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Original Article

Shorter door-to-balloon time, better long-term clinical outcomes in ST-segment elevation myocardial infarction patients: J-MINUET substudy

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ABSTRACT

Background: The impact of shorter door-to-balloon (DTB time on long-term outcomes in ST-segment elevation myocardial infarction (STEMI treated with primary percutaneous coronary intervention (PPCI has not been fully elucidated.
Methods: We investigated 3283 consecutive patients with acute myocardial infarction selected from a prospective, nationwide, multicenter registry (J-MINUET database comprising 28 institutions in Japan between July 2012 and March 2014. Among the study population, we analyzed 1639 STEMI patients who had PPCI within 12 h of onset. Patients were stratified into four groups (DTB time < 45 min, 45–60 min, 61–90 min, >90 min. The primary endpoint was a composite of all-cause death, non-fatal MI, non-fatal stroke, cardiac failure, and urgent revascularization for unstable angina up to 3 years. We performed landmark analysis for incidence of the primary endpoint from 31 days to 3 years among the four groups.
Results: The primary endpoint rate from 31 days to 3 years increased significantly and time-dependently with DTB time (10.2 % vs. 15.3 % vs. 16.2 % vs. 19.3 %, respectively; log-rank $p = 0.0129$. Higher logarithm-transformed DTB time was associated with greater risk of a primary endpoint from 31 days to 3 years, and the increased number of adverse long-term clinical outcomes persisted even after adjusting for other independent variables.
Conclusion: Shorter DTB time was associated with better long-term clinical outcomes in STEMI patients treated with PPCI in contemporary clinical practice. Further efforts to shorten DTB time are recommended to improve long-term clinical outcomes in STEMI patients.
Trial registration: UMIN Unique trial Number: UMIN000010037.

Introduction

Acute coronary syndrome (ACS is a leading cause of mortality worldwide [1–3]. Primary percutaneous coronary intervention (PPCI is an effective treatment for patients with acute ST-segment elevation myocardial infarction (STEMI [4]. Previous studies have shown that time to treatment of PPCI was strongly associated with in-hospital mortality risk in STEMI patients [5–7]. Patients in STEMI with a door-to-balloon (DTB time > 90 min displayed increased in-hospital mortality compared to those with DTB time ≤ 90 min [6,8]. Based on those results, the current guideline recommended that DTB time be shortened as much as possible [9] and recommended PPCI hospitals strive for a DTB time < 60 min [10,11]. In Japan, PPCI should be done within 90 min in STEMI patients [12]. However, the impact of short DTB time on prognosis remains controversial [13–15] and long-term outcomes of shorter DTB time have not yet been assessed. The purpose of this study was to investigate the relationship between shorter DTB time and long-term clinical outcomes in STEMI patients undergoing PPCI.

Methods

The multicenter, prospective, observational Japan Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET study enrolled consecutive patients with acute myocardial infarction (AMI between July 2012 and March 2014 [16]. Patients were diagnosed with AMI based on the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction [17]. The study was performed in accordance with the Declaration of Helsinki. Among the 3283 AMI patients in J-MINUET, the present substudy enrolled 1492 STEMI patients with DTB time data available who underwent PPCI within 12 h of onset and were alive for at least 31 days. Patients were stratified into four groups by DTB time (<45 min, 45–60 min, 61–90 min, >90 min (Fig. 1.

The primary endpoint was a composite of all-cause death, non-fatal MI, non-fatal stroke, cardiac failure, and urgent revascularization for unstable angina up to 3 years.

