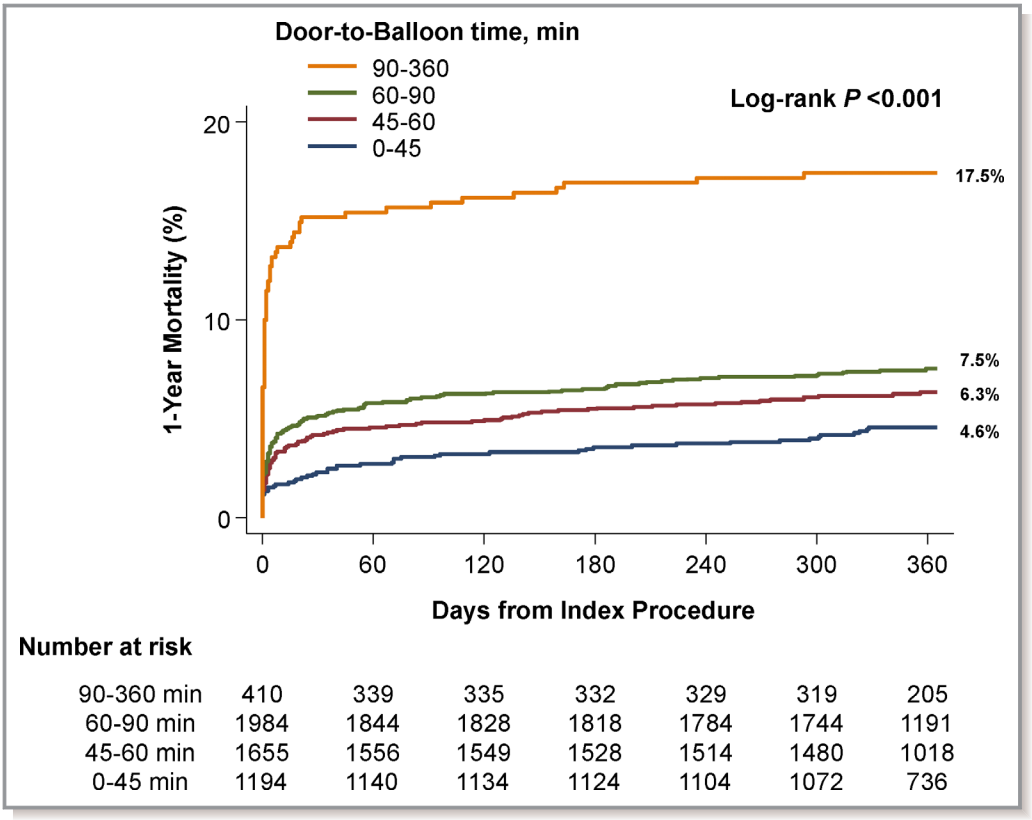


Figure 3. Comparison of clinical outcome, according to door-to-balloon (D2B) time. Comparison of all-cause mortality at 1 year among classifications by D2B time.

with or without cardiogenic shock or mechanical circulatory supports, without significant interaction *P* value (interaction *P*=0.290) (Figure S7).

Continuous Association of D2B Time and Risk of 1-Year Mortality

We further asked whether the association between 1-year mortality risk and D2B time was continuously observed over the whole range of D2B time (Figure 4). In the total study population, D2B time showed continuous risk reduction in every range of D2B time (Figure 4A). Even among patients whose D2B time was within 120 minutes (90% of total study population), the continuous association between shorter D2B time and lower relative risk of 1-year mortality was consistently observed (Figure 4B).

When the study population was categorized according to D2B time (D2B time: 0–45, 45–60, 60–90, and >90 minutes), D2B time of 0 to 45 minutes was independently associated with significantly reduced risk of 1-year mortality compared with the group with D2B time >90 minutes (HR, 0.30; 95% CI, 0.19–0.42; *P*<0.001) and the group with D2B time 60 to 90 minutes (HR, 0.67; 95% CI, 0.47–0.95; *P*=0.023) (Tables S3 and S4).

Table 4 presents the prognostic impact of reducing D2B time by means of absolute risk reduction and number needed to treat. The absolute risk reductions of 1-year mortality, reducing D2B time by 30 minutes from 120, 90, and 60 minutes, were 2.8%, 2.4%, and 2.0%, respectively, which corresponded to numbers needed to treat of 36.0, 41.9, and 49.2, respectively (Table 4).

Discussion

In this study, we investigated the prognostic implications of shortening O2D and D2B times in patients with STEMI. The main findings can be summarized as follows. First, in a univariable analysis, a 1-hour delay of D2B time was associated with a 55% increased 1-year mortality, whereas a 1-hour delay of O2D time was associated with a 4% increased 1-year mortality. Second, in a multivariable analysis, only D2B time showed an independent association with 1-year mortality. Third, there was continuous association between shortening D2B time and reduced risk of 1-year mortality, and the association between shorter D2B time and decreased risk of 1-year mortality was consistently observed, even in the range of D2B time <60 to 90 minutes.

Prognostic Impact of O2D Time and D2B Time: Previous Evidence

There have been conflicting results about the relative prognostic importance of O2D and D2B times. The US NRMI

Table 3. Multivariable Cox Regression Analysis for 1-Year All-Cause Mortality in Patients With STEMI Treated With Primary PCI

Covariables	HR (95% CI)	*P* Value
Demographics		
Age, per 10-y increase	1.89 (1.47–2.43)	<0.001
Comorbid conditions		
Previous angina pectoris	1.62 (1.15–2.29)	0.033
Chronic kidney disease	1.96 (1.47–2.43)	<0.0001
Delay to treatment		
Door-to-balloon time, per 1-h increase	1.90 (1.51–2.39)	<0.001
Transferred from another hospital	2.13 (1.28–3.55)	0.004
Clinical characteristics		
Body mass index, kg/m^2	0.93 (0.90–0.97)	0.001
Typical chest pain	0.69 (0.52–0.91)	0.01
Systolic blood pressure, per 10 mm Hg	0.90 (0.87–0.93)	<0.001
Heart rate, per 10-min increase	1.15 (1.11–1.20)	<0.001
Killip class II–IV	1.74 (1.30–2.33)	0.0002
Cardiogenic shock	2.46 (1.81–3.33)	<0.0001
Procedural characteristics		
Anterior infarct location	1.43 (1.15–1.79)	0.001
Culprit vessel left main	2.96 (2.06–4.26)	<0.001
Multivessel disease	1.44 (1.14–1.82)	0.008

Harrell's c-index of prediction model was 0.862 (95% CI, 0.845–0.880). HR indicates hazard ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

(National Registry of MI), which enrolled >20 000 patients, previously reported that shorter D2B time but not O2B time was associated with lower in-hospital mortality.[4,8] In contrast, several relatively small studies suggested a positive correlation between shorter O2B time and decreased risk of mortality.[3,10] In a single-center study of 1791 patients with STEMI treated with primary PCI, O2B time >4 hours was an independent predictor of 1-year mortality and no relationship was found between D2B time and mortality.[3] In the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) MI registry (n=3391), O2B time >3 hours was associated with higher risk of a composite of death and congestive heart failure, whereas shorter D2B time was associated with a lower risk of death and congestive heart failure, only in patients with early presentation (O2D time <2 hours).[10] In the current study, we compared the prognostic impact of O2D and D2B times on 1-year all-cause mortality. In line with the NRMI data, there was a significant association between shorter D2B time and 1-year mortality. The benefit of shorter D2B time was consistently observed between different O2D time strata, and D2B time was an independent predictor of 1-year mortality.

Prognostic Implications of O2D Time

In a stratified analysis, the reduction of risk by shorter D2B time was largest in patients within the shortest O2D time quartile. The interdependency between O2D time and D2B time suggests that any delays for patients with STEMI pose a continuum of risk. This interaction between O2D delay and the effect of D2B reduction was also observed in the CREDO-Kyoto MI registry.[10] Furthermore, the association between shorter D2B time and lower mortality was also consistently observed, according to different types of hospital visits. However, the benefit from reducing D2B time was attenuated in transferred patients, and the interaction between route of visit and D2B time on mortality was significant. The total time of transport was systematically longer in patients who were transferred from other hospitals to PCI-capable centers (Table S5). The attenuated benefit from reducing D2B time for mortality in transferred patients may reflect the risk and interaction of prehospital delay not clouded by the heterogeneity of patient recall. In a recent study that divided O2D time into "patient delay" and "prehospital system delay," patient delay did not show a significant association with in-hospital mortality after adjustment, whereas prehospital system delay was associated with increased risk of mortality and showed similar effect with in-hospital delay, D2B time.[21]

