Early initiation of oral beta-blocker improves long-term survival in patients with acute myocardial infarction who underwent primary percutaneous coronary intervention

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Abstract

Background The optimal timing for the initiation of oral beta-blockers after acute myocardial infarction (MI) remains unclear within the context of current primary percutaneous coronary intervention (PCI) practice.

Methods This retrospective cohort study included 412 consecutive patients admitted with a diagnosis of acute MI between January 2007 and August 2016 who underwent successful primary PCI and were given oral carvedilol during hospitalization. Early and late carvedilol groups were based on initiation within the first 24 h or after. Propensity score matching (1:1) incorporating 21 baseline characteristics yielded 47 matched pairs. Timing of carvedilol initiation was evaluated in relation to patient outcomes including time to all-cause mortality, using Kaplan-Meier estimates on the matched cohort and additional confirmation in multivariable regression analysis among the entire cohort.

Results Median follow-up period was 828 days. All-cause death occurred in 14 patients (4.7%) and 18 patients (15.8%) of the early and late carvedilol groups. After propensity score matching, initiation of oral carvedilol within the first 24 h was associated with lower all-cause mortality (6.4% vs. 25.5%, hazard ratio 0.28, 95% confidence interval $0.06 - 0.89$, $p = 0.036$), as well as lower in-hospital mortality (0 vs. 14.9%, $p = 0.018$).

Conclusions These results provide evidence that initiation of oral carvedilol within the first 24 h reduces the risk of long-term mortality, in acute MI patients who underwent primary PCI, supporting current guidelines recommendation.

Keywords Early oral beta-blocker, Acute myocardial infarction, Primary percutaneous coronary intervention, Propensity score matching

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Background

The first evidence of the potential for beta-blockers to reduce mortality after acute myocardial infarction (MI) was reported in 1981, by Hjalmarson and colleagues [1], which was followed by significant accumulation of additional reports supporting the use of beta-blockers in the treatment of acute MI. Studies performed prior to the primary percutaneous coronary intervention (PCI) era showed beta-blockers to be associated with reduced life-threatening arrhythmias, recurrent ischemia relief, limiting infarct size, decreased pain, and reduced mortality including sudden cardiac death [2]. Based on this evidence, multiple guidelines recommend routine use of beta-blockers after acute MI for secondary prevention unless contraindicated or not tolerated [3–6].

Recent progress in the management of acute MI, namely advances in PCI, have significantly improved the long-term survival of acute MI patients [7, 8]. In the primary PCI era, studies have shown that the prognostic benefit of oral beta-blocker is still present [9, 10]. The American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines recommend that oral beta-blocker be initiated within the first 24 h [5, 6], while the European Society of Cardiology (ESC) guidelines do not specify a time limit [3, 4]. The recommendation in the ACC/AHA guidelines is based on supportive evidence from studies of early intravenous beta-blocker infusion performed during the thrombolysis era [11, 12]. Two large trials, Effect Of Metoprolol In Cardioprotection During An Acute Myocardial Infarction (METOCARD-CNIC) and Early-Beta Blocker Administration Before Reperfusion Primary PCI In Patients With ST-elevation Myocardial Infarction (EARLY-BAMI), provided new insights into the benefit of early intravenous beta-blocker in the primary PCI era [13, 14]. However, it did not provide evidence regarding the optimal timing of initiation of oral beta-blocker.

In clinical practice, there is no sufficient evidence-based consensus to assist in decision-making on this issue of timing of the first dose of oral beta-blocker administered to acute MI patients who underwent successful primary PCI. To address these gaps, we conducted a retrospective cohort study using data from patient medical records assembled over a 9-year period to examine whether initiation of oral beta-blocker within the first 24 h is associated with improved short-term outcomes, as well as long-term survival.

Methods

The institutional review board of St. Luke's International University approved the study protocol (No. 16-J010) and all patients provided informed consent through an opt-out mechanism.

Study subjects

A total of 734 consecutive patients were admitted to our hospital and survived the first 24 h with a diagnosis of acute MI between January 2007 and August 2016 and were considered for inclusion into this retrospective cohort study. Diagnosis of acute MI in all patients was based on the universal definition of myocardial infarction [15]. Among these patients, we excluded those who declined consent, had previous MI, were already on beta-blockers before presentation, underwent coronary artery bypass grafting (CABG) during the hospitalization, did not receive successful primary PCI, and did not start oral beta-blocker during the hospitalization (Fig. 1). Since carvedilol comprised more than 90% of the oral beta-blockers prescribed to acute MI patients in our institution, we excluded patients who were given other types oral beta-blocker (Fig. 1). Finally, 412 patients were included in this analysis.