Figure 1

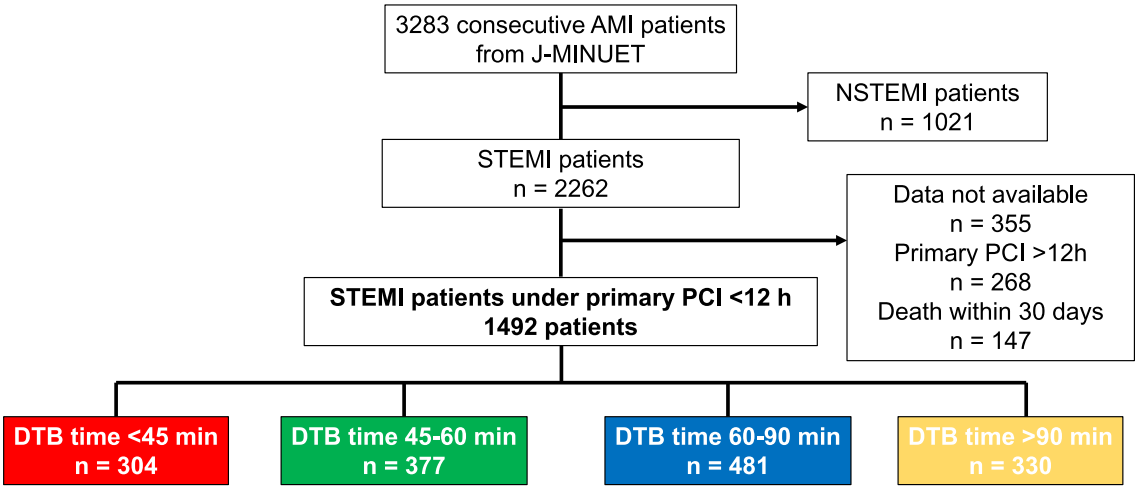


Fig. 1. Study flow chart. Of the 3283 patients with AMI enrolled in the J-MINUET study, 1639 patients were finally analyzed in this substudy. Patients were categorized into four groups according to DTB time: DTB time < 45 min group ($n = 330$, DTB time 45–60 min group ($n = 413$, DTB time 61–90 min group ($n = 524$, and DTB time > 90 min ($n = 372$.
AMI, acute myocardial infarction; J-MINUET, Japan Registry of Acute Myocardial Infarction Diagnosed by Universal Definition; DTB time, door-to-balloon time; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

We used the database of the J-MINUET study for this subanalysis. Continuous variables are presented as median and interquartile range (IQR. Categorical variables are expressed as numbers and ratios (%. Continuous variables were compared using unpaired *t*-tests or the Kruskal-Wallis test. Categorical variables were compared using the chi-square test or Fisher's exact probability test. Characteristics selected using the stepwise procedure were included in the multivariate analysis. A value of $p < 0.05$ was considered to indicate statistical significance. All data were statistically analyzed using JMP version 14.0 software (SAS Institute Inc., Cary, NC, USA. All procedures in this study were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by each participating institution's ethics committee. The ethics committee of Juntendo Clinical Research and Trial Center approved this study (IRB number RIN-242. All subjects gave their informed consent prior to study enrollment.

Results

The baseline clinical characteristics of patients are shown in Table 1. The short DTB time group included more males, and showed a lower

Table 1
The baseline clinical characteristics of patients.

