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Interventional Cardiology

Effects of Door-to-Balloon Times on Outcomes in Taiwanese Patients Receiving Primary Percutaneous Coronary Intervention: A Report of Taiwan Acute Coronary Syndrome Full Spectrum Registry

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On behalf of the Investigators of the Taiwan ACS full spectrum registry

Purpose: The impact of door-to-balloon (DTB) time on patient outcomes is unclear in a Taiwanese population receiving primary percutaneous coronary intervention (PCI). The study aimed to investigate the relationship between stratified DTB times and outcomes through analysis of the database from the Taiwan acute coronary syndrome full spectrum registry.

Methods: Relevant data were collected from case report forms of patients receiving primary PCI who were categorized as group 1, 2, 3, and 4 according to the DTB time < 45, 45-90, 91-135, and > 135 minutes, respectively. The differences were analyzed by using ANOVA and Kaplan-Meier analyses.

Results: There were significant variations in DTB times at baseline, which included patients salvaged at centers, patients with prior cardiovascular disease, and those patients with different coronary artery flows ($p < 0.01$) separated into 4 groups (n = 189, 443, 299, and 401, respectively). The in-hospital adverse event rates were identical among the 4 groups except for a higher rate of acute renal failure and a longer hospital stay observed in group 4 ($p < 0.01$). The results showed no decrease in the incidences of repeated revascularization, major adverse cardiac event, or cardiovascular composite at 1 year in group 1.

Conclusions: This study suggested that the DTB time is not a good determinant for outcomes in Taiwanese patients receiving primary PCI.

Key Words: Acute myocardial infarction • Cardiovascular outcome • Door-to-balloon time • Myocardial ischemia • Percutaneous coronary intervention

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INTRODUCTION

For patients with acute ST-segment-elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) has for many years been considered a life-saving treatment. International and national guidelines for the management of acute STEMI recommend the door-to-balloon (DTB) time should be no longer than 90 minutes.[1-3] Numerous studies have documented that DTB time below 90 minutes is associated with significantly lower incidences of in-hospital or out-of-hospital cardiovascular endpoints as compared to the DTB time exceeding 90 minutes.[4-8] A few large-scale

studies also established that the DTB time ≥ 120 minutes versus < 120 minutes was linked with an increased risk of short-term mortality.[9,10] However, the results obtained from analysis of patients with different DTB times below 90 minutes remain inconsistent in cardiovascular outcomes.[11-16] Current evidence seems insufficient to support a stringent DTB time goal, such as < 45 minutes, for instance. Several observational studies suggested that a DTB time lower than 60 or 30 minutes was associated with a significantly reduced in-hospital mortality.[11,12] In contrast, the other studies revealed identical outcomes among groups with different DTB times beneath 90 minutes.[13-17] On the other hand, additional effort has been made on numerous strategies proposed to shorten the DTB time which are intended to improve clinical outcomes.[17-24] To the best of our knowledge, no large-scale domestic research regarding the relationship between the DTB time and clinical outcome is available. Therefore, based upon the full spectrum registry of acute coronary syndrome in Taiwan (Taiwan ACS FS registry), which was the nationwide study for observation of real ACS practices,[25] participants receiving primary PCI were selected and classified into the 4 groups with the different DTB times with < 45, 45-90, 91-135, and > 135 minutes. The study aimed to: (1) clarify the extent to which domestic achievement rate of the DTB time < 90 minutes has occurred; (2) elucidate the characteristics among the 4 groups; and (3) detect the differences in clinical outcomes among groups. This study provides important real-world data which may help to clarify practices which affect DTB times, and guide further investigations.

MATERIALS AND METHODS

Study design

The Taiwan ACS full spectrum registry is a multicenter, prospective, nonrandomized, observational trial.[25,26] The present study was based upon analysis of the registry database and designed to detect the differences in clinical outcomes among 4 patient groups with acute myocardial infarction (AMI) receiving primary PCI. In the study, the definition of the symptom onset to emergency department (ED) time was as follows: the duration of time from the onset of cardiac ischemic symptoms to the ED time at which a patient presented for the delivery of the service recorded on the document in a recruitment site. The DTB time indicated the duration between the ED time and the time of the first balloon inflation. ED stay time meant the duration between the ED time and admission time. Those selected participants were categorized into 4 groups by the stratified DTB times: Group 1 with the DTB time < 45 minutes, Group 2 within 45-90 minutes, Group 3 within 91-135 minutes, and Group 4 with > 135 minutes. Patients that were excluded were those who did not receive primary PCI or directly received coronary artery bypass grafting (CABG) or received medical therapy alone, who presented with ACS secondary to another co-morbidity such as trauma or bleeding, or were previously enrolled in the registry or in a drug study. The participating sites with high annual volume of PCI were selected and certified by the Scientific Committee of the Taiwan Society of Cardiology. Each site recruited 50-200 consecutively eligible patients who were 20 years of age or older, and hospitalized within 24 hours after the onset of symptoms of AMI or transferred in from a nonparticipating site without a stay exceeding 12 hours. Clinical follow-up was scheduled at 3, 6, 9 and 12 months after discharge for data collection on clinical endpoints such as mortality, nonfatal MI, repeated revascularization, stroke, and CABG. Relevant data were recorded in the case record forms including characteristics, clinical presentations, PCI procedures, and adverse cardiovascular events during the 1-year follow-up.