Data collection and group categorization

We accessed the electronic medical records to obtain data on patient demographics, vital signs on presentation, whether presented with cardiopulmonary arrest, coronary angiographic findings, door-to-balloon time, echocardiographic findings, laboratory results during the hospitalization, medications, comorbidities, smoking status, the exact time of initiation of oral carvedilol, and major events during the follow-up period. Given the recommendations provided by the ACC/AHA guidelines [5, 6], we categorized the patients into early and late oral carvedilol groups based on whether carvedilol was initiated within the first 24 h after arrival (Fig. 1).

PCI procedure and initiation of beta-blockers

PCIs were performed according to standard procedural guidelines. All patients received a 200 mg loading dose of aspirin as well as 300 mg loading dose of clopidogrel or 20 mg loading dose of prasugrel unless they had previously received these antiplatelet therapies. Choice of stents and duration of dual antiplatelet therapy, as well as the time to initiation of oral beta-blocker and its type were at the discretion of the treating physician.

Follow-up and outcome measures

Baseline was defined as the time of presentation at the hospital, after which a diagnosis of acute MI was made. The primary outcome of this study was defined as time to all-cause death. Secondary outcomes were in-hospital mortality, time to cardiac death, and time to major adverse cardiac events (MACE) which was defined as a composite endpoint of all-cause death, heart failure re-admission, non-fatal re-infarction, and non-fatal stroke.
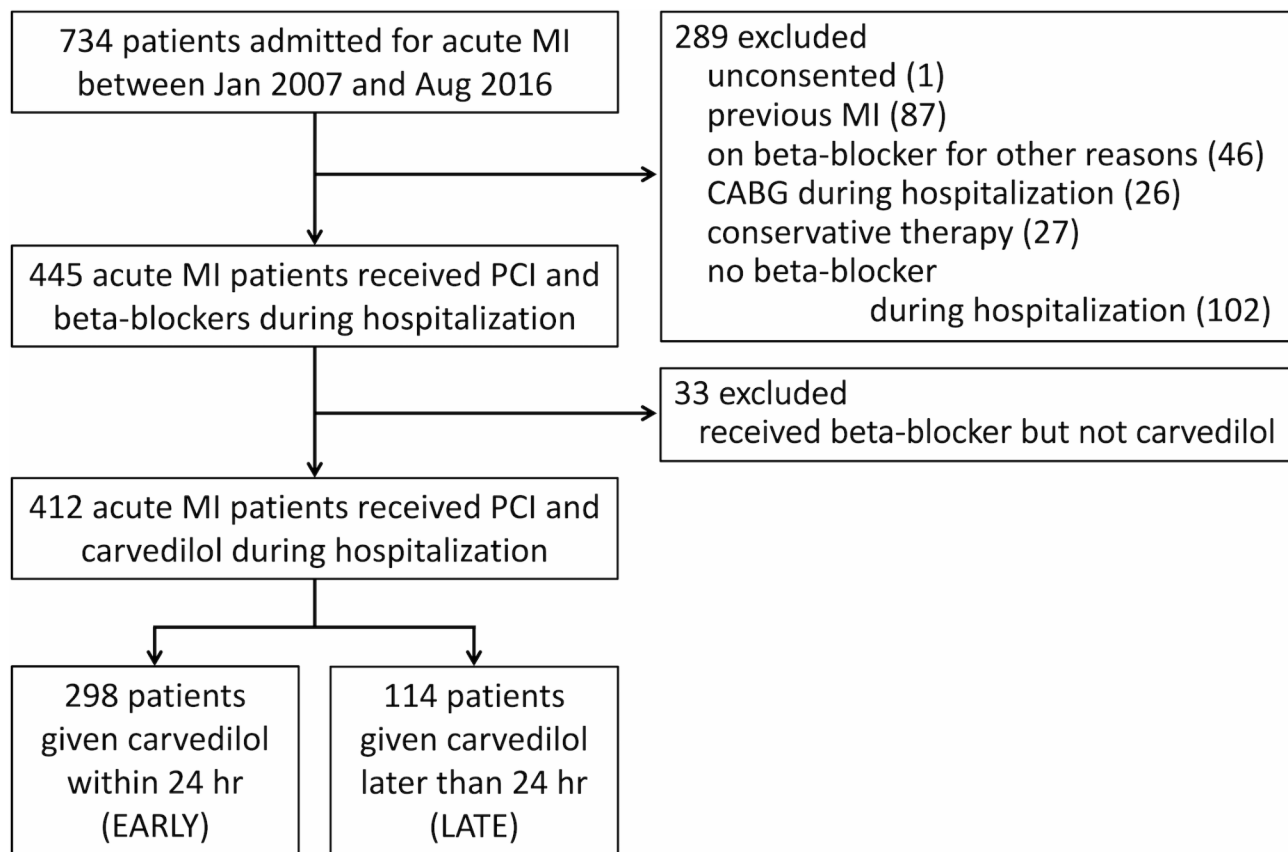
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┌─────────────────────────────────┐        ┌──────────────────────────────────────┐
│ 734 patients admitted for acute MI │        │ 289 excluded                          │
│ between Jan 2007 and Aug 2016     │──────▶│   unconsented (1)                     │
└─────────────────────────────────┘        │   previous MI (87)                    │
              │                              │   on beta-blocker for other reasons (46)│
              │                              │   CABG during hospitalization (26)    │
              ▼                              │   conservative therapy (27)           │
┌─────────────────────────────────┐        │   no beta-blocker                     │
│ 445 acute MI patients received PCI and │   │         during hospitalization (102) │
│ beta-blockers during hospitalization │──┐ └──────────────────────────────────────┘
└─────────────────────────────────┘    │   ┌──────────────────────────────────────┐
              │                          └──▶│ 33 excluded                           │
              │                              │   received beta-blocker but not carvedilol│
              ▼                              └──────────────────────────────────────┘
┌─────────────────────────────────┐
│ 412 acute MI patients received PCI and │
│ carvedilol during hospitalization │
└─────────────────────────────────┘
        │                    │
        ▼                    ▼
┌──────────────┐    ┌──────────────┐
│ 298 patients  │    │ 114 patients  │
│ given carvedilol│   │ given carvedilol│
│ within 24 hr  │    │ later than 24 hr│
│ (EARLY)       │    │ (LATE)        │
└──────────────┘    └──────────────┘
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Fig. 1 Scheme of inclusion, exclusion, and group categorization. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention

Statistical analyses and propensity score matching

Continuous variables were presented as mean±standard deviation or median (interquartile range) where appropriate, and were compared using the Student t test for parametric or the Mann-Whitney's U test for nonparametric comparisons. Categorical variables were presented as number (percentage) and were compared using Pearson's chi-square test.

To evaluate the association between the time of oral carvedilol initiation (within 24 h versus after 24 h) and prognosis, thorough consideration and adjustment of potential confounders was performed using a propensity score matching approach. The predicted probability (propensity score) of initiating carvedilol within 24 h was calculated by fitting a logistic regression model that considered 21 clinically relevant variables: age, presence of ST-segment elevation, heart rate and systolic blood pressure on presentation, left ventricular ejection fraction on the first transthoracic echocardiography, initial N-terminal pro-B-type natriuretic peptide concentration, door-to-balloon time, whether the patient had anterior wall involvement; trivessel disease; cardiopulmonary arrest, whether the patient required catecholamine use, as well as comorbidities and risk factors including hypertension, diabetes, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease, atrial fibrillation, congestive heart failure, stroke, history of coronary reperfusion therapy before presentation, and smoking. C-statistic for the logistic regression model was 0.79. We then performed propensity score matching using the 1:1 nearest neighbor method with a caliper width of 0.20 standard deviation of the logit of propensity score [16]. We calculated the absolute standardized difference to measure covariate balance. Survival curves were constructed using Kaplan-Meier methods and compared across groups with the log-rank test. Hazard ratios were calculated using Cox proportional hazard model.

In order to confirm the robustness of the results, we also performed conventional multivariable analyses in the entire cohort using Cox proportional hazards model in a time-to-event analysis and logistic regression for binary outcomes adjusting for age, smoking status, initial systolic blood pressure, left ventricular ejection fraction on the first echocardiography, initial N-terminal pro-B-type natriuretic peptide concentration, involvement of anterior wall, door-to-balloon time, and ST-segment elevation. Small number of covariates was because of limited number of events.