	DTB time <45 min n = 304	DTB time 45-60 min n = 377	DTB time 61-90 min n = 481	DTB time >90 min n = 330	*p*-value
Baseline characteristics					
Door-to-balloon time, min	37 [32, 41]	52 [49, 57]	72 [66, 80]	125 [104, 170]	<0.001
Onset-to-door time, min	120 [65, 215]	125 [70, 245.5]	120 [60.5, 225]	115 [60, 227]	0.29
Age, years	66.4±11.6	66.0±12.3	67.1±12.9	67.7±12.3	0.27
Male, %	84.2	80.1	76.7	75.8	0.03
Hypertension, %	58.0	62.3	63.3	70.0	0.02
Diabetes mellitus, %	35.1	31.9	38.6	37.9	0.19
Dyslipidemia, %	47.0	51.2	49.6	54.3	0.31
Current smoker, %	44.3	42.6	38.2	40.7	0.35
Multivessel CAD, %	33.2	39.5	39.0	47.7	<0.001
BMI, kg/m²	23.6±3.3	24.0±3.3	23.9±4.0	23.4±4.2	0.1
CKD, %	34.9	40.4	39.3	44.2	0.003
Killip 3-4, %	12.2	10.3	14.4	12.1	0.36
Final TIMI3, %	95.1	89.9	91.5	92.1	0.08
Bare metal stent, %	45.6	41.1	35.6	37.4	0.04
Drug-eluting stent, %	54.3	58.8	64.3	62.5	0.04
Culprit vessel, %					
Left main	1.4	1.7	2.5	2.9	0.5
LAD	50.5	45.9	41.5	43.2	0.1
CX	5.8	7.8	9.5	15.5	<0.001
RCA	42.3	44.5	46.5	38.4	0.15
Blood test					
Max CK, U/L	3055±142	3245±127	2910±112	2161±136	<0.001
Log max CK	7.7±0.9	7.7±1.1	7.5±1.1	7.2±12	<0.001
LDL-C, mg/dL	121.7±35.7	122.4±33.7	116.3±39.7	115.9±42.2	0.045
HDL-C, mg/dL	45.8±11.9	46.3±12.9	45.2±12.6	45.8±12.8	0.68
TG, mg/dL	96 [57.5, 156.5]	109 [69.5, 169]	95 [62, 150.3]	94 [58, 144.5]	0.26
Blood glucose, mg/dL	186±71.7	176±76.6	185±86.0	177±99.8	0.26
HbA1c, %	6.3±1.5	6.1±1.0	6.4±1.5	6.4±1.6	0.002
White blood cells, /μL	10310±3460	10600±3700	10500±3890	9800±3560	0.02
Hemoglobin, g/dL	14.0±1.8	14.1±2.0	13.9±2.5	13.8±2.7	0.25
Platelet counts ×1000/μL	21.5±10.1	21.9±9.5	21.9±14.1	21.2±6.1	0.75
Medication at discharge					
Aspirin, %	98.3	97.7	97.1	96.1	0.38
P2Y12-I, %	91.1	84.7	84.4	83.0	0.02
ACE-I/ARB, %	85.8	83.6	83.9	80.5	0.37
β-blocker, %	69.7	73.3	73.5	67.5	0.24
Statin, %	92.1	93.1	87.0	87.5	0.008

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CK, creatine kinase; CKD, chronic kidney disease; CX, left circumflex artery; DTB, door-to-balloon; HbA1c, hemoglobin A1c; HDL—C, high-density lipoprotein cholesterol; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; P2Y12-I, P2Y12 inhibitors; RCA, right coronary artery; TG, triglycerides; TIMI, thrombolysis in myocardial infarction.

prevalence of hypertension (HT, multivessel coronary artery disease (CAD, and chronic kidney disease (CKD. In the culprit vessel, the rate of left circumflex artery was higher in DTB time > 90 min group, but not significantly different in the other coronary arteries. The value of max creatine kinase (CK was significantly higher in patients with DTB time < 90 min. This trend did not change in the log transformation of CK. Negative correlation between DTB time and max CK ($r = -0.07, p = 0.007$ was weak. No significant difference in onset-to-door time was evident between the four groups.