Prognostic Implication of D2B Time

A large body of literature exists on the association of D2B time and mortality. As the benefit of reducing D2B time cannot be tested with a randomized trial, it must be conjectured from the results of large observational studies. There have been 2 types of study designs in the previous literature. In patient-level studies, the risk of mortality was evaluated using large observational cohorts. Positive correlation between shorter D2B time and lower risk of mortality was consistently observed in those studies.[3–7] The other type of study design was population-level studies, in which nationwide or institution-wide change of clinical outcomes was observed during the application of national programs to reduce in-hospital delay, with D2B time as the target quality measure. Recent population-level studies have reported that reducing D2B time in patients with STEMI undergoing primary PCI was not associated with improvement in mortality.[22–24] These results have raised questions about the value of reducing D2B time. Some have suggested that shorter D2B time could be a surrogate marker for low-risk patients or reflection of institutional or operator expertise. Although only the results from population-level studies can be translated

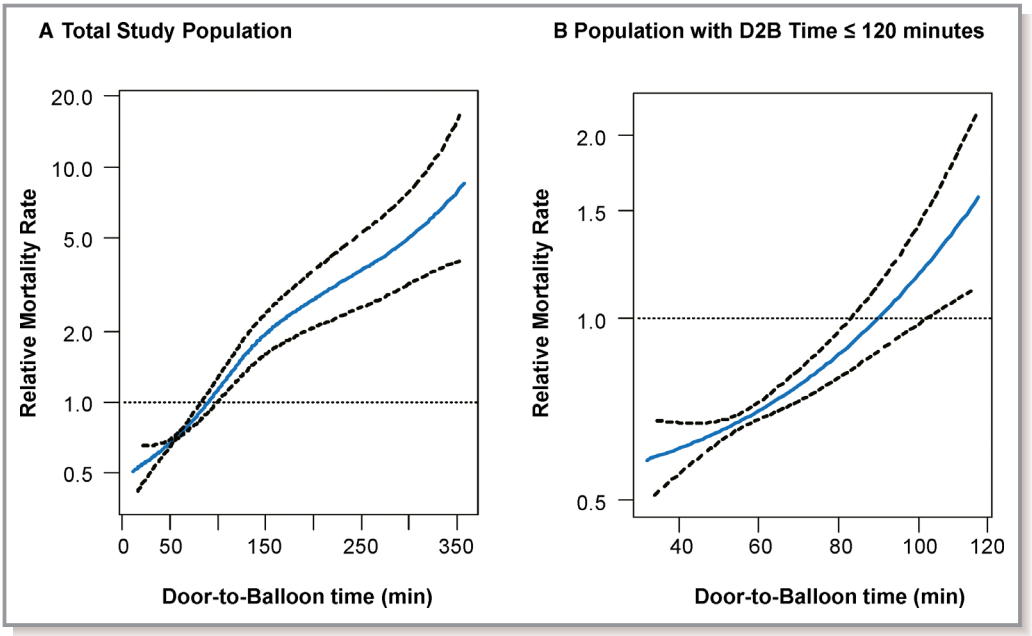


Figure 4. Association between door-to-balloon (D2B) time and 1-year mortality. The association between relative all-cause mortality rates and D2B time is presented among the total study population (**A**) and patients whose D2B time was within 120 minutes (**B**). In both populations, the continuous association between shorter D2B time and lower relative risk of 1-year mortality was consistently observed. The association between D2B time and the 1-year mortality was plotted under multivariable adjustment.

into causality, the study design has temporal differences in the distribution of confounders. In a retrospective analysis of the NCDR (National Cardiovascular Data Registry), from which a population-level analysis concluded lack of benefit of D2B reduction, Nallamothu et al showed that D2B times were consistently correlated with lower mortality at a population level; however, secular trends of increasing mortality were largely attributable to an increased proportion of high-risk patients undergoing primary PCI.[25]

The KAMIR-NIH enrolled patients from 2011 to 2015, when nationwide efforts to reduce D2B time were already established. The D2B time remained stable at ≈60 minutes during the study period. Therefore, only patient-level analysis was available in the current study. In terms of study design, statistical method, and measured confounders, the current study is comparable to previous patient-level observational registries (Table S6). The strengths of the current study come from the extensive analysis on the relationship of D2B time with the risk of 1-year mortality and the contemporary nature of the registry, which reflects most recent practice of STEMI treatment. Our study shows a continuous reduction of 1-year mortality risk, according to shortened D2B time. More important, a continuous reduction in absolute risk of mortality was observed, even at D2B time ≤60 minutes. More than 90% of our study population was treated with D2B time within 90 minutes, and >50% of the population showed D2B time within 60 minutes. In addition, most patients were treated using second-generation drug-eluting stents. In this regard, the findings of our study are more applicable to contemporary primary PCI centers with a high level of experience and suggest that short D2B time may be associated with better outcome at an individual patient level.

Table 4. Estimated Clinical Benefit of Shortening D2B Time in Reducing 1-Year Mortality in Patients With STEMI Treated With Primary PCI

	Effect of Shortening D2B Time by 30 min	
D2B Time, min	% Absolute Risk Reduction (95% CI)	Number Needed to Treat (95% CI)
From 180–150	3.7 (3.1–4.2)	27.4 (23.9–32.0)
From 150–120	3.2 (2.7–3.7)	31.2 (27.0–37.1)
From 120–90	2.8 (2.3–3.2)	36.0 (30.8–43.3)
From 90–60	2.4 (2.0–2.8)	41.9 (35.5–51.2)
From 60–30	2.0 (1.6–2.4)	49.2 (41.3–61.0)

Absolute risk reductions and numbers needed to treat for 1-year mortality were obtained from a multivariable adjusted Cox regression model. D2B indicates door to balloon; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

Clinical Implications

Treatment delay is often recognized as one of the most important factors in the quality-of-care index for patients with STEMI, with each component of delay representing a different

aspect of the healthcare delivery system. The current results suggest that D2B time was an important "modifiable" component of treatment delay. For a patient visiting a primary PCI center, shorter D2B time was associated with reduced risk of 1-year mortality regardless of the route of visit, lesion complexity, and disease severity. Considering the continuous association between shorter D2B time and reduced risk of mortality, our data suggest that there may be a potential benefit in mortality reduction through shortening D2B time below a specific cutoff (ie, 60 or 90 minutes). Therefore, for any patient with STEMI, efforts to reduce unnecessary delay may result in improved outcome. Whether a nationwide program to further reduce D2B time would improve the outcome of patients with STEMI is beyond the scope of the current analysis and calls for a future study.

In the current study, patients with STEMI who were transferred from PCI-incapable centers had a significantly increased risk of 1-year mortality than other patients (HR, 2.3; 95% CI, 1.4–3.9; P=0.001); and the benefit from reducing D2B time for mortality was attenuated in the transferred patients. These results suggest that better accessibility to PCI centers may improve the overall outcome of patients with STEMI. However, merely increasing the number of primary PCI centers may not translate into improve quality of care.[26] The tertiary PCI centers participating in KAMIR-NIH are already located to cover all regions of Korea within a 1-hour distance. Therefore, prehospital triage with early alarm systems by the emergency medical system to primary PCI-capable centers may offer potential solutions.[27–29] In addition, patients who presented late (O2B time >24 hours) and were, thus, excluded from the analysis were more likely to be older patients or women with atypical symptoms and more comorbidity. In this regard, a patient education and awareness program for acute chest pain may help, especially for these patients with a high risk of healthcare disparities.

Limitations

Our study has several limitations that merit consideration. First, we were unable to capture the time when patients first called/activated the emergency medical system. Therefore, patient and system delays could not be analyzed separately for evaluation of prehospital delay. Second, our analysis was based on observational data and there is no definite ground to claim causality. We tried to mitigate the confounding effects through vigorous risk adjustment; however, we cannot preclude the possibility of nonmeasured confounding factors (ie, prior peripheral vascular disease, prehospital system delay, and index of failed reperfusion other than epicardial TIMI [Thrombolysis in MI] flow). Third, as our analysis was based on a Korean registry from 20 tertiary centers with a high volume of PCI, the possibilities of ascertainment bias or survival bias should be considered in interpreting the results. Patients with the highest risk presenting with cardiac arrest may be underrepresented in the registry. Therefore, the result may not be generalizable to low-volume PCI centers or PCI centers with different ethnic and geographical backgrounds.

Conclusion

In patients with STEMI, shortening D2B time was significantly associated with reduced 1-year mortality. The survival benefit of shortening D2B time was consistently observed, even <60 minutes. An "as soon as possible" strategy to minimize in-hospital delay may improve outcome of patients with STEMI.

Sources of Funding

This research was supported by a fund (2016-ER6304-01) by Research of Korea Centers for Disease Control and Prevention. The Korea Centers for Disease Control and Prevention had no role in study design, conduct, data analysis, or manuscript preparation.

Disclosures

None.

References

1. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
2. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:485–510.
3. De Luca G, Suryapranata H, Zijlstra F, van 't Hof AW, Hoorntje JC, Gosselink AT, Dambrink JH, de Boer MJ; ZWOLLE Myocardial Infarction Study Group. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol*. 2003;42:991–997.
4. McNamara RL, Wang Y, Herrin J, Curtis JP, Bradley EH, Magid DJ, Peterson ED, Blaney M, Frederick PD, Krumholz HM; NRMI Investigators. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2006;47:2180–2186.
5. Brodie BR, Gersh BJ, Stuckey T, Witzenbichler B, Guagliumi G, Peruga JZ, Dudek D, Grines CL, Cox D, Parise H, Prasad A, Lansky AJ, Mehran R, Stone GW. When is door-to-balloon time critical? Analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials. *J Am Coll Cardiol*. 2010;56:407–413.