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To further investigate the timeframe of the effects of early oral carvedilol on the primary endpoint, post-hoc landmark analysis was conducted using a cutoff point of 60 days after admission in both propensity score matched analysis and conventional multivariable analysis [17]. All statistical analyses were conducted using JMP Pro 13.1.0 (SAS Institute Inc., Cary, NC, USA). All tests were 2-tailed, and a value of $p < 0.05$ was considered statistically significant.

Results

Baseline and procedural characteristics

Entire cohort Of the 412 included patients, 298 (72%) received oral carvedilol within the first 24 h as suggested by the clinical guidelines. Initiation of oral carvedilol within the first 24 h was associated with younger age

$(60 \pm 13$ year vs. 66 ± 14 year, $p < 0.001)$, higher initial systolic blood pressure $(140 \pm 29$ mm Hg vs. 132 ± 32 mm Hg, $p = 0.009)$, lower N-terminal pro-B-type natriuretic peptide level (607 [167–1682] pg/nl vs. 1346 [214–2949] pg/nl, $p < 0.001$), less requirement of catecholamine use (15% vs. 39%, $p < 0.001$), shorter door-to-balloon time (81 [64–105] min vs. 94 [72–161] min, $p = 0.004$), less comorbidities such as hypertension (56% vs. 68%, $p = 0.044$), diabetes (31% vs. 43%, $p -0.028$), chronic kidney disease (8% vs. 17%, $P = 0.012$), and stroke (2% vs. 11%, $p < 0.001$). Initial carvedilol dose was comparable between the 2 groups. Peak creatine kinase-MB level during the clinical course was lower in patients who received carvedilol within the first 24 h $(258 \pm 178$ IU/L vs. 338 ± 274 IU/L, $p = 0.001)$, as shown in Table 1; left column.

Table 1 Baseline and clinical characteristics of study subjects among the entire cohort and propensity score matched cohort

	Entire cohort (n = 412)				Propensity score matched cohort (n = 94)			
	Early carvedilol (n = 298)	Late carvedilol (n = 114)	Absolute standardized difference	*p* value	Early carvedilol (n = 47)	Late carvedilol (n = 47)	Absolute standardized difference	*p* value
Age (yr)	60 ± 13	66 ± 14	0.46	< 0.001	67 ± 13	66 ± 16	0.07	0.464
Male sex	250 (84)	93 (82)	0.06	0.678	37 (79)	38 (81)	0.05	1.000
Body mass index (kg/m²)	25 ± 4	25 ± 4	0.16	0.212	25 ± 3	24 ± 4	0.09	0.694
STEMI/NSTEMI				0.990				1.000
STEMI	279 (94)	106 (93)	0.02		43 (91)	44 (94)	0.08	
NSTEMI	19 (6)	8 (7)	0.02		4 (9)	3 (6)	0.08	
Heart rate on presentation (beats/min)	78 ± 21	81 ± 21	0.11	0.326	79 ± 26	81 ± 26	0.08	0.693
Systolic BP on presentation (mm Hg)	140 ± 29	132 ± 32	0.28	0.009	127 ± 30	130 ± 35	0.08	0.686
LVEF on first TTE (%)	56 ± 10	53 ± 13	0.23	0.038	52 ± 11	51 ± 15	0.08	0.282
Initial NT-proBNP (pg/ml)	607 (167–1682)	1346 (214–2949)	0.04	< 0.001	671 (214–1918)	854 (123–1944)	0.06	0.973
Peak CK-MB (IU/L)	258 ± 178	338 ± 274	0.35	0.001	299 ± 176	387 ± 326	0.34	0.106
Anterior involved	156 (52)	69 (61)	0.16	0.167	24 (51)	27 (57)	0.12	0.679
Trivessel disease	34 (11)	18 (16)	0.13	0.302	6 (13)	8 (17)	0.11	0.574
Cardiopulmonary arrest	15 (5)	5 (4)	0.03	0.986	1 (2)	1 (2)	0	1.000
Use of catecholamine	45 (15)	44 (39)	0.55	< 0.001	23 (49)	23 (49)	0	1.000
Door-to-balloon time (min)	81 (64–105)	94 (72–161)	0.09	0.004	79 (65–98)	89 (73–126)	0.10	0.053
Comorbidities and health status								
Hypertension	167 (56)	77 (68)	0.24	0.044	27 (57)	29 (62)	0.09	0.834
Diabetes Mellitus	92 (31)	49 (43)	0.25	0.028	19 (40)	18 (38)	0.04	1.000
Dyslipidemia	187 (63)	69 (61)	0.05	0.762	29 (62)	30 (64)	0.04	1.000
CKD (≥ Stage G2)	23 (8)	19 (17)	0.28	0.012	7 (15)	5 (11)	0.12	0.757
COPD	4 (1)	2 (2)	0.03	1.000	2 (4)	1 (2)	0.12	1.000
Atrial fibrillation	11 (4)	6 (5)	0.08	0.659	2 (4)	2 (4)	0	1.000
Congestive heart failure	1 (0)	3 (3)	0.19	0.118	1 (2)	1 (2)	0	1.000
History of stroke	5 (2)	13 (11)	0.40	< 0.001	2 (4)	2 (4)	0	1.000
History of reperfusion	5 (2)	2 (2)	0.01	1.000	2 (4)	1 (2)	0.12	1.000
Smoking	220 (74)	74 (65)	0.19	0.095	33 (70)	33 (70)	0	1.000
Initial carvedilol dose (mg)	1.25 (1.25–2.5)	1.25 (1.25–2.5)	0.22	0.193	1.25 (1.25–1.25)	1.25 (1.25–2.5)	0.05	0.996
Discharge carvedilol dose (mg)	2.5 (2.5–5.0)	2.5 (1.25–3.75)	0.20	0.008	2.5 (2.5–3.75)	2.5 (2.5–3.75)	0.15	0.098