The registry and the present study were performed in accordance with the Declaration of Helsinki and local regulatory guidelines. At each participating site, the affiliated medical ethics committee approved the study protocol. Written informed consent was obtained from all participants. We were authorized to conduct the analysis of the registry database regarding clinical outcomes among groups with different DTB times, and the study protocol had been examined and accepted by the Publication Committee of the registry.

Adverse events in hospital and at 1 year

A cardiovascular composite included all-cause mortality, nonfatal MI, nonfatal hemorrhagic or ischemic stroke, ischemia-driven repeated revascularization and CABG at 1 year. Major adverse cardiac event (MACE) was defined as a composite of all-cause mortality, non-

fatal MI, and target vessel revascularization (TVR). The happening of a cardiovascular event was confirmed by local and central physicians according to the patient's clinical symptoms and signs, electrocardiographic findings, levels of cardiac enzymes, and/or diagnostic images. In-hospital adverse events were assessed including mortality, nonfatal MI, unplanned PCI, stroke, and acute renal failure.

Statistical analysis

All variables were analyzed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) in the analytic center of the registry. All categorical data and rates are displayed as percentages and numbers, and the continuous data are shown as means ± standard deviation. Baseline and outcome data were compared between groups using chi-square test or Fisher's exact test for categorical variables, and the ANOVA test was utilized for continuous variables. Kaplan-Meier analysis with log-rank test was used to detect differences in cumulative event-free survival at 1 year among groups. Hazard ratios (HRs) and 95% confidence interval (CI) for the cardiovascular composite events were calculated from a Cox regression model in an unadjusted and adjusted manner for other covariates. Each of the relevant variables was used for its association with all-cause mortality, nonfatal re-MI, repeated PCI, stroke and CABG in the Cox regression model. Covariates that were significantly associated with the events with a significance level of p value < 0.05 were selected for multivariate Cox model. Stepwise model selection was used to determine the critical value of p value > 0.25, and p value < 0.15 for variable selection and for variable elimination. A p value < 0.05 with two-sided 95% CI was considered statistically significant for all tests. Analysis was conducted based upon the time to first event without double counting of events, within analysis involving composite endpoints. In the registry, patients who were lost to follow-up were censored at the time of last contact with their vital status designated as alive and event-free at that time.

RESULTS

Patients' demographic data and characteristics

A total of 3183 eligible patients were enrolled between October 2008 and January 2010.[25,26] Among them, 1332 participants with AMI who received primary PCI were analyzed in this study: 189 participants in group 1 with the DTB time < 45 minutes, 443 in group 2 with 45-90 minutes, 299 in group 3 with 91-135 minutes, and 401 in group 4 with > 135 minutes (Figure 1).

