【 ORIGINAL ARTICLE 】

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

Takunori Tsukui, Kenichi Sakakura, Yousuke Taniguchi, Kei Yamamoto, Masaru Seguchi, Hiroshi Wada, Shin-ichi Momomura and Hideo Fujita

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

(Intern Med 59: 1597-1603, 2020)
(DOI: 10.2169/internalmedicine.4287-19)

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 pa-tients 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 bra-

chial 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 χ^2 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 lank 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
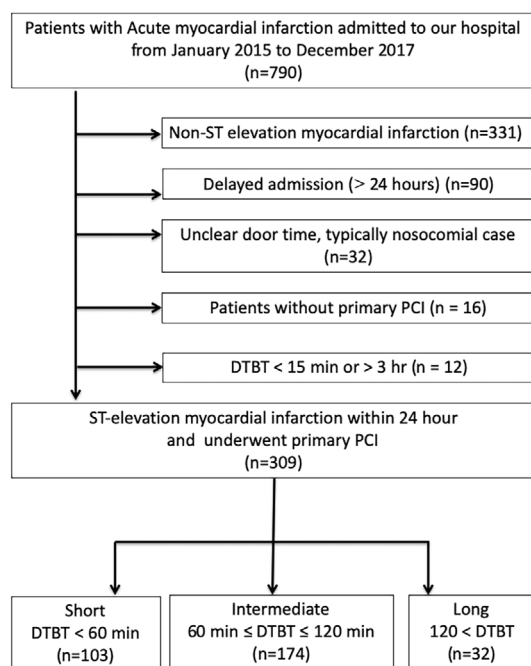
Figure 1.   Study flowchart. PCI: percutaneous intervention, DTBT: door-to-balloon time

lowest in the short DTBT group (8.7%) (p=0.008). Mechanical support, including intra-aortic balloon pumping and veno-arterial extracorporeal membrane oxygenation (V-A ECMO), was most frequently used in the long DTBT group, followed by the intermediate DTBT group, and was least commonly used in the short DTBT group. A radial approach was most frequently applied in the short DTBT group (73.0%), followed by the intermediate DTBT group (59.0%), and was least frequently applied in the long DTBT group (44.4%) (p<0.033).

Kaplan-Meier curves were constructed to compare all-cause death among the 3 groups (Fig. 2). All-cause death was most frequently observed in the long DTBT group, followed by the intermediate group, and least frequently observed in the short DTBT group (p<0.001) (Fig. 2).

Table 3 shows the multivariate Cox regression models used to investigate the association between the DTBT and all-cause death after controlling for covariates. In model 1, while a short DTBT was not significantly associated with all-cause death (HR 1.00, 95% CI 0.39-2.55, p=0.99), a long DTBT (HR 2.80, 95% CI 1.26-6.17, p=0.011) was significantly associated with all-cause death after controlling for Killip class 4, eGFR, and triple vessel disease. In model 2, a long DTBT (HR 2.73, 95% CI 1.29-5.77, p=0.009) was also associated with all-cause death after controlling for age, mechanical support, and left main-left anterior descending artery (LM-LAD) lesions.

Discussion

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-

Table 1.   The Comparison of Patient Clinical Characteristic among the Short, Intermediate and Long DTBT Groups.

