Association between the Door-to-balloon Time and Mid-term Clinical Outcomes in Patients with ST-Segment Elevation Myocardial Infarction

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Abstract:
Objective In primary percutaneous coronary intervention (PCI), the door-to-balloon time (DTBT) is known to be associated with in-hospital death in patients with ST-segment elevation myocardial infarction (STEMI). However, little is known regarding the association between the DTBT and the mid-term clinical outcomes in patients with STEMI. The purpose of this study was to investigate the association between the DTBT and mid-term all-cause death.

Methods The study population included 309 STEMI patients, who were divided into the short DTBT (DTBT<60 minutes, n=103), intermediate DTBT (DTBT 60-120 minutes, n=174) and long DTBT (DTBT >120 minutes, n=32) groups. The median follow-up period was 287 days (interquartile range: 182-624 days).

Results The incidence of all-cause death in the long DTBT group was significantly higher in comparison to the other groups (p<0.001). In the multivariate Cox regression analysis, although a short DTBT [vs. intermediate DTBT: hazard ratio (HR) 1.00, 95% confidence interval (CI) 0.39-2.55, p=0.99] was not associated with all-cause death, a long DTBT (vs. intermediate DTBT: HR 2.80, 95% CI 1.26-6.17, p=0.011) was significantly associated with all-cause death, after controlling for confounding factors such as Killip class 4, an impaired renal function, and the number of diseased vessels.

Conclusion The DTBT was significantly associated with the incidence of mid-term all-cause death. Our results support the strong adherence to the DTBT in patients with STEMI.

Key words: percutaneous coronary intervention, ST-elevation acute myocardial infarction, door to balloon time, all-cause death

Introduction
Since the door-to-balloon time (DTBT) is considered to be associated with mortality and morbidity in patients with ST-segment elevation myocardial infarction (STEMI) (1, 2), the current guidelines recommend that a DTBT of ≤90 min or ≤60 min be achieved (3, 4). However, early studies have mainly focused on the association between the DTBT and short-term mortality (5). Our previous study, which investigated the determinants of short and long DTBTs, also showed that the rate of in-hospital mortality in STEMI patients with a short DTBT was lower than that in those with a long DTBT (6). On the other hand, there are few studies about the association between the DTBT and mid-term or long-term clinical outcomes (7, 8). The purpose of this study was to investigate the association between the DTBT and mid-term all-cause death in patients with STEMI.

Materials and Methods
Study patients
We identified acute myocardial infarction (AMI) patients
from hospital records of patients who were managed in our medical center from January 2015 to December 2017. The diagnosis of AMI required the following criteria: symptoms consistent with AMI; elevated cardiac enzymes, including Troponin T, Troponin I, and/or creatinine kinase (at least a 2-fold increase from the upper normal limit); and ST-segment elevation or depression on electrocardiograms that was compatible with AMI (6). We defined the DTBT as the time from hospital arrival to the time of balloon dilation or thrombus aspiration (6). The exclusion criteria were as follows: 1) non-ST-elevation myocardial infarction (NSTEMI); 2) delayed admission (>24 hours from the onset of AMI to hospital arrival); 3) unclear door time, typically nosocomial cases; 4) patients without primary percutaneous coronary intervention (PCI); and 5) patients with a DTBT of <15 minutes or >3 hours (2, 9). We divided our study population into short DTBT (DTBT <60 minutes), intermediate DTBT (DTBT 60-120 minutes), and long DTBT (DTBT ≥120 minutes) groups according to our previous criteria (6). The primary endpoint was all-cause death. We acquired this information from hospital records. The day of admission was defined as the index day (day 1). Patients were followed until death or until the end of the study (March 2019).

Definitions

Hypertension was defined as medical treatment for hypertension and/or a history of hypertension before admission (6). Dyslipidemia was defined as total cholesterol ≥220 mg/dL or low-density lipoprotein cholesterol ≥140 mg/dL or medical treatment for dyslipidemia or a history of dyslipidemia (6). Diabetes mellitus was defined as hemoglobin A1c ≥6.5% [as National Glycohemoglobin Standardization Program (NGSP) value], medical treatment for diabetes mellitus, or a history of diabetes mellitus (6). We also calculated estimated glomerular filtration rate (eGFR) from the serum creatinine level, age, weight, and sex using the following formula: eGFR=194×Cr−1.094×age−0.287 (male), eGFR=194×Cr−1.094×age−0.287×0.739 (female) (10). Shock was defined as systolic blood pressure <90 mmHg or vasopressors required to maintain blood pressure or attempted cardiopulmonary resuscitation (11). Patient symptoms were classified as either typical symptoms or atypical symptoms. Typical symptoms was defined as acute onset chest pain or chest oppression, whereas atypical symptoms was defined as other symptoms, such as chest discomfort, shortness of breath, nausea, syncope or the absence of these symptoms (12). We investigated an onset time from our hospital records. However, in some cases, the hospital records only described the onset time as morning, evening, bed-time, or midnight, rather than the exact time. Thus, we translated these vague expressions into the exact time to calculate the onset-to-balloon time. We defined getting up as 6:00 am, morning as 9:00 am, noon as 12:00 pm, evening as 18:00 pm, bedtime as 21:00 pm, and midnight as 0:00 am.