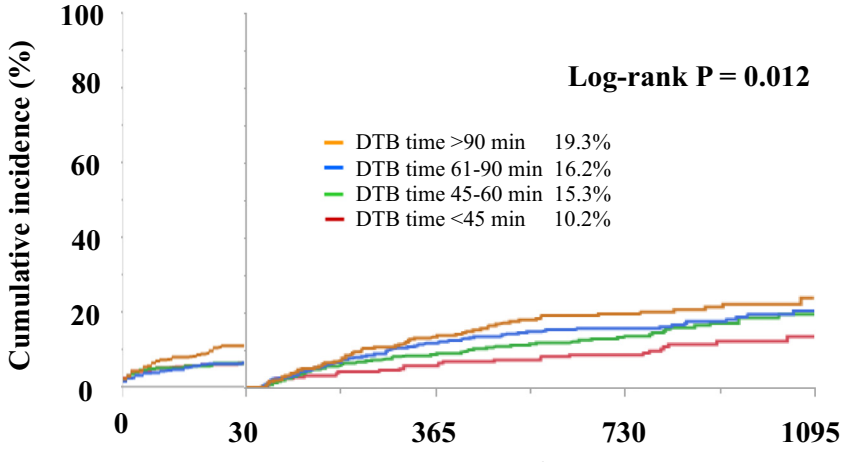
Median follow-up period was 777 days (IQR, 416–987 days. Fig. 2 shows landmark Kaplan-Meier analyses for primary endpoints. From day 0, the Kaplan-Meier curves began to diverge for the primary endpoint in favor of DTB time > 90 min group for up to 30 days. The 30-day event rate was significantly higher in DTB time > 90 min group than the other three groups (6.1 % vs. 6.1 % vs. 6.4 % vs. 10.8 %, respectively; $p = 0.03$. A primary endpoint occurred in 226 patients (15.1 % from 31 days to 3 years, including all-cause death in 78 patients (5.2 %, non-fatal MI in 18 (1.2 %, non-fatal stroke in 20 (1.3 %, cardiac failure in 38 (2.5 %, and urgent revascularization for unstable angina in 72 (4.8 %. The primary endpoint rate from 31 days to 3 years showed a significant and time-dependent increase with DTB time (10.2 % vs. 15.3 % vs. 16.2 % vs. 19.3 %, respectively; log-rank $p = 0.012$. Table 2 shows the Cox proportional hazard model for primary endpoints between DTB time groups. After adjusting for confounding factors, longer DTB time was significantly associated with higher risk of a primary endpoint compared with the shortest DTB time. The Cox proportional hazard model for each event between DTB time groups is shown in Online Table 1. Hazard ratios for all-cause death increased significantly with increasing DTB time. For cardiac failure and cardiovascular death, the hazard ratio increased with increasing DTB time, although not significantly.

Discussion

The major findings of the present study were as follows: (1 the short DTB time group included more males, with lower prevalence of HT, multivessel CAD, and CKD, (2 DTB time was significantly and time-dependently associated with the rate of primary endpoints (10.2 % vs. 15.3 % vs. 16.2 % vs. 19.3 %, respectively; log-rank $p = 0.0129$, (3 The increased number of adverse long-term clinical outcomes persisted even after adjusting for other independent variables.

The association between DTB time and long-term clinical outcomes for STEMI patients in the present study could have resulted from several mechanisms. First, early revascularization in AMI patients may result in less myocardial damage, improving long-term outcomes. The current guidelines recommend shortening DTB time [9,18]. Although reductions in DTB time have not been associated with decreased mortality at the population level [13,14], the American national registry reported that shorter patient-specific DTB times were consistently associated with lower mortality in patients with STEMI undergoing primary PCI. Nallamothu et al. conducted evaluations at the individual level and showed that shorter DTB time was consistently associated with lower 6-month mortality [7]. In addition, other studies have shown that shorter DTB time improved prognosis in terms of 1-year mortality [19]. However, the impact of shorter DTB time on longer-term outcomes of shorter DTB time have not been evaluated previously. Our study showed that shorter DTB time was significantly and time-dependently associated with the rate of long-term clinical outcomes. Our results suggested that DTB time may be a prognostic factor with respect to long-term prognosis. Even in the guideline-recommended DTB <90 min group, the shorter DTB time was associated with better prognosis. Data from the Japanese Percutaneous Coronary Intervention (J-PCI registry showed that DTB time was <60 min in 31.7 %, 60–90 min in 40.9 %, and > 90 min in 27.4 % [20]. In our study, the rate of DTB time > 90 min was 22.1 %, consistent with the J-PCI registry. Further reduction of DTB time is thus required. A target DTB time < 90 min may contribute to further improvements in the prognosis of STEMI patients. Additional data collection and analysis are needed for more aggressive interventions to attain a DTB time < 45 min.