	All (n=309)	Short DTBT group (n=103)	Intermediate DTBT group (n=174)	Long DTBT group (n=32)	p value
Age (years)	67.6±13.6	65.8±15.1	68.8±12.9	66.8±11.6	0.34
Female sex, n (%)	70 (21.8)	17 (16.5)	39 (22.4)	14 (31.8)	0.12
Height, n (%)	163±9.53 (n=305)	163±9.93	163±9.14	162±10.7	0.83
Body weight, n (%)	64.5±14.2 (n=305)	66.5±15.5	63.4±13.2	63.0±14.2	0.46
Body mass index, n (%)	24.1±4.08 (n=305)	24.8±4.20	23.9±3.65	23.7±3.53	0.28
Hypertension, n (%)	214 (70.9)	61 (61.0)	129 (75.4)	24 (77.4)	0.029
Diabetes mellitus, n (%)	109 (35.5)	39 (38.2)	57 (32.8)	13 (41.9)	0.48
Dyslipidemia, n (%)	123 (41.4)	45 (45.5)	64 (38.3)	14 (45.2)	0.47
Current smoker, n (%)	170 (56.7)	58 (57.4)	93 (55.4)	19 (61.3)	0.81
History of previous MI, n (%)	23 (7.5)	8 (7.8)	11 (6.3)	4 (12.9)	0.43
History of previous PCI, n (%)	29 (9.4)	8 (7.8)	16 (9.2)	5 (16.1)	0.38
History of previous CABG, n (%)	2 (0.60)	1 (1.0)	0 (0.0)	1 (3.2)	0.11
History of previous CVD, n (%)	31 (10.1)	7 (6.8)	17 (9.8)	7 (22.6)	0.037
Hemodialysis, n (%)	11 (3.6)	2 (1.9)	7 (4.0)	2 (6.5)	0.44
Atypical symptoms, n (%)	60 (19.4)	12 (11.7)	36 (20.7)	12 (37.6)	0.004
Access to our hospital					0.007
Direct admission by ambulance	183 (59.2)	49 (47.6)	111 (63.8)	23 (71.9)	
Transfer from local clinics	45 (14.6)	21 (20.4)	22 (12.6)	2 (6.3)	
Transfer from local hospitals	75 (24.3)	33 (32.0)	37 (21.3)	5 (15.6)	
Direct visit by walk	6 (1.9)	0 (0.0)	4 (3.3)	2 (6.3)	
Cardiac arrest at out of hospital	22 (7.1)	5 (4.9)	13 (7.5)	4 (12.5)	0.33
Shock on admission	34 (11.0)	9 (8.7)	21 (12.1)	7 (21.9)	0.032
Killip class 3	23 (7.4)	2 (1.9)	14 (8.0)	7 (21,9)	0.013
Killip class 4	36 (11.7)	5 (4.9)	24 (13.8)	7 (21.9)	<0.001
Region of infraction					0.12
Anterior	167 (54.2)	58 (56.3)	92 (52.9)	17 (54.8)	
Inferior	119 (38.6)	42 (40.8)	68 (39.1)	9 (19.0)	
Posterior	22 (7.1)	3 (2.9)	14 (8.0)	5 (16.1)	
Total cholesterol, mg/dL	180±45.0 (n=301)	188±48.5	180±42.5	165±42.0	0.09
Triglyceride, mg/dL	121±118 (n=303)	144±169	112±82.2	96.0±38.3	0.53
LDL-cholesterol, mg/dL	111±37.7 (n=297)	116±38.2	110±37.1	104±39.5	0.35
HDL-cholesterol, mg/dL	44.0±12.0 (n=294)	43.9±12.4	44.3±11.2	42.3±14.5	0.74
HbA1c, %	6.42±1.32 (n=302)	6.68±1.66	6.28±1.11	6.34±0.98	0.28
eGFR, mL/min/1.73 m^2	69.4±29.1 (n=308)	78.5±29.0	66.3±27.4	56.1±31.3	0.001
Medical therapy on admission					
ACE inhibitor	11 (3.6)	4 (3.9)	5 (2.9)	2 (6.7)	0.59
ARB	90 (29.7)	24 (23.5)	52 (30.4)	14 (46.7)	0.049
Beta-blocker	25 (8.3)	4 (3.9)	14 (8.2)	7 (23.3)	0.003
Diuretics	24 (7.9)	4 (2.9)	17 (9.9)	4 (13.3)	0.06
Calcium channel blocker	88 (29.0)	21 (20.6)	56 (32.7)	11 (36.7)	0.063
Statin	67 (21.9)	21 (20.4)	36 (20.8)	10 (33.3)	0.28
Oral antidiabetic	63 (20.6)	22 (21.4)	31 (17.9)	10 (33.3)	0.15
Insulin	13 (4.2)	6 (5.8)	6 (3.5)	1 (3.3)	0.62

DTBT: door-to-balloon time, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CVD: cerebrovascular disease, LDL: low-density lipoprotein, HDL: high-density lipoprotein, eGFR: estimated glomerular filtration rate, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker

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.