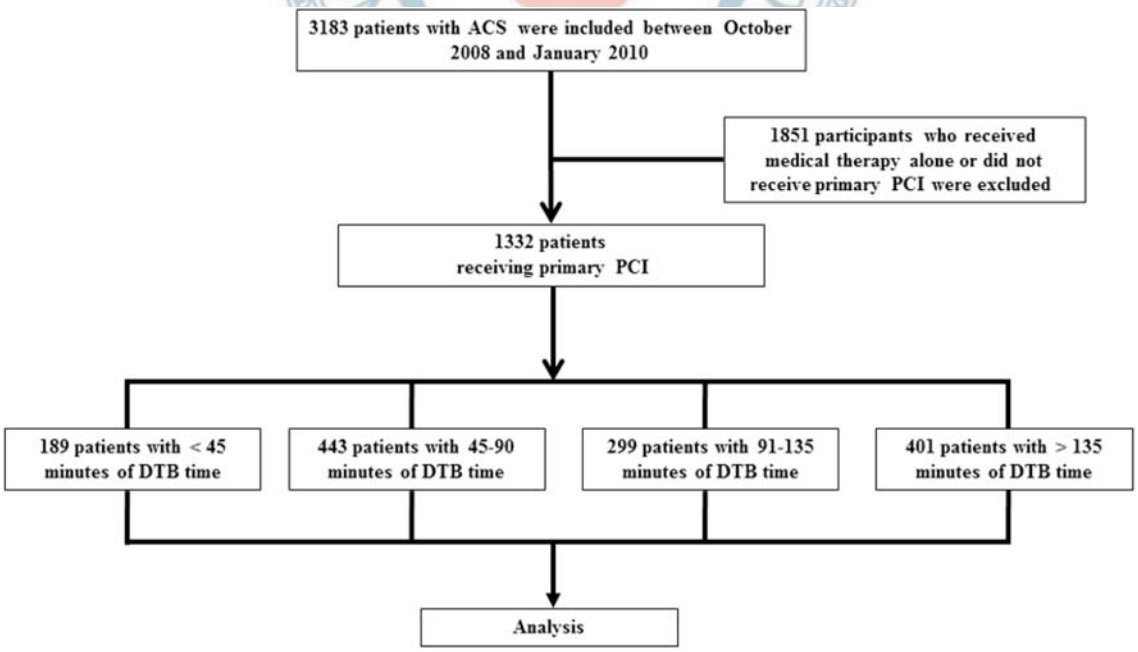

Figure 1. *The patient flow chart. ACS, acute coronary syndrome; DTB, door-to-balloon; PCI, percutaneous coronary intervention.*

The subjects with the DTB time < 90 minutes occupied only 47.5%. Demographics, characteristics and presentations at ED are shown in Table 1. Angiographic and procedural data are summarized in Table 2.

In-hospital adverse events

No differences in in-hospital cardiovascular events were found among the 4 groups (p > 0.05), including mortality, nonfatal re-MI, unplanned PCI, MACE, and ischemic stroke. Group 4 had the highest rate of in-hospital acute renal failure and the longest hospital stay (p < 0.01). The in-hospital outcomes are demonstrated in Table 3.

One-year cardiovascular outcomes

The all-cause mortality rate was 5.5% at 1 year. The

Table 1. Baseline characteristics and presentations at emergency departments among groups stratified by door-to-balloon times

Door-to-balloon time (minutes)	< 45	45-90	91-135	> 135	p-value
Primary PCI enrolled, n (%)	189 (14.2%)	443 (33.3%)	299 (22.4%)	401 (30.1%)	-
Hospital type, n (%)					
Medical center	174 (92.1%)	312 (70.4%)	172 (57.5%)	268 (66.8%)	< 0.01*
Age (years), mean ± SD	58.7 ± 13.2	59.9 ± 13.2	61.3 ± 13.0	62.1 ± 14.2	0.02*
Male, n (%)	170 (90.0%)	374 (84.4%)	250 (83.6%)	335 (83.5%)	0.19
BMI (kg/m^2), mean ± SD	25.6 ± 3.2	25.5 ± 3.7	25.1 ± 3.7	25.3 ± 4.0	0.40
Killip class, n (%)					
I	121 (67.6%)	278 (66.2%)	172 (59.3%)	214 (56.9%)	0.04*
II	31 (17.3%)	77 (18.3%)	60 (20.7%)	74 (19.7%)	
III/IV	27 (15.1%)	65 (15.5%)	58 (20.0%)	88 (23.4%)	
Risk factors, n (%)					
Dyslipidemia	51 (27.0%)	137 (31.4%)	108 (36.6%)	135 (34.0%)	0.14
Hypertension	98 (51.9%)	227 (52.1%)	167 (56.6%)	235 (58.8%)	0.18
Diabetes	44 (23.3%)	120 (27.4%)	92 (31.1%)	116 (28.9%)	0.29
Current smoker	110 (58.5%)	236 (54.1%)	155 (52.4%)	190 (48.5%)	0.13
FH of vascular disease	34 (23.8%)	75 (21.0%)	53 (23.0%)	76 (24.8%)	0.71
Known CAD	16 (8.5%)	55 (12.4%)	39 (13.0%)	54 (13.5%)	0.36
Prior CVD	5 (2.7%)	16 (3.6%)	13 (4.4%)	35 (8.7%)	< 0.01*
ED presentation, mean ± SD					
Symptom Onset to ED time	237.2 ± 261.4	207.7 ± 231.7	239.3 ± 395.5	270.7 ± 346.4	0.05*
Transfer from other hospital	97 (51.3%)	141 (31.8%)	77 (25.8%)	95 (23.7%)	< 0.01*
ED stay time, minutes	137.2 ± 480.6	128.6 ± 449.6	128.4 ± 290.0	236.3 ± 547.4	< 0.01*
Examinations, n (%)					
First ECG within 10 min	157 (83.1%)	349 (78.8%)	200 (66.9%)	203 (50.6%)	< 0.01*
ST-elevation of MI location					
Anterior	91 (49.5%)	216 (49.5%)	143 (49.8%)	174 (47.5%)	0.93
Inferior	83 (45.1%)	205 (47.0%)	132 (46.0%)	161 (44.0%)	0.86
Lateral	12 (6.5%)	30 (6.9%)	19 (6.6%)	30 (8.2%)	0.83
Left bundle branch block	1 (0.5%)	1 (0.2%)	2 (0.7%)	4 (1.1%)	0.49
Right bundle branch block	4 (2.2%)	9 (2.1%)	7 (2.4%)	11 (3.0%)	0.85
Cardiac Enzyme (U/L)					
Initial CK	983.4 ± 1792.8	472.8 ± 1258.8	424.1 ± 776.0	580.8 ± 1258.4	< 0.01*
Initial CK-MB	79.6 ± 133.8	36.3 ± 89.6	25.6 ± 43.4	34.0 ± 58.1	< 0.01*
Peak CK	1280.4 ± 1836.7	1357.1 ± 2225.7	1264.1 ± 2237.1	1564.0 ± 2161.9	0.30
Peak CK-MB	92.4 ± 148.7	90.9 ± 168.6	77.6 ± 148.9	91.3 ± 137.9	0.64

ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAG, coronary arteriogram; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CK, creatinine kinase; CK-MB, creatinine kinase-myocardial isoform; CVD, cardiovascular disease; ECG, electrocardiogram; ED, emergency department; FH, family history; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, thrombolysis in myocardial infarction.

* Comparison among groups by chi-square test for categorical variables and by ANOVA test for continuous variables.

Table 2. Interventional data and cardiovascular drugs among groups stratified by door-to-balloon times

Door-to-balloon time (minutes)	< 45	45-90	91-135	> 135	p-value
Diagnostic cardiac angiography					
Cardiac angiography n (%)	189 (100.0%)	443 (100.0%)	293 (98.0%)	398 (99.3%)	< 0.01*
Median time to, hours	0.5 (0.4-0.6)	1.0 (0.8-1.2)	1.6 (1.4-1.9)	3.03 (2.4-4.9)	< 0.01*
Culprit artery territory, n (%)					
Left main	11 (5.8%)	7 (1.6%)	4 (1.3%)	3 (0.8%)	< 0.01*
Left artery disease	115 (60.9%)	230 (51.9%)	152 (50.8%)	209 (52.1%)	0.14
Left circumflex	45 (23.8%)	46 (10.4%)	31 (10.4%)	55 (13.7%)	< 0.01*
Right coronary artery	97 (51.3%)	185 (41.8%)	120 (40.1%)	156 (38.9%)	0.03*
Culprit lesion stenosis	95.5 ± 12.5	95.4 ± 12.1	96.0 ± 8.8	94.8 ± 11.2	0.55
Initial coronary flow, n (%)					
TIMI 0/1	151 (84.8%)	302 (71.6%)	208 (72.2%)	260 (69.0%)	< 0.01*
TIMI 2	13 (7.3%)	73 (17.3%)	39 (13.5%)	72 (19.1%)	
TIMI 3	14 (7.9%)	47 (11.1%)	41 (14.2%)	45 (11.9%)	
Unknown	11	21	11	24	
IABP	85 (45.0%)	82 (18.5%)	53 (17.7%)	92 (22.9%)	< 0.01*
Echocardiography, n (%)					
Normal	91 (57.2%)	221 (59.3%)	149 (60.3%)	206 (63.4%)	0.42
Mild LV systolic dysfunction	52 (32.7%)	104 (27.9%)	72 (29.2%)	78 (24.0%)	
Moderate LV systolic dysfunction	14 (8.8%)	35 (9.4%)	18 (7.3%)	35 (10.8%)	
Severe LV systolic dysfunction	2 (1.3%)	13 (3.5%)	8 (3.2%)	6 (1.9%)	
Median ejection fraction	53.0 (47.0, 60.0)	53.0 (46.0, 63.0)	54.0 (46.0, 61.0)	54.0 (46.0, 62.0)	0.92
PCI					
Median time to (minutes)	31.0 (23.0-40.0)	69.0 (58.0-79.0)	111.0 (102.0-124.0)	197.5 (160.0-308.0)	< 0.01*
Stent type, n (%)					
Bare-metal stents	142 (78.9%)	328 (75.6%)	200 (68.3%)	274 (71.0%)	0.04*
Drug-eluting stents	25 (13.9%)	75 (17.3%)	64 (21.8%)	80 (20.7%)	
Both	7 (3.9%)	4 (0.9%)	6 (2.1%)	10 (2.6%)	
None	6 (3.3%)	27 (6.2%)	23 (7.9%)	22 (5.7%)	
Unknown	3	4	5	6	
Lesion successfully treated	1.3 ± 0.6	1.2 ± 0.6	1.3 ± 0.6	1.3 ± 0.6	0.57
Cardiovascular drugs					
DAPT, n (%)					
At discharge	172 (91.0%)	375 (84.7%)	256 (85.6%)	334 (83.3%)	0.09
At 6 months	116 (72.1%)	260 (65.0%)	165 (62.5%)	229 (64.7%)	0.24
At 12 months	38 (25.3%)	97 (25.9%)	70 (29.2%)	73 (22.3%)	0.33
Beta blockers, n (%)					
At discharge	113 (59.8%)	245 (55.4%)	173 (57.9%)	237 (59.1%)	0.64
At 6 months	104 (64.6%)	250 (62.5%)	170 (64.4%)	235 (66.4%)	0.74
At 12 months	92 (61.3%)	237 (63.2%)	159 (66.3%)	211 (64.5%)	0.77
ACEI/ARB, n (%)					
At discharge	132 (69.8%)	302 (68.2%)	223 (74.6%)	262 (65.3%)	0.07
At 6 months	102 (63.4%)	264 (66.0%)	176 (66.7%)	236 (66.7%)	0.89
At 12 months	89 (59.3%)	249 (66.4%)	150 (62.5%)	204 (62.4%)	0.43
Statin, n (%)					
At discharge	124 (65.6%)	280 (63.2%)	207 (69.2%)	264 (65.8%)	0.41
At 6 months	100 (62.1%)	266 (66.5%)	188 (71.2%)	225 (63.6%)	0.15
At 12 months	101 (67.3%)	246 (65.6%)	165 (68.8%)	189 (57.8%)	0.03*