Previously, total ischemic time has been the focus of investigations into the prognosis of STEMI patients, in addition to DTB time [14]. Shiomi et al. showed that DTB time < 90 min was associated with a lower incidence of a composite of death and congestive heart failure only in patients with early presentation (onset-to-door time < 2 h in the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto MI registry [21]. Our study showed that onset-to-door time for patients was not significantly different for all groups and median onset-to-door time over all was 120 min [65, 225],



Number at risk

All patients	1523	1457	1168	829	212
DTB time <45 min	330	295	239	187	50
DTB time 45-60 min	414	372	310	230	54
DTB time 60-90 min	525	470	370	239	65
DTB time >90 min	372	321	249	173	43

Fig. 2. Landmark analyses for 0–30-day and 31-day to 3-year incidence of the primary endpoint. Note that scale of the X-axis is different for 0–30 days and 31 days to 3 years. The rate of primary endpoint from 31 days to 3 years increased significantly and time-dependently with DTB time (10.2 % vs. 15.3 % vs. 16.2 % vs. 19.3 %, respectively; log-rank $p = 0.012$. MI, myocardial infarction; DTB time, door-to-balloon time.

Table 2
The Cox proportional hazard model for primary endpoints between DTB time groups.

	Univariate				Multivariate			
	HR	95%CI	*p*-value	*p* for trend	HR	95%CI	*p*-value	*p* for trend
(Ref; DTB time < 45 min				0.001				0.001
DTB time 45–60 min	1.49	0.97–2.4	0.07		1.51	0.96–2.44	0.08	
DTB time 61–90 min	1.68	1.11–2.59	0.013		1.65	1.07–2.6	0.02	
DTB time > 90 min	2.02	1.32–3.17	0.001		2.17	1.38–3.48	< 0.001	

Adjusted for age, sex, HT, DL, DM, CKD, current smoker status, BMI, Killip 3-4, and multivessel CAD.
HR, hazard ratio; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DL, dyslipidemia; DM, diabetes mellitus; DTB time, door-to-balloon time; HT, hypertension.

consistent with the CREDO-Kyoto MI registry. This suggests that a nationwide effort to reduce onset-to-door time, including prehospital management, is required to improve outcomes for patients with STEMI.

A reduction in myocardial ischemic time is associated with myocardial salvage, and myocardial salvage is closely related to prognosis in STEMI patients [22]. In an evaluation of myocardial salvage using contrast-enhanced magnetic resonance imaging in STEMI patients, short DTB time was associated with significantly higher myocardial viability. In other studies, improvements in infarct size and microvascular obstruction were significantly associated with shorter ischemic time and microvascular obstruction was strongly associated with all-cause mortality and hospitalization for heart failure [23,24]. Shortening DTB time was expected to increase myocardial salvage and improve prognosis. In addition, myocardial salvage was significantly associated with thrombolysis in myocardial infarction (TIMI flow [25] and final TIMI flow grade ≤ 2 during PCI was significantly associated with major adverse cardiac events [26]. In this study, the percentage of patients who obtained final TIMI 3 did not differ significantly. The percentage with final TIMI 3 was no different from the percentage in previous studies [26,27]. Myocardial salvage was inferred to be increased due to the high rate of effective revascularization in this study and was thought to also improve the long-term prognosis. In an analysis by event, prolonged DTB time was significantly correlated with the hazard ratio for all-cause death. In terms of myocardial salvage, the hazard ratios for heart failure and cardiovascular death increased with prolonged DTB time, even though this was not significant. Shortening DTB time and obtaining myocardial salvage may contribute to long-term prognosis by decreasing the incidence of heart failure and cardiovascular death. However, the value of max CK was significantly higher in patients with DTB time < 90 min. CK was the most common marker of myocardial necrosis and was still widely used for diagnosis and prognosis of myocardial infarction [28–30]. The highest value of CK reflects the amount of myocardial necrosis, but the previous studies shows that CK value after early reperfusion therapy overestimate infarct size. It has been reported that peak serum CK is shifted in patients who underwent early reperfusion. Previously, it was shown that the speed of CK elevation also varies with the time to reperfusion in animal studies [31,32]. The highest CK value in the DTB time < 90 min group did not indicate the size of myocardial necrosis, and it was speculated that early reperfusion increased the value of CK.