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

	All (n=309)	Short DTBT group (n=103)	Intermediate DTBT group (n=174)	Long DTBT group (n=32)	p value
Angiographic lesion characteristics					
Infarct related artery					0.001
Left main	9 (2.9)	2 (1.9)	2 (1.1)	5 (15.6)	
Left anterior descending artery	159 (51.5)	55 (53.4)	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

Conclusion

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.
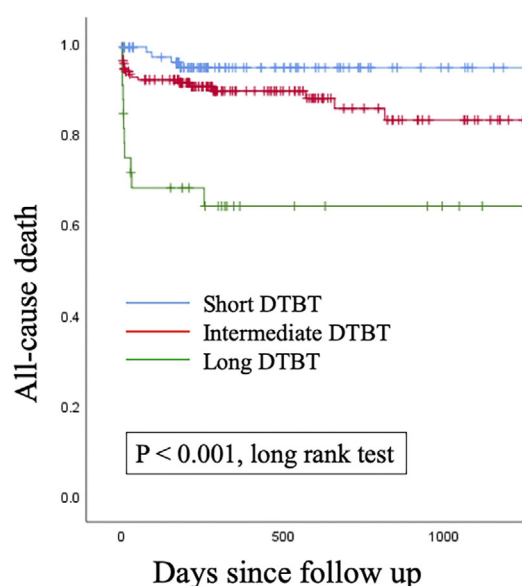
Figure 2. Kaplan-Meier curves for all-cause mortality in the short DTBT, intermediate DTBT and long DTBT groups. All-cause mortality survival in the three groups is shown. The difference was statistically significant the groups (p<0.001). DTBT: door-to-balloon time

Table 3. Multivariate Cox Regression Analysis to Predict the All-cause Death.

Model 1.

	HR	95% CI	p value
Intermediate DTBT	-	-	0.34
Short DTBT (vs. intermediate)	1.00	0.39-2.55	0.99
Long DTBT (vs. intermediate)	2.80	1.26-6.17	0.011
Killip 4 (vs. others)	4.74	2.32-9.68	<0.001
eGFR (every 10)	0.78	0.69-0.88	<0.001
TVD (vs. SVD/DVD)	2.37	1.12-4.79	0.02

All variables were simultaneously adjusted in one step.

DTBT: door-to-balloon time, eGFR: estimated glomerular filtration, TVT: triple vessels disease, SVD: single vessel disease, DVD: double vessels disease

Model 2.

	HR	95% CI	p value
Intermediate DTBT	-	-	0.01
Short DTBT (vs. intermediate)	0.66	0.26-1.67	0.38
Long DTBT (vs. intermediate)	2.73	1.29-5.77	0.009
Age	1.05	1.02-1.08	0.002
Mechanical support	7.18	3.5-14.7	<0.001
LMT/LAD (vs. others)	0.79	0.40-1.57	0.50

All variables were simultaneously adjusted in one step.