CABG, coronary artery bypass grafting; CAG, coronary artery angiogram; IABP, intra-aortic balloon pump; LV, left ventricle; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in myocardial infarction.

* Comparison among groups by chi-square test for categorical variables and by ANOVA test for continuous variables.

Table 3. In-hospital outcomes among stratified door-to-balloon times

Door-to-balloon time (minutes)	< 45	45-90	91-135	> 135	p-value
Death, n (%)	5 (2.7%)	9 (2.03%)	5 (1.7%)	9 (2.2%)	0.90
Cardiac	4 (80.0%)	7 (77.8%)	5 (100.0%)	7 (87.5%)	0.71
Non-cardiac	1 (20.0%)	2 (22.2%)	0 (0.0%)	1 (12.5%)	
Re-MI	0 (0.0%)	6 (1.4%)	2 (0.7%)	2 (0.5%)	0.27
Unplanned PCI	0 (0.0%)	3 (0.7%)	0 (0.0%)	1 (0.3%)	0.31
Stroke	1 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	0.29
MACE	5 (2.7%)	17 (3.8%)	7 (2.3%)	12 (3.0%)	0.68
MACE or stroke	6 (3.2%)	17 (3.8%)	7 (2.3%)	14 (3.5%)	0.73
MACE or CABG or stroke	7 (3.7%)	18 (4.1%)	8 (2.7%)	18 (4.5%)	0.65
Acute renal failure	2 (1.1%)	3 (0.7%)	3 (1.0%)	14 (3.5%)	< 0.01*
Total hospital stay, day	6.6 ± 6.5	6.7 ± 6.4	6.3 ± 4.8	8.3 ± 10.8	< 0.01*

MACE, major adverse cardiac event(s) indicating mortality, re-MI and unplanned PCI; MI, myocardial infarction; PCI, percutaneous coronary intervention.

* Comparison among groups by chi-square test for categorical variables and by ANOVA test for continuous variables.

four groups significantly differed in the rates of TVR (p < 0.01), repeated PCI (p = 0.01), and MACE (p = 0.03) at 1 year, with the highest event rates observed in Group 1. In contrast, there was no difference in the rates of mortality, nonfatal re-MI, and stroke (p > 0.05) among groups. However, the cumulative incidence of the cardiovascular composite of all-cause mortality, re-MI, TVR, CABG or stroke at 1 year did not differ between Group 1 plus Group 2 (DTB time < 90 minutes) and Group 3 plus 4 (DTB time ≥ 90 minutes) (p = 0.45 by log-rank test) (Figure 2). Kaplan-Meier analysis showed statistical significance in the 1-year cumulative incidence of the cardiovascular composite between the 4 groups (p = 0.02 by log-rank test) (Figure 3). One-year cardiovascular outcomes among groups are shown in Table 4. Variables associated with cardiovascular composite risk at 1 year are demonstrated using the univariate and multivariate analyses in Table 5. Group 1 was associated with a higher cardiovascular risk (hazard ratio: 2.21; 1.33-3.68; p < 0.01). Killip I class, compared with Killip II-IV class, was associated with a significantly lower rate of inci-