The clinical condition of the patient is also relevant to DTB time. Another study showed an association between prolonged DTB time and CKD [33]. In this study, the short DTB time group had lower prevalence of CKD and multivessel CAD. The reason for CKD prolonging DTB was thought to be that the operator is more cautious in the use of contrast media, thus taking more time to decide on the procedure and treatment plan. The reason for the longer DTB time for multivessel CAD is assumed to be that the treatment strategy for PCI is more complex than that for single-vessel lesions. The previous study showed that DTB time was reduced by using a single universal guiding catheter to simplify a complicated procedure [34]. Further investigation is needed to determine which PCI strategy will achieve early revascularization in patients with such complications.

This study had some limitations. First, enrolled patients may have been subject to selection bias. This was a multicenter study that investigated the treatment of Japanese patients with acute MI diagnosed under a universal definition, so the frequency and timing of CK measurements were not specified in advance and were left to the discretion of the physician. Second, selection bias may exist because 355 patients without DTB time data were excluded from the analysis. Third, we did not investigate the relationship between total ischemic time on outcomes. However, DTB time is a simple index and no major errors in measurement were present; we simply focused on and analyzed DTB time. Fourth, no index was used to quantitatively evaluate myocardial salvage, and myocardial damage can be predicted only from the CK values. Finally, the majority of patients in the present study were Japanese. Regional differences may exist in the characteristics of patients with myocardial infarction, the care received in the hospital, and the clinical course after discharge.

Conclusion

Shorter DTB time was associated with better long-term clinical outcomes in STEMI patients treated with PPCI in contemporary clinical practice. Further efforts to shorten DTB time are recommended to improve long-term clinical outcomes in STEMI patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2023.01.008.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. J-MINUET investigators