6. Brodie BR, Hansen C, Stuckey TD, Richter S, Versteeg DS, Gupta N, Downey WE, Pulsipher M. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. *J Am Coll Cardiol*. 2006;47:289–295.
7. Brodie BR, Stuckey TD, Wall TC, Kissling G, Hansen CJ, Muncy DB, Weintraub RA, Kelly TA. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 1998;32:1312–1319.
8. Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, Gore JM, Weaver WD, Rogers WJ, Tiefenbrunn AJ. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000;283:2941–2947.
9. Hannan EL, Zhong Y, Jacobs AK, Holmes DR, Walford G, Venditti FJ, Stamato NJ, Sharma S, King SB III. Effect of onset-to-door time and door-to-balloon time on mortality in patients undergoing percutaneous coronary interventions for ST-segment elevation myocardial infarction. *Am J Cardiol*. 2010;106:143–147.
10. Shiomi H, Nakagawa Y, Morimoto T, Furukawa Y, Nakano A, Shirai S, Taniguchi R, Yamaji K, Nagao K, Suyama T, Mitsuoka H, Araki M, Takashima H, Mizoguchi T, Eisawa H, Sugiyama S, Kimura T; CREDO-Kyoto AMI Investigators. Association of onset to balloon and door to balloon time with long term clinical outcome in patients with ST elevation acute myocardial infarction having primary percutaneous coronary intervention: observational study. *BMJ*. 2012;344:e3257.
11. Bradley EH, Nallamothu BK, Herrin J, Ting HH, Stern AF, Nembhard IM, Yuan CT, Green JC, Kline-Rogers E, Wang Y, Curtis JP, Webster TR, Masoudi FA, Fonarow GC, Brush JE Jr, Krumholz HM. National efforts to improve door-to-balloon time results from the Door-to-Balloon Alliance. *J Am Coll Cardiol*. 2009;54:2423–2429.
12. Daudelin DH, Sayah AJ, Kwong M, Restuccia MC, Porcaro WA, Ruthazer R, Goetz JD, Lane WM, Beshansky JR, Selker HP. Improving use of prehospital 12-lead ECG for early identification and treatment of acute coronary syndrome and ST-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2010;3:316–323.
13. Nestler DM, Noheria A, Haro LH, Stead LG, Decker WW, Scanlan-Hanson LN, Lennon RJ, Lim CC, Holmes DR Jr, Rihal CS, Bell MR, Ting HH. Sustaining improvement in door-to-balloon time over 4 years: the Mayo Clinic ST-elevation myocardial infarction protocol. *Circ Cardiovasc Qual Outcomes*. 2009;2:508–513.
14. Pitta SR, Myers LA, Bjerke CM, White RD, Ting HH. Using prehospital electrocardiograms to improve door-to-balloon time for transferred patients with ST-elevation myocardial infarction: a case of extreme performance. *Circ Cardiovasc Qual Outcomes*. 2010;3:93–97.
15. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
16. Kim JH, Chae SC, Oh DJ, Kim HS, Kim YJ, Ahn Y, Cho MC, Kim CJ, Yoon JH, Park HY, Jeong MH; Korea Acute Myocardial Infarction-National Institutes of Health Registry Investigators. Multicenter cohort study of acute myocardial infarction in Korea—interim analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry. *Circ J*. 2016;80:1427–1436.
17. Lee JM, Rhee TM, Hahn JY, Kim HK, Park J, Hwang D, Choi KH, Kim J, Park TK, Yang JH, Song YB, Choi JH, Choi SH, Koo BK, Kim YJ, Chae SC, Cho MC, Kim CJ, Gwon HC, Kim JH, Kim HS, Jeong MH; KAMIR Investigators. Multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction with cardiogenic shock. *J Am Coll Cardiol*. 2018;71:844–856.
18. Govindarajulu US, Malloy EJ, Ganguli B, Spiegelman D, Eisen EA. The comparison of alternative smoothing methods for fitting non-linear exposure-response relationships with Cox models in a simulation study. *Int J Biostat*. 2009;5:Article 2.
19. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol*. 2010;63:46–55.
20. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. *BMC Med*. 2017;15:112.
21. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, Vach W, Johnsen SP, Thuesen L, Lassen JF. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA*. 2010;304:763–771.
22. Flynn A, Moscucci M, Share D, Smith D, LaLonde T, Changezi H, Riba A, Gurm HS. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Arch Intern Med*. 2010;170:1842–1849.
23. Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, Gurm HS. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med*. 2013;369:901–909.
24. Wang TY, Fonarow GC, Hernandez AF, Liang L, Ellrodt G, Nallamothu BK, Shah BR, Cannon CP, Peterson ED. The dissociation between door-to-balloon time improvement and improvements in other acute myocardial infarction care processes and patient outcomes. *Arch Intern Med*. 2009;169:1411–1419.
25. Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush JE Jr, Messenger JC, Bradley EH, Rumsfeld JS, Krumholz HM. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. *Lancet*. 2015;385:1114–1122.
26. Girotra S, Cram P. Universal access to a percutaneous coronary intervention hospital: is it feasible or desirable? *Circ Cardiovasc Qual Outcomes*. 2012;5:9–11.
27. Brunetti ND, De Gennaro L, Correale M, Santoro F, Caldarola P, Gaglione A, Di Biase M. Pre-hospital electrocardiogram triage with telemedicine near halves time to treatment in STEMI: a meta-analysis and meta-regression analysis of non-randomized studies. *Int J Cardiol*. 2017;232:5–11.
28. Chan AW, Kornder J, Elliott H, Brown RI, Dorval JF, Charania J, Zhang R, Ding L, Lalani A, Kuritzky RA, Simkus GJ. Improved survival associated with pre-hospital triage strategy in a large regional ST-segment elevation myocardial infarction program. *JACC Cardiovasc Interv*. 2012;5:1239–1246.
29. Patel M, Dunford JV, Aguilar S, Castillo E, Patel E, Fisher R, Ochs G, Mahmud E. Pre-hospital electrocardiography by emergency medical personnel: effects on scene and transport times for chest pain and ST-segment elevation myocardial infarction patients. *J Am Coll Cardiol*. 2012;60:806–811.

SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics and Outcomes of Excluded Patients with STEMI.

	Excluded*	Included	*P*-value
No. of patients	**582**	**5,243**	
Demographics			
Age, years	68 [57-76]	62 [53-72]	<.0001
Female	197 (33.8)	1081 (20.6)	<.0001
Body mass index, kg/m^2	23.4 [21.3-25.4]	23.9 [22.1-26]	<.0001
First medical contact			<.0001
Emergency medical service	54 (9.3)	1105 (21.1)	
Transferred from other hospital	366 (62.9)	2669 (50.9)	
Direct visit to emergency department	162 (27.8)	1469 (28)	
Process of care index			
Symptom-onset-to-balloon time, hours	47 [26.8-74.3]	3.2 [2.1-5.3]	<.0001
Symptom-onset-to-door time, hours	38.2 [24-72]	2 [1-4.2]	<.0001
Door-to-balloon time, minutes	74 [54-158]	58 [46-72]	<.0001
Symptom status			
Typical chest pain	485 (83.3)	4844 (92.4)	<.0001
Dyspnea	138 (23.7)	965 (18.4)	0.0023
Killip class			<.0001
1	419 (72)	4055 (77.4)	
2	68 (11.7)	406 (7.7)	
3	50 (8.6)	282 (5.4)	
4	45 (7.7)	498 (9.5)	
First 12-lead electrocardiography			
Anterior location	318 (54.6)	2713 (51.7)	0.1998
Q-wave	71 (12.2)	415 (7.9)	0.0005
ST-segment depression	70 (12)	935 (17.8)	0.0005
Left bundle branch block	5 (0.9)	38 (0.7)	0.9172
Atrial fibrillation	32 (5.5)	281 (5.4)	0.9649
AV block (2nd degree or complete)	11 (1.9)	69 (1.3)	0.3467
Wide QRS tachycardia	7 (1.2)	41 (0.8)	0.4102
Previous medical history			
Hypertension	312 (53.6)	2422 (46.2)	0.0008