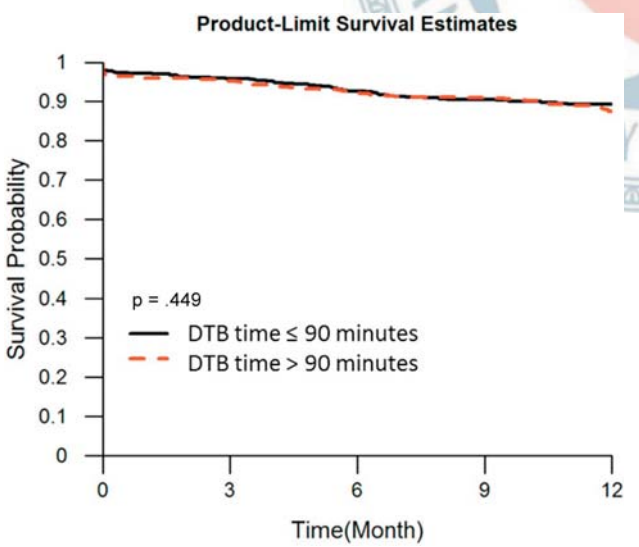

Figure 2. *Kaplan-Meier survival analysis shows no difference in the cumulative incidence of the composite of all-cause mortality, myocardial infarction, target vessel revascularization, stroke and bypass surgery at 1 year between groups with the DTB time ≥ 90 minutes and < 90 minutes. DTB, door-to-balloon.*

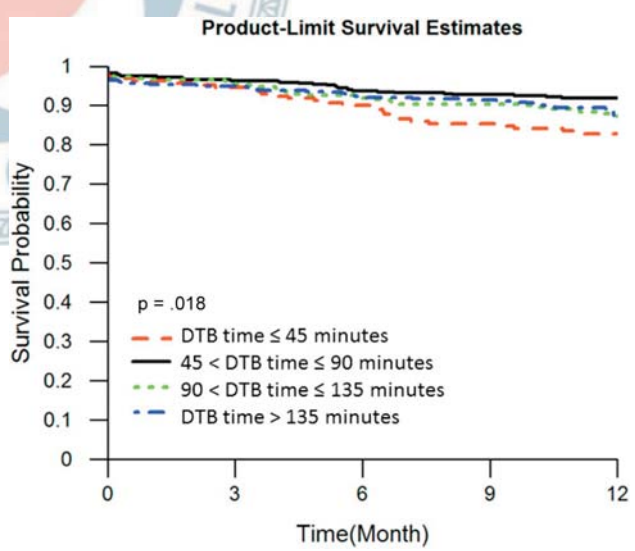

Figure 3. *A significant difference in the cumulative incidence of the composite of all-cause mortality, myocardial infarction, repeat revascularization, stroke and bypass surgery at 1 year among 4 groups with the DTB time < 45, 46-90, 91-135, > 135 minutes. An increase in the cardiovascular composite is shown in Group 1 with the DTB time < 45 minutes. DTB, door-to-balloon.*

Table 4. One-year cardiovascular outcomes among groups stratified by door-to-balloon times

Door-to-balloon time (minutes)	< 45	45 - 90	91 - 135	> 135	p-value
Finish 12-month follow-up	149 (93.7%)	374 (95.4%)	240 (94.1%)	326 (94.2%)	0.82
Death within 12 months	10 (6.3%)	18 (4.6%)	15 (5.9%)	20 (5.8%)	0.82
Cardiac	4 (2.6%)	8 (2.1%)	8 (3.3%)	11 (3.3%)	0.14
Non-cardiac	5 (3.2%)	4 (1.0%)	0 (0.0%)	4 (1.2%)	
Unknown	1	6	7	5	
MI	4 (2.7%)	16 (4.3%)	6 (2.5%)	13 (3.9%)	0.60
TVR	21 (14.0%)	15 (4.0%)	16 (6.6%)	23 (7.0%)	< 0.01*
Re-PCI	45 (29.6%)	70 (18.6%)	44 (18.3%)	58 (17.6%)	0.01*
CABG	2 (1.3%)	2 (0.5%)	3 (1.2%)	2 (0.6%)	0.67
Stroke	2 (1.3%)	5 (1.3%)	4 (1.7%)	4 (1.2%)	0.97
MACE	34 (21.7%)	46 (11.9%)	34 (13.6%)	50 (14.5%)	0.03*
A composite endpoints (death, MI, TVR, Re-PCI, CABG, and stroke)	55 (34.6%)	85 (21.9%)	54 (21.7%)	73 (21.2%)	< 0.01*

CABG, coronary artery bypass grafting; MACE, major adverse cardiac events; MI, myocardial infarction. PCI, percutaneous coronary intervention; TVR, target vessel revascularization.
* Comparison among groups by chi-square test for categorical variables and by ANOVA test for continuous variables.