Primary PCI was performed using standard techniques via the radial artery, the femoral artery, or—in rare cases—the brachial artery. First, we advanced a conventional guidewire across the lesion, and used a small (diameter: 2.0 mm) balloon or thrombus aspiration catheter (balloon time). The choice of devices was left to the discretion of each interventional cardiologist. The activated coagulation time (ACT) was maintained at >250 seconds during PCI.

Statistical analysis

Data are expressed as the mean±standard deviation (SD) or percentage. Categorical variables are presented as the number (percentage) and were compared with Pearson’s χ² test. The Shapiro-Wilk test was performed to determine if continuous variables were normally distributed. Normally distributed continuous variables were compared using a one-way analysis of variance (ANOVA). Otherwise, continuous variables were compared using the Kruskal-Wallis test. Event free survival curves were constructed using the Kaplan-Meier method, and the differences between curves were statistically assessed by the log rank test. P values of < 0.05 were considered to indicate statistical significance. We also performed a multivariate Cox regression analysis to investigate the association between short or long DTBT and all-cause death after controlling for confounders, which were known clinical factors (e.g., Killip 4, eGFR, or triple vessel disease) (12-16). Hazard ratios (HRs) and the 95% confidence intervals (CIs) were calculated. All analyses was performed using the SPSS 24.0 for Windows software program (SPSS, Chicago, USA).

Results

A total of 790 AMI patients admitted to our hospital from January 2015 to December 2017. From these, 469 patients were excluded (NSTEMI, n=331; delayed admission, n=90; unclear door time, n=32; and without primary PCI, n=16). Furthermore, we excluded 12 patients because their DTBT was ≥3 hours. Thus, our final study population included 309 STEMI patients who were divided, according to their DTBT, into the short DTBT (n=103), intermediate DTBT group (n=174) and long DTBT (n=32) groups (Fig. 1). The median follow-up period was 287 days (Interquartile range: 182-624). The mean and median DTBT were 75.1±30.8 min and 69 min (interquartile range: 53-92 min), respectively.

Table 1 shows the comparison of patient characteristics among the 3 groups. The prevalence of atypical symptoms was highest in the long DTBT group (37.6%), followed by the intermediate DTBT group (20.7%), and lowest in the short DTBT group (11.7%) (p=0.004). The prevalence of Killip class 3 and 4 was highest in the long DTBT group (21.9% and 21.9%, respectively), followed by the intermediate DTBT group (8.0% and 13.8%), and lowest in the short DTBT group (1.9% and 4.9%) (p=0.013 and <0.001). Table 2 shows the comparison of angiographic and procedural characteristics among the 3 groups. The prevalence of triple vessel disease was highest in the long DTBT group (34.4%), followed by the intermediate DTBT group (20.7%), and
Patients with Acute myocardial infarction admitted to our hospital from January 2015 to December 2017 (n=790)

- Non-ST elevation myocardial infarction (n=331)
- Delayed admission (> 24 hours) (n=90)
- Unclear door time, typically nosocomial case (n=32)
- Patients without primary PCI (n = 16)
- DTBT < 15 min or > 3 hr (n = 12)

ST-elevation myocardial infarction within 24 hour and underwent primary PCI (n=309)

- Short DTBT < 60 min (n=103)
- Intermediate 60 min ≤ DTBT ≤ 120 min (n=174)
- Long DTBT > 120 min (n=32)

**Figure 1. Study flowchart. PCI: percutaneous coronary intervention, DTBT: door-to-balloon time**

The present study analyzed 309 STEMI patients who underwent primary PCI to investigate the association between the DTBT and mid-term all-cause death. Mid-term all-cause death was more frequently observed in the long DTBT group. The multivariate Cox regression analysis showed a significant association between a long DTBT and mid-term all-cause death after controlling for confounding factors, such as Killip class 4, eGFR, triple vessel disease, age, use of mechanical support, and LM-LAD lesion. Our results suggest that reducing the DTBT is important for achieving better clinical outcomes.