Diabetes	184 (31.6)	1272 (24.3)	0.0001
treated with insulin	20 (3.4)	88 (1.7)	0.0048
Dyslipidemia	57 (9.8)	558 (10.6)	0.57
Previous myocardial Infarction	33 (5.7)	298 (5.7)	1
Previous angina pectoris	34 (5.8)	330 (6.3)	0.74
Heart failure	10 (1.7)	39 (0.7)	0.028
Previous symptomatic stroke	37 (6.4)	269 (5.1)	0.25
Current smoker	211 (36.3)	2374 (45.3)	<.0001
Familial history of ischemic heart disease	29 (5)	326 (6.2)	0.28
Anemia (hemoglobin < 11.0 g/dl)	64 (11)	319 (6.1)	<.0001
Chronic kidney disease (eGFR < 60ml/min/1.73m2)	156 (26.8)	1044 (19.9)	0.0001
Initial hemodynamics			
Systolic BP, mmHg	122.5 [110-140]	127 [109-144]	0.18
Diastolic BP, mmHg	77.5 [64.8-89]	80 [66-90]	0.08
Heart rate, per min	80 [68-96]	76 [64-88]	<.0001
LV ejection fraction, %	48 [42-55]	51 [45-57]	<.0001
Cardiogenic shock, %	39 (6.7)	386 (7.4)	0.62
Culprit vessel			0.0272
Left anterior descending artery	330 (56.7)	2639 (50.3)	
Left circumflex artery	53 (9.1)	494 (9.4)	
Right coronary artery	190 (32.6)	2025 (38.6)	
Left main coronary artery	9 (1.5)	85 (1.6)	
Multivessel disease	277 (47.6)	2259 (43.1)	0.0416
Procedural characteristics			
Trans-radial approach	158 (27.1)	1285 (24.5)	0.20
Glycoprotein IIb/IIIa inhibitor use	117 (20.1)	1165 (22.2)	0.26
Thrombus aspiration	171 (29.4)	2008 (38.3)	<.0001
Culprit vessel treated with			0.03
Bare metal stent	29 (5)	153 (2.9)	
1st generation drug-eluting stent	5 (0.9)	69 (1.3)	
2nd generation drug-eluting stent	502 (86.3)	4515 (86.1)	
Balloon angioplasty	31 (5.3)	299 (5.7)	
Use of IABP	29 (5)	264 (5)	1.0
Use of ECMO	8 (1.4)	88 (1.7)	0.71

Pre-PCI TIMI flow			0.008
0-1	414(71.2)	3,981 (75.9)	
2	72 (12.4)	539 (10.3)	
3	96 (16.5)	723 (13.8)	
Post-PCI TIMI flow			0.30
0-1	9 (1.6)	50 (1.0)	
2	24 (4.1)	188 (3.6)	
3	549 (94.3)	5005 (95.5)	
Discharge medications			
Dual antiplatelet agent	563 (96.7)	5057 (96.5)	0.85
Aspirin	569 (97.8)	5103 (97.3)	0.63
Clopidogrel	404 (69.4)	3332 (63.6)	0.006
Prasugrel	49 (8.4)	642 (12.2)	0.008
Ticagrelor	111 (19.1)	1098 (20.9)	0.32
Beta-blocker	449 (77.1)	4438 (84.6)	<.0001
ACEI/ARB	426 (73.2)	4126 (78.7)	0.003
Statin	521 (89.5)	4797 (91.5)	0.1271
Clinical Outcome			
In-hospital death	36 (6.2)	233 (4.4)	0.07
1-year mortality	58 (10)	374 (7.1)	0.02

* Patients who had PCI > 24 hours after symptom onset and who had PCI after 6 hours after admission were included

Table S2. Baseline Characteristics and Outcomes by Classifications of Door-to-Balloon Time.

	Classifications (door-to-balloon time)				
	0-45	**45-60**	**60-90**	**>90**	***P* value**
No. of patients	**1194**	**1655**	**1984**	**410**	
Demographics					
Age, y	61 (52-71)	62 (53-73)	63 (53-73)	61 (53-72)	0.167
Female	209 (17.5)	335 (20.2)	441 (22.2)	96 (23.4)	0.006
Body mass index, kg/m^2	24.2 (22.2-26.1)	23.9 (22.1-25.9)	23.9 (22.0-26.0)	24.0 (22.1-26.0)	0.111
Process of care index					
Symptom-onset-to-balloon time, hours	2.7 (1.6-4.3)	3.0 (2.0-5.0)	3.3 (2.2-5.6)	4.7 (3.2-7.5)	<0.001
Symptom-onset-to-door time, hours	2.0 (1.0-3.7)	2.1 (1.1-4.2)	2.0 (1-4.4)	1.9 (0.9-4.9)	0.216
Door-to-balloon time, minutes	37 (33-42)	52 (48-57)	70 (66-79)	127 (105-166)	<0.001
First medical contact					<0.001
Emergency medical service	208 (17.4)	331 (20.0)	447 (22.5)	119 (29.0)	
Transferred from other hospital	733 (61.4)	890 (53.8)	898 (45.3)	148 (36.1)	
Direct visit to emergency department	253 (21.2)	434 (26.2)	639 (32.2)	143 (34.9)	
Calendar time					0.063
First year (2012)	351 (29.4)	422 (25.5)	522 (26.3)	97 (23.7)	
Second year (2013)	305 (25.5)	451 (27.3)	527 (26.6)	104 (25.4)	
Third year (2014)	336 (28.1)	449 (27.1)	535 (27.0)	130 (31.7)	
Fourth year (2015)	202 (16.9)	333 (20.1)	400 (20.2)	79 (19.3)	
Symptom status					
Typical chest pain	1137 (95.2)	1542 (93.2)	1823 (91.9)	342 (83.4)	<0.001
Dyspnea	179 (15.0)	287 (17.3)	397 (20.0)	102 (24.9)	<0.001
Killip score					<0.001
Killip class 1	971 (81.4)	1292 (78.1)	1516 (76.4)	276 (67.3)	
Killip class 2	69 (5.8)	143 (8.7)	166 (8.4)	28 (6.8)	
Killip class 3	40 (3.4)	81 (4.9)	133 (6.7)	28 (6.8)	
Killip class 4	113 (9.5)	138 (8.3)	169 (8.5)	78 (19.0)	
First 12-lead ECG					
Anterior location	624 (52.3)	885 (53.5)	1012 (51.0)	192 (46.8)	0.089
Q-wave	135 (11.3)	127 (7.7)	112 (5.7)	41 (10.0)	<0.001
ST-segment depression	254 (21.3)	284 (17.2)	336 (16.9)	61 (14.9)	0.003
Left bundle branch block	4 (0.3)	6 (0.4)	20 (1.0)	8 (2.0)	0.001
Atrial fibrillation	57 (4.8)	89 (5.4)	106 (5.3)	29 (7.1)	0.364
AV block (2nd degree or complete)	21 (1.8)	19 (1.2)	25 (1.3)	4 (1.0)	0.601
Wide QRS tachycardia	11 (0.9)	9 (0.5)	14 (0.7)	7 (1.7)	0.103

Previous medical history					
Hypertension	498 (41.7)	751 (45.4)	971 (48.9)	202 (49.3)	0.001
Diabetes	279 (23.4)	390 (23.6)	483 (24.3)	120 (29.3)	0.087
treated with insulin	11 (0.9)	19 (1.2)	38 (2.0)	20 (4.88)	<0.001
Dyslipidemia	120 (10.1)	168 (10.2)	228 (11.5)	42 (10.2)	0.487
Previous myocardial Infarction	64 (5.4)	94 (5.7)	114 (5.8)	26 (6.3)	0.901
Previous angina pectoris	59 (4.9)	91 (5.5)	147 (7.4)	33 (8.1)	0.008
Heart failure	9 (0.8)	7 (0.4)	21 (1.1)	2 (0.5)	0.149
Previous symptomatic stroke	53 (4.4)	81 (4.9)	113 (5.7)	22 (5.4)	0.438
Current smoker	597 (50.0)	754 (45.6)	877 (44.2)	146 (35.6)	<0.001
Familial history of ischemic heart disease	60 (5.0)	106 (6.4)	131 (6.6)	29 (7.1)	0.258
Anemia (hemoglobin < 11.0 g/dl)	56 (4.7)	78 (4.7)	136 (6.9)	49 (12.0)	<0.001
Chronic kidney disease (eGFR < 60ml/min/1.73m2)	183 (15.3)	312 (18.9)	442 (22.3)	107 (26.1)	<0.001
Initial hemodynamics					
Systolic BP, mmHg	122 (107-140)	126 (110-145)	128 (110-145)	130 (109-147)	0.041
Diastolic BP, mmHg	80 (65-90)	80 (66-90)	80 (67-90)	80 (62-90)	0.035
Heart rate, per min	76 (64-86)	76 (64-88)	76 (64-88)	76 (64-90)	0.090
LV ejection fraction, %	51 (45-57)	51 (45-58)	51 (45-57)	51 (44-57)	0.301
Cardiogenic shock, %	139 (11.64)	184 (11.12)	230 (11.59)	95 (23.17)	<.001
Culprit vessel					0.003
Left anterior descending artery	564 (47.2)	847 (51.2)	1023 (51.6)	205 (50.0)	
Left circumflex artery	105 (8.8)	150 (9.1)	199 (10.0)	40 (9.8)	
Right coronary artery	512 (42.9)	631 (38.1)	729 (36.7)	153 (37.3)	
Left main coronary artery	13 (1.1)	27 (1.6)	33 (1.6)	12 (2.9)	
Multi-vessel disease	490 (41.0)	691 (41.8)	899 (45.3)	179 (43.7)	0.055
Complex lesion (Type B2 / C)	1083 (90.7)	1488 (89.91)	1727 (87.05)	360 (87.8)	0.005
Procedural characteristic					
Trans-radial approach	308 (25.8)	381 (23.0)	501 (25.3)	95 (23.2)	0.450
Glycoprotein IIb/IIIa inhibitor use	323 (27.1)	365 (22.1)	386 (19.5)	91 (22.2)	<0.001
Thrombus aspiration	472 (39.5)	671 (40.5)	729 (36.7)	136 (33.2)	0.012
Culprit vessel treated with					<0.001
Bare metal stent	38 (3.2)	50 (3.0)	52 (2.6)	13 (3.2)	
1st generation drug-eluting stent	15 (1.3)	13 (0.8)	38 (1.9)	3 (0.7)	
2nd generation drug-eluting stent	1042 (87.3)	1472 (88.9)	1652 (83.3)	349 (85.1)	
Balloon angioplasty	80 (6.7)	73 (4.4)	110 (5.5)	36 (8.8)	
Use of IABP	51 (4.3)	73 (4.4)	99 (5.0)	41 (10.0)	<0.001
Use of ECMO	6 (0.5)	17 (1.0)	32 (1.6)	33(8.1)	
Pre-PCI TIMI flow					<0.001