Data are presented as number (percentage), mean ± standard deviation, or median (interquartile range) where appropriate. BP, blood pressure; CK, creatine kinase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; STEMI, ST-segment elevation myocardial infarction; TTE, transthoracic echocardiography

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Propensity score matched cohort After performing propensity score matching, a total of 94 matched patients were available for analysis. Compared with the entire cohort, the matched cohort was older with an average age of 67±15 year and had more use of catecholamine. Propensity score matching produced an appropriate balance in covariates between groups as indicated by absolute standardized differences of <0.20 (Table 1; right column). Among patients who were not included in the propensity score matched cohort, those in the late carvedilol group appeared to be higher-risk patients as expected (Table 2).

Table 2 Characteristics of patients not included in the propensity score matched cohort

	Early carvedilol (*n*=251)	Late carvedilol (*n*=67)	*p* value
Age (yr)	59±12	67±13	<0.001
Male sex	213 (85)	55 (82)	0.715
Body mass index (kg/m2)	25±4	25±4	0.400
STEMI/NSTEMI			0.871
STEMI	236 (94)	62 (93)	
NSTEMI	15 (6)	5 (7)	
Heart rate on presentation (beats/min)	78±20	80±17	0.492
Systolic BP on presentation (mmHg)	143±28	133±29	0.013
LVEF on first TTE (%)	56±10	55±11	0.500
Initial NT-proBNP (pg/ml)	583 (151–1633)	1685 (715–3149)	<0.001
Peak CK-MB (IU/L)	250±177	303±227	0.040
Anterior involved	132 (53)	42 (63)	0.181
Trivessel disease	28 (11)	10 (15)	0.763
Cardiopulmonary arrest	14 (6)	4 (6)	1.000
Use of catecholamine	22 (9)	21 (31)	<0.001
Door-to-balloon time (min)	81 (63–108)	96 (72–119)	0.042
Comorbidities and health status			
Hypertension	140 (56)	48 (72)	0.027
Diabetes Mellitus	73 (29)	31 (46)	0.012
Dyslipidemia	158 (63)	39 (58)	0.570
CKD (≧Stage G2)	16 (6)	14 (21)	0.001
COPD	2 (1)	1 (1)	1.000
Atrial fibrillation	9 (4)	4 (6)	0.597
Congestive heart failure	0 (0)	2 (3)	0.061
History of stroke	3 (1)	11 (16)	<0.001
History of reperfusion	3 (1)	1 (1)	1.000
Smoking	187 (75)	41 (61)	0.046
Carvedilol dose (mg)	1.25 (1.25–2.5)	1.25 (1.25–2.5)	0.493