Table 5. Univariate and multivariate analyses for a composite of all-cause mortality, re-MI, TVR, bypass surgery, and stroke

	Univariate analysis			Multivariate analysis	
	HR (95% CI)	p-value*		HR (95% CI)	p-value*
DTB time < 45 minutes	2.17 (1.33, 3.55)	< 0.01*	DTB time < 45 minutes	2.21 (1.33, 3.68)	< 0.01*
45 ≤ DTB time < 90 minutes	1		45 ≤ DTB time < 90 minutes	1	-
90 ≤ DTB time < 135 minutes	1.55 (0.96, 2.49)	0.07	90 ≤ DTB time < 135 minutes	1.44 (0.88, 2.36)	0.15
DTB time ≥ 135 minutes	1.50 (0.96, 2.34)	0.07	DTB time ≥ 135 minutes	1.31 (0.82, 2.08)	0.26
Age	1.04(1.02, 1.05)	< 0.01*	Age	1.03 (1.02, 1.05)	< 0.01*
Male	0.62 (0.41, 0.93)	0.02*	Killip class		
BMI	0.96 (0.92, 1.01)	0.13	I	0.53 (0.35, 0.79)	< 0.01*
Weekend procedure	1.06 (0.75, 1.51)	0.74	II	0.67 (0.41, 1.11)	0.12
Killip class			III/IV	1	-
I	0.41 0.28, 0.60)	< 0.01*			
II	0.54 (0.34, 0.88)	0.01*			
III/IV	1				
Dyslipidemia	0.64 (0.44, 0.94)	0.02*	Dyslipidemia	0.64 (0.42, 0.95)	0.03*
Hypertension	1.29 (0.92, 1.80)	0.14			
Diabetes	1.56 (1.11, 2.19)	< 0.01*	Diabetes	1.28 (0.89, 1.84)	0.18
Current smoker	0.66 (0.47, 0.92)	0.01*			
FH of vascular disease	0.53 (0.31, 0.90)	0.02*			
Systolic blood pressure	1.00 (0.99, 1.00)	0.07			
Diastolic blood pressure	0.99 (0.98, 1.00)	< 0.01*	Diastolic blood pressure	0.99 (0.98, 1.00)	0.05*
Heart rate	1.01 (1.00, 1.02)	< 0.01*	Heart rate	1.01 (1.00, 1.02)	0.01*

CI, conference interval; DTB, door to balloon; HR, hazard ratio; TVR, target vessel revascularization.
* Risk for cardiovascular events using univariate and multivariate analyses.

dence for cardiovascular composite events at 1 year in subgroup analysis of group 1 (Table 6).

DISCUSSION

The analysis of the Taiwan ACS full spectrum registry generated three major findings: (1) The goal of DTB time < 90 minutes for primary PCI was achieved in only 47.5% of subjects in the registry; (2) Group 1 with the DTB time < 45 minutes had no decrease in the rates of TVR, repeated PCI, MACE or the cardiovascular composite at 1 year; (3) In-hospital cardiovascular endpoints did not differ among the 4 groups stratified by different DTB times.

International and national guidelines currently re-

Table 6. Subgroup analysis of Group 1 for the rates of the cardiovascular composite events at 1 year

Category	Cardiovascular events at 1 year (n, %)	p-value
Symptom onset to ED time (minutes)	≥ 120 minutes: (20, 17.4%) < 120 minutes: (17, 24.3%)	0.42
TIMI flow at baseline	TIMI 0/1: (30, 19.9%) TIMI 2/3: (6, 22.2%)	0.92
Killip classification	Killp I: (19, 15.7%) Killip II, III, or IV: (17, 29.3%)	0.02*
Transfer	Yes: (16, 16.5%) No: (21, 22.8%)	0.41
Culprit lesion	LM/LAD: (20, 17.4%) Non-LM/LAD: (17, 23.0%)	0.30
Initial CK level (U/L)	≥ 800: (9, 18.4%) < 800: (28, 20.6%)	0.85
Initial CK-MB level (U/L)	≥ 60: (7, 13.2%) < 60: (29, 21.8%)	0.32

Events were defined as all-cause mortality, nonfatal myocardial infarction (MI), target vessel revascularization (TVR), bypass surgery, and stroke. CK, creatinine kinase; CK-MB, creatinine kinase, myocardial form; ED, emergency department; LAD, left anterior descending artery; TIMI, thrombolysis in myocardial infarction.

commend that the DTB time should be no greater than 90 minutes in order to minimize cardiac damage and improve the clinical outcome.[1-3] A recent study reinforced that guideline, and non-system reasons for delay in the DTB time led to an increase in in-hospital mortality.[7] In the registry, over a half of the participants did not reach the goal of DTB time < 90 minutes. Aggressive actions are needed to address the apparent gap between the guidelines and DTB times in real practices throughout the country. Various strategies have been proposed to shorten the DTB time,[17-24] such as use of electrocardiogram (ECG)-guided intervention,[17] pre-hospital ECG,[18] mobile cloud ECG system,[19] data feedback,[20] and ED physicians activation.[21] Remarkably, the achievement rates relating to DTB time < 90 minutes and < 75 minutes have been improved over the past 6 years (2005-2010) in the United States.[27]