0-1	953 (79.8)	1283 (77.5)	1444 (72.8)	301 (73.4)	
2	126 (10.6)	168 (10.2)	198 (10.0)	47 (11.5)	
3	115 (9.6)	204 (12.3)	342 (17.2)	62 (15.1)	
Post-PCI TIMI flow					0.002
0-1	9 (0.8)	8 (0.5)	23 (1.2)	10 (2.4)	
2	37 (3.1)	51 (3.1)	79 (4.0)	21 (5.1)	
3	1148 (96.2)	1596 (96.4)	1882 (94.9)	379 (92.4)	
Discharge medications					
Dual antiplatelet agent	1161 (97.2)	1605 (97.0)	1914 (96.5)	377 (92.0)	<0.001
Aspirin	1172 (98.2)	1619 (97.8)	1929 (97.2)	383 (93.4)	<0.001
Clopidogrel	758 (63.5)	1027 (62.1)	1289 (65.0)	258 (62.9)	0.335
Prasugrel	135 (11.3)	22.6 (13.7)	246 (12.4)	35 (8.5)	0.025
Ticagrelor	273 (22.9)	357 (21.6)	384(19.3)	84 (20.5)	0.105
Beta-blocker	1038 (86.9)	1422 (85.9)	1675 (84.4)	303 (73.9)	<0.001
ACEI/ARB	981 (82.2)	1350 (81.6)	1518 (76.5)	277 (67.6)	<0.001
Statin	1128 (94.5)	1529 (92.4)	1800 (90.7)	340 (82.9)	<0.001

Values are median (Q1, Q3) or n (%).

ACE-I/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker; BP, blood pressure; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LV, left ventricular; PCI, percutaneous coronary intervention.

Table S3. Univariable Cox Regression Analysis with Categorical Classification of Door-to-Balloon Time for 1-year All-Cause Mortality in Patients with ST-Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention.

Covariables	Valid Cases	Deaths†	HR (95% CI)	Wald test	*P* value
Demographics					
Age, per 10-year increase	5243		2.01 (1.82-2.22)	192	<0.001
Female	5243	132	2.17 (1.75-2.67)	51.5	<0.001
Comorbid conditions					
Hypertension	5243	220	1.70 (1.38-2.08)	25.4	<0.001
Diabetes	5243	133	1.76 (1.42-2.17)	27.4	<0.001
Previous myocardial infarction	5243	26	1.24 (0.84-1.85)	7.73	0.276
Previous angina pectoris	5243	36	1.62 (1.15-2.29)	6.71	0.006
Previous congestive heart failure	5243	9	3.43 (1.82-6.48)	14.5	<0.001
Dyslipidemia	5243	26	0.61 (0.41-0.91)	5.86	0.015
Active or previous smoker	5243	185	0.50 (0.41-0.61)	45.7	<0.001
Delay to treatment, per 1h increase					
Symptom-onset-to-door time	**5243**				0.019
> 4 hours	1401	123	1 [Reference]	9.94	
2-4 hours	1387	101	0.82 (0.63-1.07)		0.142
1-2 hours	1153	75	0.73 (0.55-0.97)		0.031
< 1 hour	1302	75	0.65 (0.49-0.87)		0.003
Door-to-balloon time	**5243**				<0.001
D2B > 90 min	410	71	1 [Reference]	77.3	
D2B 60-90 min	1984	147	0.39 (0.30-0.53)		<0.001
D2B 45-60 min	1655	103	0.33 (0.24-0.45)		<0.001
D2B 0-45 min	1194	53	0.23 (0.16-0.33)		<0.001
First medical contact	**5243**				
Direct visit to PCI center	1469	68	1 [Reference]	18.8	<0.001
Emergency medical service (911)	1105	85	1.70 (1.23-2.33)		0.001
Transport from other hospital	2669	221	1.81 (1.38-2.38)		<0.001
Clinical characteristics					
Typical chest pain	**5243**	80	0.28 (0.22-0.36)	103	<0.001
Body mass index, per 1-unit increase	5063		0.85 (0.82-0.89)	54.2	<0.001
Systolic blood pressure, per 10mmHg	5227		0.82 (0.80-0.84)	248	<0.001
Diastolic blood pressure, per 10mmHg	5227		0.76 (0.73-0.79)	211	<0.001
Heart rate, per 10/ minute increase	5227		1.19 (1.11-1.27)	25.0	<0.001
Killip class	5241	374			

I	4055	137	1 [Reference]	417	
II	406	37	2.78 (1.94-3.99)	30.8	<0.001
III	282	53	6.08 (4.44-8.33)	127	<0.001
IV	498	147	10.5 (8.31-13.2)	397	<0.001
Cardiogenic shock	5,243	129	8.3 (6.7-10.3)	19.43	<0.001
Anterior infarct location	5243	221	1.36 (1.11-1.67)	8.7	0.003
Left bundle branch block	5243	10	4.30 (2.26-8.19)	19.8	<0.001
Atrial fibrillation	5243	42	2.33 (1.69-3.20)	27.0	<0.001
Culprit vessel Left main	5243	46	4.25 (3.12-5.80)	83.9	<0.001
Multivessel disease	5243	192	1.41 (1.15-1.73)	11.1	0.001

[†] Total number of deaths = 374

CI, confidence intervals; HR, hazard ratio; PCI, percutaneous coronary intervention.

Table S4. Multivariable Cox Regression Analysis with Categorical Classification of Door-to-Balloon Time for 1-year All-Cause Mortality in Patients with ST-Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention.

Covariables	HR (95% CI)	*P* value
Demographics		
Age, per 10-year increase	1.92 (1.49-2.46)	<0.001
Comorbid conditions		
Previous angina pectoris	1.44 (1.00-2.09)	0.05
Chronic Kidney disease	1.99 (1.56-2.54)	<.0001
Delay to treatment		
Door-to-balloon time (group)		<0.001
D2B > 90 min	1 [Reference])	
D2B 60-90 min	0.41 (0.30-0.57)	<0.001
D2B 45-60 min	0.33 (0.24-0.47)	<0.001
D2B 0-45 min†	0.27 (0.18-0.41)	<0.001
First medical contact		
Direct visit to PCI center	1 [Reference]	
Emergency medical service (911)	1.01 (0.72-1.42)	0.95
Transport from other hospital	1.40 (1.03-1.89)	0.03
Clinical characteristics		
Body mass index, kg/m^2	0.93 (0.90-0.97)	<.0001
Typical chest pain	0.69 (0.52-0.91)	0.01
Systolic blood pressure, per 10mmHg	0.89 (0.86-0.93)	<0.001
Heart rate, per 10-minute increase	1.15 (1.11-1.20)	<0.001
Killip class II-IV	1.66 (1.23-2.22)	0.001
Cardiogenic shock	2.38 (1.76-3.24)	<.0001
Procedural Characteristics		
Anterior infarct location	1.43 (1.15-1.79)	0.002
Culprit vessel Left main	2.82 (1.96-4.06)	<0.001
Multi-vessel disease	1.41 (1.11-1.78)	0.004

Harrell's c-index of prediction model was 0.866 (0.848-0.883).

† When using D2B 60-90 minutes group as reference, D2B 0-45 minutes group also showed further decreased risk of 1-year mortality (HR 0.66, 95% CI 0.46-0.93, *P* = 0.018).

CI, confidence intervals; HR, hazard ratio.

Table S5. Prehospital and In-hospital Delays in Patient Subgroups according to the Route of Visit to Primary PCI Centers.