Data are presented as number (percentage), mean±standard deviation, or median (interquartile range) where appropriate. BP, blood pressure; CK, creatine kinase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; STEMI, ST-segment elevation myocardial infarction; TTE, transthoracic echocardiography

Clinical outcomes

Over the median follow-up period of 828 days among the entire cohort, a total of 32 all-cause deaths were observed. Among the propensity score matched cohort, 15 all-cause deaths were observed during a median follow-up of 724 days. In the analysis of the matched cohort, initiation of oral carvedilol within the first 24 h was associated with a lower all-cause mortality (6.4% vs. 25.5%, hazard ratio [HR] 0.28, 95% confidence interval [CI] 0.06−0.89, log-rank *p*=0.036), which was the primary outcome of the present study. Similarly, the composite endpoint of MACE (HR 0.37, 95%CI 0.12−0.96, log-rank *p*=0.047), as well as cardiac death (HR 0.23, 95%CI 0.05−1.05, log-rank *p*=0.038), were observed less frequently in the early carvedilol group (Table 3; **right column**, Fig. 2). As a secondary outcome measuring short-term prognosis, in-hospital mortality, was also significantly lower in the early carvedilol group (0 vs. 15%, *p*=0.018) (Table 3; **right column**). In the post-hoc landmark analysis, all-cause mortality tended to be lower in the early carvedilol group in the first 60 days (HR 0.17, 95%CI 0.02−1.43, log-rank *p*=0.064), and was more similar between the 2 groups thereafter (HR 0.41, 95%CI 0.08−2.03, log-rank *p*=0.257); however, the estimates were not statistically significant (Fig. 3).

In parallel, we also performed conventional multivariable regression analyses within the entire cohort to confirm the consistency of associations using a different method which also allowed us to evaluate the generalizability of the findings among the broader study population. The Cox proportional hazard regression analysis that adjusted for a wide range of potentially confounding clinical variables also showed early initiation of carvedilol to be independently associated with reduction in all-cause mortality (HR 0.45, 95%CI 0.21−1.00, *p*=0.050), and MACE (HR 0.49, 95%CI 0.28−0.88, *p*=0.015), but was not significantly associated with cardiac death (HR 0.45, 95%CI 0.18−1.12, *p*=0.087). Regarding short-term prognosis, early carvedilol was also independently associated with lower in-hospital mortality (odds ratio 0.01, 95%CI 0.00−0.98, *p*=0.045) (Table 3; **left column**). Results of the post-hoc landmark analysis showed early carvedilol to be independently associated with lower all-cause mortality in the first 60 days (HR 0.07, 95%CI 0.01−0.75, *p*=0.028), and the association was no longer observed thereafter (HR 0.89, 95%CI 0.34−2.29, *p*=0.804).

Discussion

The present study used a rigorous propensity score matching approach in parallel with multivariable regression analysis to evaluated the influence of the timing of oral beta-blocker administration in the context of current real-world practice. Results of both analytical approaches

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Table 3 Association analysis of the timing of carvedilol initiation and clinical outcomes among the entire cohort and propensity score matched cohort

		Entire cohort (*n* = 412)				Propensity score matched cohort (*n* = 94)		
		Early carvedilol (*n* = 298)	Late carvedilol (*n* = 114)	Adjusted hazard ratio or odds ratio (95% CI)	*p* value	Early carvedilol (*n* = 47)	Late carvedilol (*n* = 47)	*p* value
Primary outcome	All-cause death	14 (5)	18 (16)	0.45 (0.21 − 1.00)	0.050	3 (6)	12 (26)	0.036
Secondary outcomes	In-hospital mortality	2 (1)	8 (7)	0.01 (0.00 − 0.98)	0.045	0 (0)	7 (15)	0.018
	Heart failure re-admission	9 (3)	13 (11)	0.47 (0.19 − 1.17)	0.100	2 (4)	4 (9)	0.763
	Non-fatal re-infarction	4 (1)	1 (1)	1.23 (0.08 − 19.08)	0.880	1 (2)	0 (0)	0.300
	Non-fatal stroke	2 (1)	3 (3)	0.12 (0.01 − 1.16)	0.067	0 (0)	3 (6)	0.133
	Cardiac death	10 (3)	14 (12)	0.45 (0.18 − 1.12)	0.087	2 (4)	10 (21)	0.038
	Major adverse cardiac events	26 (9)	30 (26)	0.49 (0.28 − 0.88)	0.015	5 (11)	16 (34)	0.047