Shiomi et al. analyzed 3,391 patients with STEMI, and reported a significant association between a short DTBT and better long-term outcomes in patients who presented within 2 hours of the onset of symptoms (17). Our results showed a significant association between a long DTBT and all-cause death, but not between a short-DTBT and all-cause death. In our study, the mean onset to balloon time was approximately 6 hours, which might have affected the negative association between a short-DTBT and all-cause death. An Australian registry (n=1,926) also showed that a door-to-balloon time of ≤90 min was associated with a lower risk of major adverse cardiac events (MACE) (adjusted odds ratio 0.48, 95% CI 0.33-0.73, p<0.01) (18). Furthermore, national registry data (n=150,116) from the USA showed a significant relationship between a shorter DTBT and reduced 6-month mortality (2). In comparison to these national registry data, the study population of the present study was relatively small, which might have affected the negative association between a short-DTBT and all-cause death. However, similarly to the above studies, our results also showed the importance of reducing the DTBT, because of the significant association between a long-DTBT and all-cause death.

Our multivariate analysis showed that factors such as Killip class 4, triple vessel disease, an impaired renal function, age, and the use of mechanical support were significantly associated with mid-term all-cause death. These factors, which reflect the severity of AMI, have been reported to be associated with poor clinical outcomes (16, 19-23). Therefore, our multivariate analysis confirmed the strong association between established risk factors and mid-term clinical outcomes.

The clinical implications of the present study should be noted. In general, the Killip class, number of diseased vessels, and the renal function are pre-defined conditions for each patient that cannot be changed in primary treatment for STEMI. On the other hand, the DTBT is an issue that we can modify. Since a delayed DTBT was significantly associated with mid-term all-cause death in this study, efforts should be made to shorten the DTBT, as mentioned in recent guidelines (24). Furthermore, the catheter laboratory team might shorten the DTBT through their collaboration (25). Although our results showed the strong adherence to the DTBT in patients with STEMI, when STEMI patients present with Killip class 4, adequate respiratory support or mechanical circulatory support should be prioritized over the DTBT to achieve better clinical outcomes (26-29). Furthermore, the favorable association between the DTBT and in-
hospital outcomes has been established (5). Therefore, we should seek a short DTBT for patients with STEMI, as long as the patient’s hemodynamics are stable.

**Study limitations**

The present study was associated with some limitations. First, since this study was a single-center retrospective observational study, there is a risk of selection bias. Since the study population was relatively small, the statistical analysis has an inherent risk of beta error (30). Because the clinical follow-up was confirmed by retrospective reviews of hospital charts, the follow-up periods varied widely. As we described in the Methods section, the vague expression regarding the time of onset was arbitrary translated into an exact time. Thus, our onset-to-door time was not exactly accurate.
The DTBT was significantly associated with the mid-term all-cause death, as well as established factors, such as Killip class, triple vessel disease and an impaired renal function. Our results support the strong adherence to the DTBT in patients with STEMI.

This study was approved by the institutional review board and the requirement for written informed consent was waived because of the retrospective study design. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Author’s disclosure of potential Conflicts of Interest (COI).
Kenichi Sakakura: Advisory role, Boston Scientific and Abbott

Table 2. The Compassion of Angiographic and Procedural Characteristics among the Short, Intermediate and Long DTBT Groups.