LMT: left main trunk, LAD: left anterior descending

References

1. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol **47**: 2180-2186, 2006.
2. Nallamothu BK, Normand SL, Wang Y, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. Lancet **385**: 1114-1122, 2015.
3. O'Gara PT, Kushner FG, Ascheim DD, et al. 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. Circulation **127**: 529-555, 2013.
4. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart Journal **33**: 2569-2619, 2012.
5. Rathore SS, Curtis JP, Chen J, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ **338**: b 1807, 2009.
6. Tsukui T, Sakakura K, Taniguchi Y, et al. Determinants of short and long door-to-balloon time in current primary percutaneous coronary interventions. Heart Vessels **33**: 498-506, 2018.
7. Yudi MB, Ramchand J, Farouque O, et al. Impact of door-to-balloon time on long-term mortality in high- and low-risk patients with ST-elevation myocardial infarction. Int J Cardiol **224**: 72-78, 2016.
8. Lee WC, Fang HY, Chen HC, et al. Effect of improved door-to-balloon time on clinical outcomes in patients with ST segment elevation myocardial infarction. Int J Cardiol **240**: 66-71, 2017.
9. Menees DS, Peterson ED, Wang Y, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. New Engl J Med **369**: 901-909, 2013.
10. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53**: 982-992, 2009.
11. Hoebers LP, Vis MM, Claessen BE, et al. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. Eur J Heart Fail **15**: 425-432, 2013.
12. Fujino M, Ishihara M, Ogawa H, et al. Impact of symptom presentation on in-hospital outcomes in patients with acute myocardial infarction. J Cardiol **70**: 29-34, 2017.
13. Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. J Am Coll Cardiol **60**: 2490-2499, 2012.
14. Sabate M, Brugaletta S, Cequier A, et al. The EXAMINATION trial (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction): 2-year results from a multicenter randomized controlled trial. JACC Cardiovasc Interv **7**: 64-71, 2014.

15. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. Circulation 104: 636-641, 2001.

16. Halkin A, Singh M, Nikolsky E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. J Am Coll Cardiol 45: 1397-1405, 2005.

17. Shiomi H, Nakagawa Y, Morimoto T, et al. 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 344: e3257, 2012.

18. Brennan AL, Andrianopoulos N, Duffy SJ, et al. Trends in door-to-balloon time and outcomes following primary percutaneous coronary intervention for ST-elevation myocardial infarction: an Australian perspective. Intern Med J 44: 471-477, 2014.

19. Garg S, Sarno G, Serruys PW, et al. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) trials. JACC Cardiovasc Interv 4: 66-75, 2011.

20. Akgun T, Oduncu V, Bitigen A, et al. Baseline SYNTAX score and long-term outcome in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Clin Appl Thromb Hemost 21: 712-719, 2015.

21. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. New Engl J Med 367: 1287-1296, 2012.

22. Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. J Am Coll Cardiol 52: 1584-1588, 2008.

23. Hiew C, Williams T, Hatton R, et al. Influence of age on long-term outcome after emergent percutaneous coronary intervention for ST-elevation myocardial infarction. J Invasive Cardiol 22: 273-277, 2010.

24. Ibanez B, James S, Agewall S, et al. 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 39: 119-177, 2018.

25. Akashi N, Sakakura K, Yamamoto K, et al. Minimization of door-to-balloon time for ST-elevation acute myocardial infarction: a case report. Clin Case Rep 5: 787-791, 2017.

26. Yonezu K, Sakakura K, Watanabe Y, et al. Determinants of survival and favorable neurologic outcomes in ischemic heart disease treated by veno-arterial extracorporeal membrane oxygenation. Heart Vessels 2017.

27. Loehn T, O'Neill WW, Lange B, et al. Long term survival after early unloading with Impella CP® in acute myocardial infarction complicated by cardiogenic shock. Eur Heart J Acute Cardiovasc Care 9: 149-157, 2020.

28. Esper SA, Bermudez C, Dueweke EJ, et al. Extracorporeal membrane oxygenation support in acute coronary syndromes complicated by cardiogenic shock. Catheter Cardiovasc Interv 86 (Suppl): S45-S50, 2015.

29. Abdel-Wahab M, Saad M, Kynast J, et al. Comparison of hospital mortality with intra-aortic balloon counterpulsation insertion before versus after primary percutaneous coronary intervention for cardiogenic shock complicating acute myocardial infarction. Am J Cardiol 105: 967-971, 2010.

30. Brown CG, Kelen GD, Ashton JJ, Werman HA. The beta error and sample size determination in clinical trials in emergency medicine. Ann Emerg Med 16: 183-187, 1987.