Delay	Direct visit	EMS	Transferred	*P*-value
Onset-to-Door, min	99 [52-235]	60 [35-120]	175 [102-310]	<0.0001
Door-to-Balloon, min	62 [49-77]	61 [48-76]	55 [44-68]	<0.0001
Onset-to-Balloon, min	171 [113-309]	135 [100-193]	230 [155-375]	<0.0001

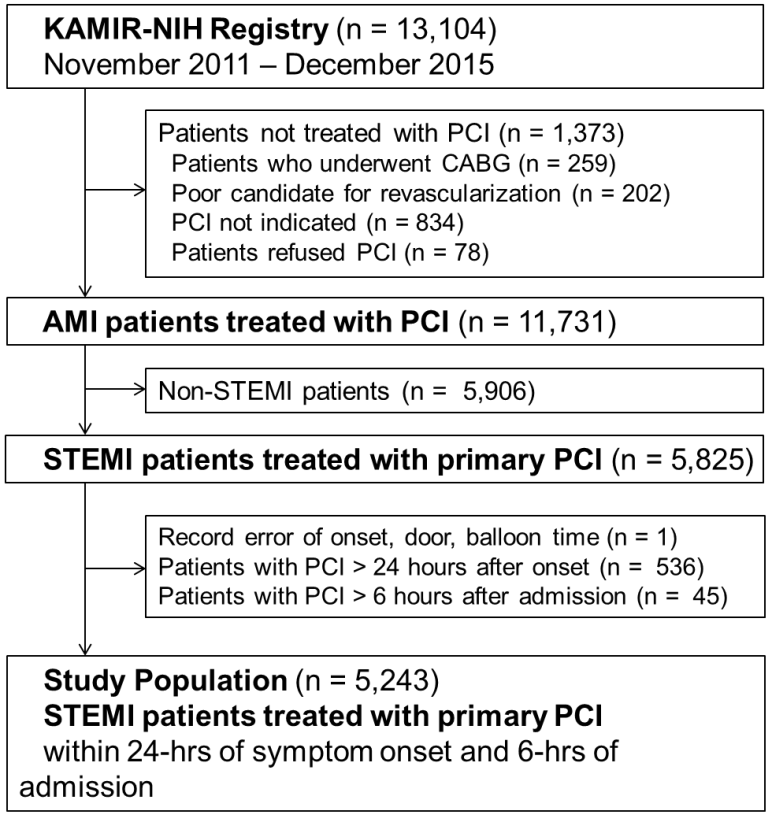
Values are median [Q1, Q3]
EMS, emergency medical service.

Table S6. Comparison of KAMIR-NIH study to Other Studies on Door-to-Balloon Time of Patients with STEMI.

Study Name	KAMIR-NIH D2B	Nallamothu et al.	Menees et al.	Flynn et al.	Gibson et al.
Registry	KAMIR-NIH	NCDR CathPCI	NCDR CathPCI	BMC2 consortium	NRMI
Region	South Korea	USA	USA	USA	USA
Time period	Nov. 2011 ~ Oct. 2015	Jan. 2005 ~ Dec. 2011	Jul. 2005 ~ Jun. 2009	Jan. 2003 ~ Dec. 2008	1990 ~ 2006
Study participant no.	5,243	150,116	96,738	8,771	774,279
D2B effect on outcome at	Patient-level	Patient-level & population-level	Population-level	Population-level	Population-level
D2B time by year	2012: 63 min 2013: 62 min 2014: 64 min 2015: 66 min	2005: 86 min 2007: 72 min 2009: 66 min 2011: 63 min	2005: 83 min 2006: 76 min 2007: 70 min 2008: 67 min	2003: 113 min 2004: 104 min 2006: 89 min 2008: 76 min	1994: 107 min 1998: 104 min 2002: 101 min 2006: 79 min
O2D time	Reported	Reported in category	Not reported	Reported	Reported
Primary outcome	1-year mortality	In-hospital mortality & 6-month mortality	30-day mortality	In-hospital mortality	In-hospital mortality
Statistical method	Cox regression model	Multilevel logistic regression model	Hierarchial logistic regression model	Standardized mortality ratio	Logistic regression
Clinical and procedural factors in the model	Age, sex, heart rate, BMI, SBP, atypical chest pain, route of visit, prior hypertension, diabetes, anemia, chronic kidney disease, dyslipidemia, heart failure, angina, smoking, Killip classification, cardiogenic shock, anterior location, lesion complexity, multi-vessel ds., LM ds., LBBB, A.fib	Age, BMI, DM, ESRD, cerebrovascular ds., peripheral vascular ds., chronic lung ds., prior CHF, heart valve ds., prior heart valve op., prior PCI, NYHA class., cardiogenic shock, IABP placement, PCI status of 'salvage', lesion location, SCAI lesion classification, pre-procedure TIMI flow, LVEF(%), GFR.	Age, BMI, DM, ESRD, cerebrovascular ds., peripheral vascular ds., chronic lung ds., prior CHF, heart valve ds., prior heart valve op., prior PCI, NYHA class., cardiogenic shock, IABP placement, PCI status of 'salvage', lesion location, SCAI lesion classification, pre-procedure TIMI flow, LVEF(%), GFR, subacute thrombosis.	Age, sex, prior CHF, prior extracardiac vascular ds., prior valve ds., emergency PCI, baseline MI, cardiac arrest, cardiogenic shock, anemia, serum creatinine level, LVEF(%).	Age, sex, race, payer, hospital location, angina, prior CABG, prior CAD, prior CHF, prior dyslipidemia, prior HTN, prior MI, prior PCI, smoker, prior cerebrovascular ds., O2D time, Killip class, HR, SBP, anterior MI.

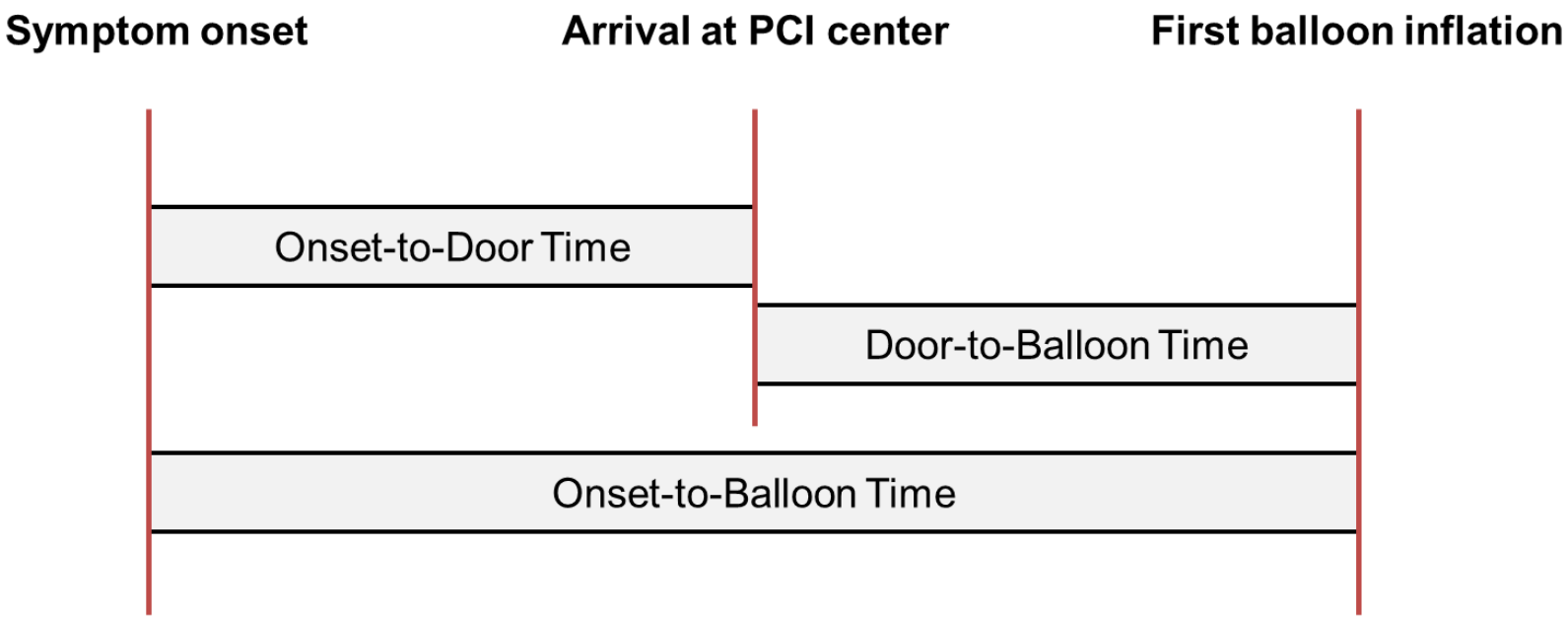
Study Name	KAMIR-NIH D2B	Shiomi et al.	Terkelsen et al.	Rathore et al.	McNamara et al.
Registry	KAMIR-NIH	CREDO-Kyoto	Denmark Heart Registry	NCDR	NRMI-3, 4
Region	South Korea	Japan	Denmark	USA	USA
Time period	Nov. 2011 ~ Oct. 2015	Jan. 2005 ~ Dec. 2007	Jan. 2001 ~ Dec. 2008	Jan. 2005 ~ Dec. 2006	Jan. 1999 ~ Dec. 2002
Study participant no.	5,243	3,391	6,209	43,801	29,222
D2B effect on	Patient-level	Patient-level	Patient-level	Patient-level	Patient-level
D2B time by year	2012: 63 min 2013: 62 min 2014: 64 min 2015: 66 min	Overall: 60 min	Field triaged: 39 min Transferred: 29 min	Overall: 83 min	1999: 105 min 2000: 102 min 2001: 100 min 2002: 102 min
O2D time	Reported	Reported	Reported	Reported in category	Reported in category
Primary outcome	1-year mortality	Death + CHF at 30 days and 3-years	Long-term (> 6y) mortality	In-hospital mortality	In-hospital mortality
Statistical model	Cox regression	Cox regression	Cox regression	Logistic regression	Logistic regression
Clinical and procedural factors for adjustment	Age, sex, heart rate, BMI, SBP, atypical chest pain, route of visit, prior hypertension, diabetes, anemia, chronic kidney disease, dyslipidemia, heart failure, angina, smoking, Killip classification, cardiogenic shock, anterior location, lesion complexity, multi-vessel ds., LM ds., LBBB, A.fib	Age, sex, BMI, HTN, DM on insulin, smoking, CHF, severe MR, prior MI, prior stroke, peripheral vascular ds., GFR, ESRD on HD, A. fib., anemia, thrombocytopenia, COPD, liver cirrhosis, malignancy, Killip class 4, multi-vessel disease, proximal LAD ds., left main ds., CTO, bifurcation, DES, thrombectomy, distal protection, cilostazole, statin, beta-blockers, ACEI/ARB, nitrates, CCB, Nncorandil, warfarin, PPI, H2-blockers	Age, sex, BMI, prior MI, HTN, DM, CHF, smoking, systolic BP, Killip class, Anterior location, Bundle-branch block, multivessel disease.	- Patient level: age, sex, race, cardiogenic shock, renal failure, O2D category, prior DM, chronic lung ds., LVEF(%), IABP use, use of thrombin inhibitor, time of day, week-end procedure, left main ds., proximal LAD ds. - Hospital level: annual primary PCI volume, teaching status, ownership, rural location	Age, sex, smoking, prior CKD, DM, dyslipidemia, FHx of CAD, prior PCI, CABG, stroke, chest pain at presentation, SBP, HR, presentation with sign of heart failure, anterior location on ECG, number of ST segment elevation, left bundle branch block, Q-wave on ECG.