Current evidence appears conflicting in clinical outcomes when a DTB time less than 90 minutes is further reduced, such as < 60, < 45, or < 30 minutes. One study showed that there was no significant difference in unadjusted and adjusted in-hospital mortality when comparing two patient groups with the mean DTB time of 83 minutes and the other 67 minutes, respectively.[13] Similar results were also disclosed in a several other studies.[14,16,28] As a result, shortening the DTB time for purposes of enhancing prognostic performance associated with the DTB time may not prove efficacious.[4,9,11,15,29] Additionally, the impact of shortening DTB time on outcomes varies in different populations. Shortening DTB time has been verified to benefit patients presenting early and/or with high risk in terms of reduced mortality.[6,8,10,28] The present report showed no difference in in-hospital mortality among groups and a paradoxical increase in Group 1 in 1-year cardiovascular endpoints, mostly contributed by repeated revascularizations. Group 1 seemed to also have higher rates of severely clinical presentations and hospital transfers. Clinical urgency and hospital connection before transferring might make physicians rapidly activate a system for primary PCI and subsequently shorten the DTB time. Nevertheless, the beneficial effects derived from the shortest DTB time did not totally counteract the detrimental effects from the other disadvantageous variables in Group 1. These may partially account for the poorest cardiovascular outcomes at 1 year in Group 1. This scenario was supported by the following observations. First, most hospital transfers occurred in Group 1, and extra transferring time potentially affected the outcomes. For those patients transferred from other hospitals, their DTB times by definition are mostly shorter than those in the patients without hospital transfer. Therefore, the issue must affect the DTB time and even the long-term outcomes. Second, Group 1 compared with other groups had the highest rates of TIMI 0/1 flows, use of IABP, and use of bare-metal stents. These disadvantageous factors might result in an un-

predicted increase in the cardiovascular events, particularly in repeated revascularizations at 1 year in Group 1. Subgroup analysis of Group 1 reveals Killip class is still a critical factor for the 1-year cardiovascular composite. In practice, the DTB time should be shortened to some degree if possible without causing delay, despite an absence of outcome benefit observed in the analysis. Aggressively shortening the DTB time may not lead to better 1-year cardiovascular outcome and the DTB time < 90 minutes may be enough to improve the outcome, but we should focus on more effective avenues to reduce total ischemic time or prehospital time from symptom onset in the future.

On the other hand, a couple of studies revealed that the DTB time > 120 minutes, and not 60-90 or 91-120 minutes, was related to an increased in-hospital mortality as compared with the DTB time < 60 minutes or 120 minutes.[9,10] Some studies pointed out that the DTB time > 90 minutes was linked with more cardiovascular events in a high-risk patient group, but not in a low-risk patient group.[6,10,28] The findings indicate that an interventional delay deteriorates cardiovascular outcomes particularly in certain subgroups. In addition, the longer-term outcome is affected not only by the DTB time but also by other factors. The detrimental effects derived from the longer DTB time particularly on long-term outcome may be neutralized by other advantageous factors. These possibly explain why Group 4 was not associated with the worst outcome. Furthermore, Group 4 included patients with the highest rates of prior cardiovascular disease, Killip III/IV, delayed ECG performance, and the older age. For in-hospital adverse events, it is genuinely unknown whether the negative factors associated with Group 4 are related to the highest incidence of in-hospital acute renal failure. Any delay to PCI such as the DTB time > 135 minutes may deteriorate clinical outcome, at least in terms of increased in-hospital acute renal failure and prolonged hospital stay in the report.

Several limitations should be emphasized here. First, we should avoid over-interpreting the analysis associated with low event rates. The enrollment of ACS patients in each hospital was not complete and comprehensive. It means that STEMI patients enrolled in this study may be highly selected because the in-hospital mortality and one-year mortality were relatively low. Second, the heterogeneity at baseline had made the evaluation of risk more difficult even though potential confounders were adjusted. Far more other unmeasured confounders may affect the outcomes. Third, lesion characteristics (vessel size, lesion length, and thrombus burden), use of anti-thrombotic, anti-hypertensive, and lipid-lowering agents, angiographic findings after PCI, and stent properties like those were not investigated in the study. These factors could potentially influenced outcomes. Fourth, it was not mandatory to routinely check echocardiography and angiography in the registry. Relevant events like as TVR might be underreported because proportional patients who had coronary artery restenosis did not receive subsequent angiography. Finally, one-year period of follow-up for cardiovascular outcomes may be inadequate.

CONCLUSIONS

The results of this study suggested that the DTB time is not a good determinant for outcomes in Taiwanese patients receiving primary PCI.

DISCLOSURES

Chi-Cheng Lai (none), Kuan-Cheng Chang (none), Pen-Chih Liao (none), Chia-Tung Wu (none), Wen-Ter Lai (none), Chiung-Jen Wu (none), Shu-Chen Chang (none), Guang-Yuan Mar (none).

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APPENDIX

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