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References

[1] Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736–88.
[2] Hartley A, Marshall DC, Salciccioli JD, Sikkel MB, Maruthappu M, Shalhoub J. Trends in mortality from ischemic heart disease and cerebrovascular disease in Europe: 1980 to 2009. Circulation 2016;133:1916–26.
[3] Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J 2016;37:3232–45.
[4] Eagle KA, Nallamothu BK, Mehta RH, Granger CB, Steg PG, Van de Werf F, et al. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go. Eur Heart J 2008;29:609–17.
[5] Berger PB, Ellis SG, Holmes Jr DR, Granger CB, Criger DA, Betriu A, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in acute coronary syndromes (GUSTO-IIb) trial. Circulation 1999;100:14–20.
[6] McNamara RL, Wang Y, Herrin J, Curtis JP, Bradley EH, Magid DJ, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006;47:2180–6.
[7] Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush Jr JE, Messenger JC, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. Lancet 2015;385:1114–22.
[8] Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–7.
[9] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, 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 2018;39:119–77.
[10] Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the task force on the management of ST-segment elevation acute myocardial infarction of the european Society of Cardiology. Eur Heart J 2008;29:2909–45.
[11] Kushner FG, Hand M, Smith Jr SC, King 3rd SB, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2009;54:2205–41.
[12] Ozaki Y, Hara H, Onuma Y, Katagiri Y, Amano T, Kobayashi Y, et al. CVIT expert consensus document on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) update 2022. Cardiovasc Interv Ther 2022;37:1–34.
[13] Flynn A, Moscucci M, Share D, Smith D, LaLonde T, Changezi H, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Arch Intern Med 2010;170:1842–9.
[14] Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. N Engl J Med 2013;369:901–9.
[15] Nestler DM, Noheria A, Haro LH, Stead LG, Decker WW, Scanlan-Hanson LN, et al. Sustaining improvement in door-to-balloon time over 4 years: the Mayo clinic ST-elevation myocardial infarction protocol. Circ Cardiovasc Qual Outcomes 2009;2:508–13.
[16] Ishihara M, Fujino M, Ogawa H, Yasuda S, Noguchi T, Nakao K, et al. Clinical presentation, management and outcome of japanese patients with acute myocardial infarction in the troponin era - japanese registry of acute myocardial infarction diagnosed by universal definition (J-MINUET). Circ J 2015;79:1255–62.
[17] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.
[18] O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, de Lemos JA, 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. J Am Coll Cardiol 2013;61:485–510.
[19] Park J, Choi KH, Lee JM, Kim HK, Hwang D, Rhee TM, et al. 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. J Am Heart Assoc 2019;8:e012188.
[20] Yamaji K, Kohsaka S, Inohara T, Numasawa Y, Ishii H, Amano T, et al. Population density analysis of percutaneous coronary intervention for ST-segment-elevation myocardial infarction in Japan. J Am Heart Assoc 2020;9:e016952.
[21] Shiomi H, Nakagawa Y, Morimoto T, Furukawa Y, Nakano A, Shirai S, 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 2012;344:e3257.
[22] Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. J Am Coll Cardiol 2010;55:2470–9.
[23] de Waha S, Patel MR, Granger CB, Ohman EM, Maehara A, Eitel I, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. Eur Heart J 2017;38:3502–10.
[24] Redfors B, Mohebi R, Giustino G, Chen S, Selker HP, Thiele H, et al. Time delay, infarct size, and microvascular obstruction after primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2021;14:e009879.
[25] Joost A, Stiermaier T, Eitel C, Fuernau G, de Waha S, Desch S, et al. Impact of initial culprit vessel flow on infarct size, microvascular obstruction, and myocardial salvage in acute reperfused ST-elevation myocardial infarction. Am J Cardiol 2016;118:1316–22.
[26] Tsukui T, Sakakura K, Taniguchi Y, Yamamoto K, Seguchi M, Jinnouchi H, et al. Factors associated with poor clinical outcomes of ST-elevation myocardial infarction in patients with door-to-balloon time <90 minutes. PLoS One 2020;15:e0241251.
[27] Daida H, Miyauchi K, Ogawa H, Yokoi H, Matsumoto M, Kitakaze M, et al. Management and two-year long-term clinical outcome of acute coronary syndrome in

Japan: prevention of atherothrombotic incidents following ischemic coronary attack (PACIFIC) registry. Circ J 2013;77:934–43.
[28] Halkin A, Stone GW, Grines CL, Cox DA, Rutherford BD, Esente P, et al. Prognostic implications of creatine kinase elevation after primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol 2006;47:951–61.
[29] Ahumada G, Roberts R, Sobel BE. Evaluation of myocardial infarction with enzymatic indices. Prog Cardiovasc Dis 1976;18:405–20.
[30] Lee TH, Goldman L. Serum enzyme assays in the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis. Ann Intern Med 1986;105:221–33.
[31] Vatner SF, Baig H, Manders WT, Maroko PR. Effects of coronary artery reperfusion on myocardial infarct size calculated from creatine kinase. J Clin Invest 1978;61:1048–56.
[32] Tamaki S, Murakami T, Kadota K, Kambara H, Yui Y, Nakajima H, et al. Effects of coronary artery reperfusion on relation between creatine kinase-MB release and infarct size estimated by myocardial emission tomography with thallium-201 in man. J Am Coll Cardiol 1983;2:1031–8.
[33] Bessonov IS, Kuznetsov VA, Gorbatenko EA, Dyakova AO, Sapozhnikov SS. Influence of total ischemic time on clinical outcomes in patients with ST-segment elevation myocardial infarction. Kardiologiia 2021;61:40–6.
[34] Torii S, Fujii T, Murakami T, Nakazawa G, Ijichi T, Nakano M, et al. Impact of a single universal guiding catheter on door-to-balloon time in primary transradial coronary intervention for ST segment elevation myocardial infarction. Cardiovasc Interv Ther 2017;32:114–9.