Figure S1. Study Flow.



Study population was derived from a nationwide, multicenter, prospective registry of acute myocardial infarction, the Korea Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH) registry.

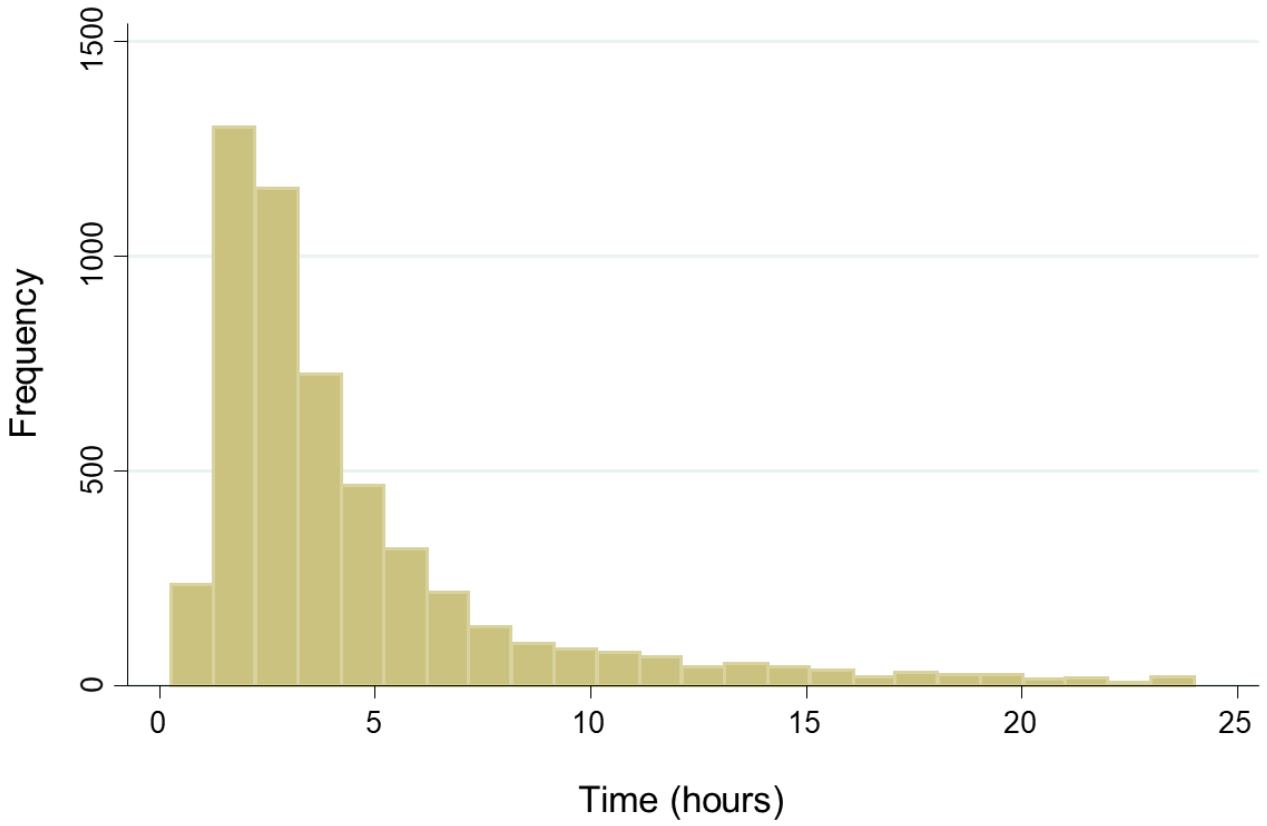
Figure S2. Delays from Symptom Onset to Primary Percutaneous Coronary Intervention in Patients with ST-Segment Elevation Myocardial Infarction.



Delays from symptom onset to primary PCI are presented. Time intervals for symptom onset-to-door time, door-to-balloon time, and symptom onset-to-balloon time were calculated from the corresponding time entries.

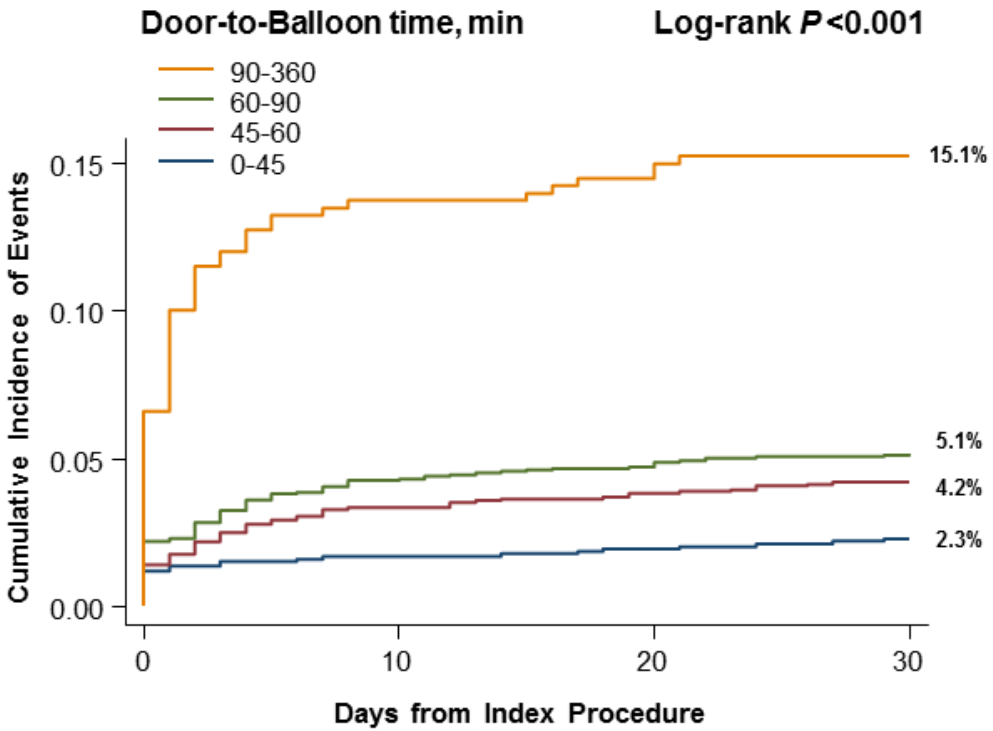
PCI, percutaneous coronary intervention.

Figure S3. Distribution of Symptom Onset-to-Balloon Time.



Distribution of symptom onset-to-balloon time of the study population.

Figure S4. Comparison of 30-day Mortality According to Door-to-Balloon Time.