| Angiographic lesion characteristics | All (n=309) | Short DTBT group (n=103) | Intermediate DTBT group (n=174) | Long DTBT group (n=32) | p value |
|-------------------------------------|------------|--------------------------|---------------------------------|------------------------|---------|
| Left main                            | 9 (2.9)    | 2 (1.9)                  | 2 (1.1)                         | 5 (15.6)               | 0.001   |
| Left anterior descending artery      | 159 (51.5) | 55 (33.4)                | 91 (52.3)                       | 13 (40.6)              |         |
| Left circumflex artery               | 28 (9.1)   | 8 (7.8)                  | 16 (9.2)                        | 4 (12.5)               |         |
| Right coronary artery                | 113 (36.6) | 38 (36.9)                | 65 (37.4)                       | 8 (31.3)               |         |
| Number of narrowed coronary artery   |            |                          |                                 | 0.008                  |         |
| Single vessel disease                | 167 (54.0) | 60 (58.3)                | 95 (54.6)                       | 12 (37.5)              |         |
| Double vessel disease                | 86 (27.8)  | 34 (33.0)                | 43 (24.7)                       | 14 (28.1)              |         |
| Triple vessel disease                | 656 (18.1) | 9 (8.7)                  | 36 (20.7)                       | 11 (34.4)              |         |
| Initial TIMI flow grade              |            |                          | 0.001                           |                       |         |
| 0                                   | 181 (58.6) | 74 (71.8)                | 97 (55.7)                       | 10 (31.3)              |         |
| 1                                   | 42 (13.6)  | 13 (12.6)                | 21 (12.1)                       | 8 (25.0)               |         |
| 2                                   | 51 (16.5)  | 12 (11.7)                | 32 (18.4)                       | 7 (21.9)               |         |
| 3                                   | 35 (11.3)  | 4 (3.9)                  | 24 (13.8)                       | 7 (21.9)               |         |
| Final TIMI flow grade                |            |                          | 0.64                            |                       |         |
| 0                                   | 1 (0.3)    | 0 (0.0)                  | 1 (0.6)                         | 0 (0.0)                |         |
| 1                                   | 2 (0.6)    | 0 (0.0)                  | 2 (1.1)                         | 0 (0.0)                |         |
| 2                                   | 15 (4.9)   | 3 (2.9)                  | 11 (6.3)                        | 1 (3.1)                |         |
| 3                                   | 291 (94.2) | 100 (97.1)               | 160 (92.0)                      | 31 (96.9)              |         |
| Procedure characteristics           |            |                          |                                 |                       |         |
| Door to balloon time                 | 75.1±30.8  | 45.3±9.83                | 81.0±16.1                       | 139.1±16.2             | <0.001  |
| Onset to balloon time                | 371±361    | 320±296                  | 378±393                         | 505±343                | <0.001  |
| Pre-dilatation by small balloon      | 278 (90.0) | 96 (93.2)                | 152 (87.4)                      | 30 (93.8)              | 0.22    |
| Thrombus aspiration                  | 98 (31.8)  | 24 (23.3)                | 70 (40.5)                       | 4 (12.5)               | 0.001   |
| Bare metal stent                     | 16 (5.2)   | 6 (5.8)                  | 9 (5.2)                         | 1 (3.1)                | 0.83    |
| Drug-eluting stent                   | 271 (87.7) | 95 (92.2)                | 151 (86.8)                      | 25 (78.1)              | 0.09    |
| Drug coated balloon                  | 3 (1.0)    | 0 (0.0)                  | 2 (1.1)                         | 1 (3.1)                | 0.27    |
| Post-dilatation after stenting       | 128 (41.4) | 47 (45.6)                | 63 (36.2)                       | 18(56.3)               | 0.06    |
| Rotational atherectomy               | 1 (0.3)    | 1 (1.0)                  | 0 (0.0)                         | 0 (0.0)                | 0.37    |
| Distal protection                    | 1 (0.3)    | 0 (0.0)                  | 1 (0.6)                         | 0 (0.0)                | 0.68    |
| Micro catheter                       | 50 (16.2)  | 11 (10.7)                | 27 (15.5)                       | 12 (37.5)              | 0.001   |
| Intra-aortic balloon pumping         | 33 (10.7)  | 6 (5.9)                  | 20 (11.5)                       | 7(21.9)                | 0.032   |
| V-A ECMO                             | 12 (3.9)   | 1 (1.0)                  | 5 (2.9)                         | 6(18.8)                | <0.001  |
| Mechanical support                   | 44 (14.2)  | 7 (6.8)                  | 25 (14.4)                       | 12 (37.5)              | <0.001  |
| Temporary pacemaker                  | 40 (13.0)  | 7 (6.9)                  | 28 (16.1)                       | 5 (15.6)               | 0.08    |
| Initial access site                  |            |                          | 0.033                           |                       |         |
| Radial artery                        | 190 (62.3) | 73 (73.0)                | 102 (59.0)                      | 15 (44.4)              |         |
| Brachial artery                      | 2 (0.7)    | 0 (0.0)                  | 1 (0.6)                         | 1 (3.1)                |         |
| Femoral artery                       | 113 (37.0) | 27 (27.0)                | 70 (40.5)                       | 17 (53.1)              |         |

* In some cases, expression regarding onset time was described in hospital records as just morning, evening, bed-time, or mid-night rather than the exact time. Those vague expressions were translated into the exact time to calculate onset-to-balloon time as follows: Getting up as 6:00 am, morning as 9:00 am, noon as 12:00 pm, evening as 18:00 pm, bedtime as 21:00 pm, mid-night as 0:00 am.

DTBT: door-to-balloon time, TIMI: thrombolysis in myocardial infarction, V-A ECMO: veno-arterial extracorporeal membrane oxygenation
Vascular; Honoraria, Abbott Vascular, Boston Scientific, Medtronic Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Kaneka and NIPRO. Hideo Fujita: Advisory role, Mehergen Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Vascular; Honoraria, Abbott Vascular, Boston Scientific, Medtronic Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Kaneka and NIPRO. Hideo Fujita: Advisory role, Mehergen Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Vascular; Honoraria, Abbott Vascular, Boston Scientific, Medtronic Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Kaneka and NIPRO. Hideo Fujita: Advisory role, Mehergen Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Vascular; Honoraria, Abbott Vascular, Boston Scientific, Medtronic Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Kaneka and NIPRO. 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