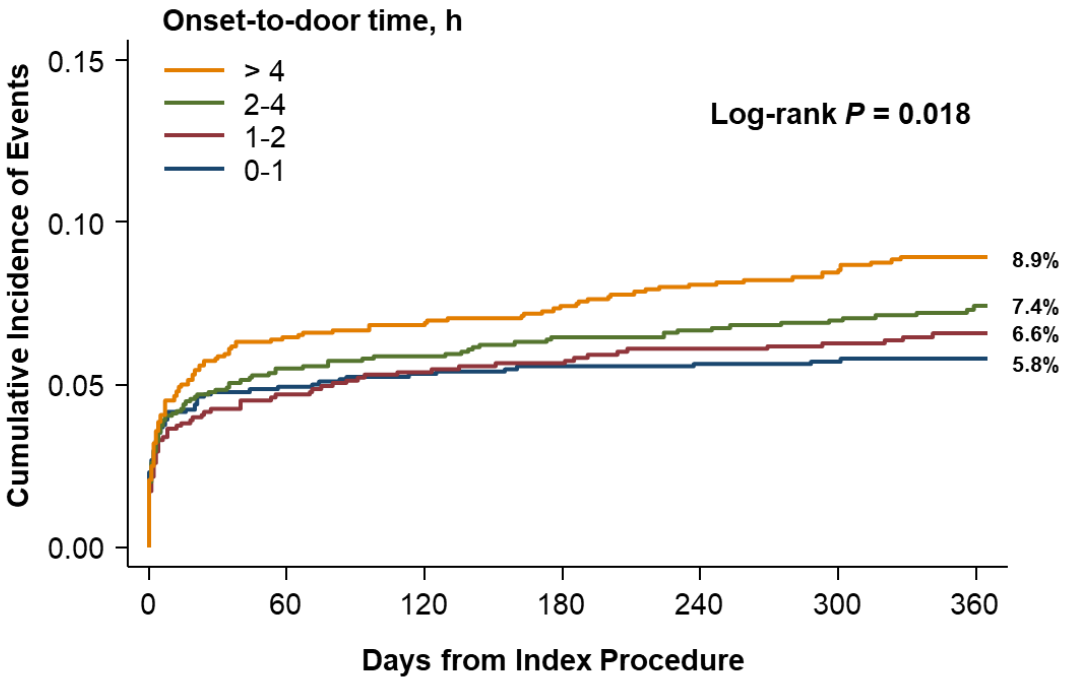


Number at risk

90-360	410	347	344	340
60-90	1984	1881	1866	1857
45-60	1655	1580	1571	1563
0-45	1194	1154	1149	1145

Comparison of all-cause mortality at 30-day among classifications by D2B time.

Figure S5. Comparison of Clinical Outcome According to Onset-to-Door Time.

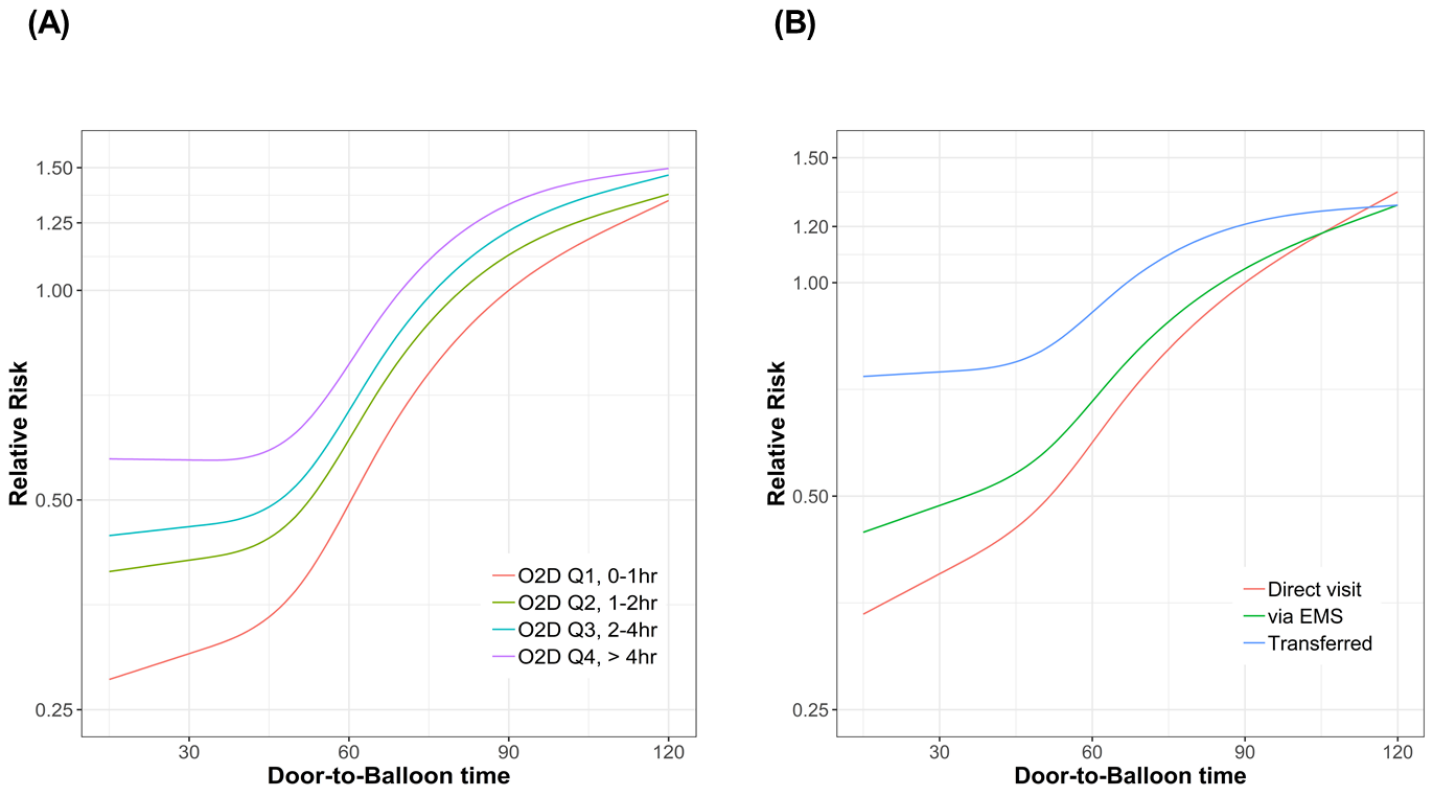


Number at risk

> 4h	1401	1285	1275	1258	1232	1200	807
2-4h	1387	1292	1283	1272	1257	1234	844
1-2h	1153	1088	1080	1071	1054	1032	714
0-1h	1302	1214	1208	1201	1188	1149	785

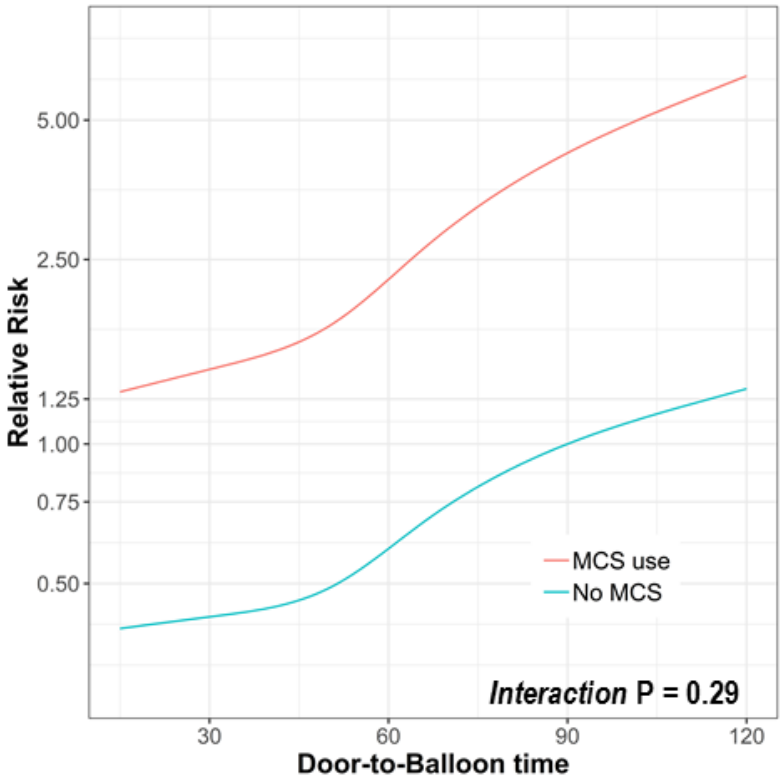
Comparison of all-cause mortality at 1-year among classifications by O2D time.

Figure S6. Association between D2B time and 1-year mortality by Onset-to-Door Time Group and Route of Visit.



The association between relative all-cause mortality rates and D2B time in patients grouped by (A) O2D time quartile and (B) route of visit to primary PCI centers.

Figure S7. Association between D2B time and 1-year mortality by Requirement of Mechanical Circulation Support Devices.



The association between relative all-cause mortality rates and D2B time in patients with or without cardiogenic shock or mechanical circulatory supports.