Data are presented as number (percentage) and are compared in a time-to-event manner by using a Cox proportional hazard model in the entire cohort (adjustment stated in the Methods section), and log-rank test in the propensity score matched cohort, except in-hospital mortality, which is compared using a logistic regression model in the entire cohort (adjustment stated in the Methods section) and Pearson's chi-square test, in the propensity score matched cohort. CI, confidence interval
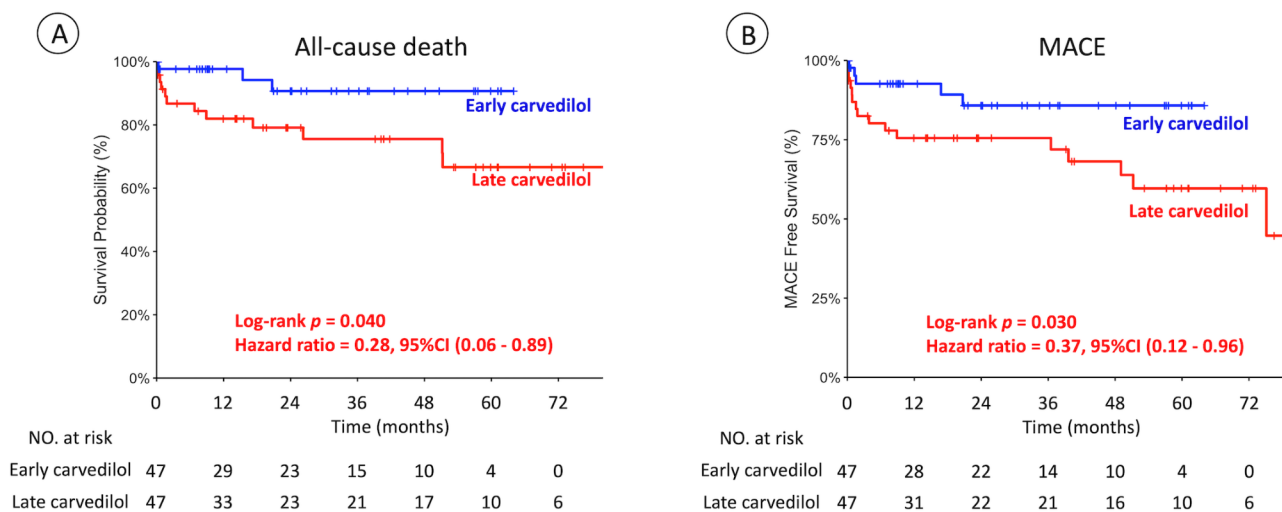

Fig. 2 Kaplan-Meier curves for all-cause death and MACE in early versus late carvedilol groups in the propensity score matched population. In the propensity score matched population, patients in early carvedilol group had lower all-cause mortality (**A**), as well as lower incidence of major adverse cardiac events (MACE) (**B**). CI, confidence interval

showed that oral carvedilol initiated within the first 24 h, compared to later than 24 h, was associated with lower incidence of all-cause mortality in patients diagnosed with acute MI who underwent primary PCI, which appeared to be driven by an early effect during the first 60 days and to a lesser extent thereafter. To the best of our knowledge, this is the first report to evaluate a potential prognostic impact of initiating oral beta-blocker within the first 24 h, although it has been recommended by major guidelines for more than a decade [5, 6, 18, 19]. The present results support the recommendation for early beta-blocker initiation in the primary PCI era.

Beneficial effects of beta-blockers on patients after acute MI have been hypothesized to work through the following mechanisms: decrease of myocardial oxygen demand by reducing heart rate, cardiac contractility, and systolic blood pressure [20]; decrease of malignant arrhythmia and reduction in sudden cardiac death [2, 21, 22]; reduction in remodeling and limit infarct size [23–26]; inhibition of platelet aggregation [27]. Although these were reported in the thrombolysis era or prior to, it has been reconfirmed that acute MI patients still benefit from oral beta-blockers in the primary PCI era [10].

The trials that compared the outcomes of an early dose of beta-blocker with deferred dose date back to the 1990s. The Thrombolysis In Myocardial Infarction II-B study did not find differences in mortality between the immediate (within 2 h of initiating thrombolysis) intravenous metoprolol and deferred (day 6) oral metoprolol groups, but observed fewer deaths in the immediate
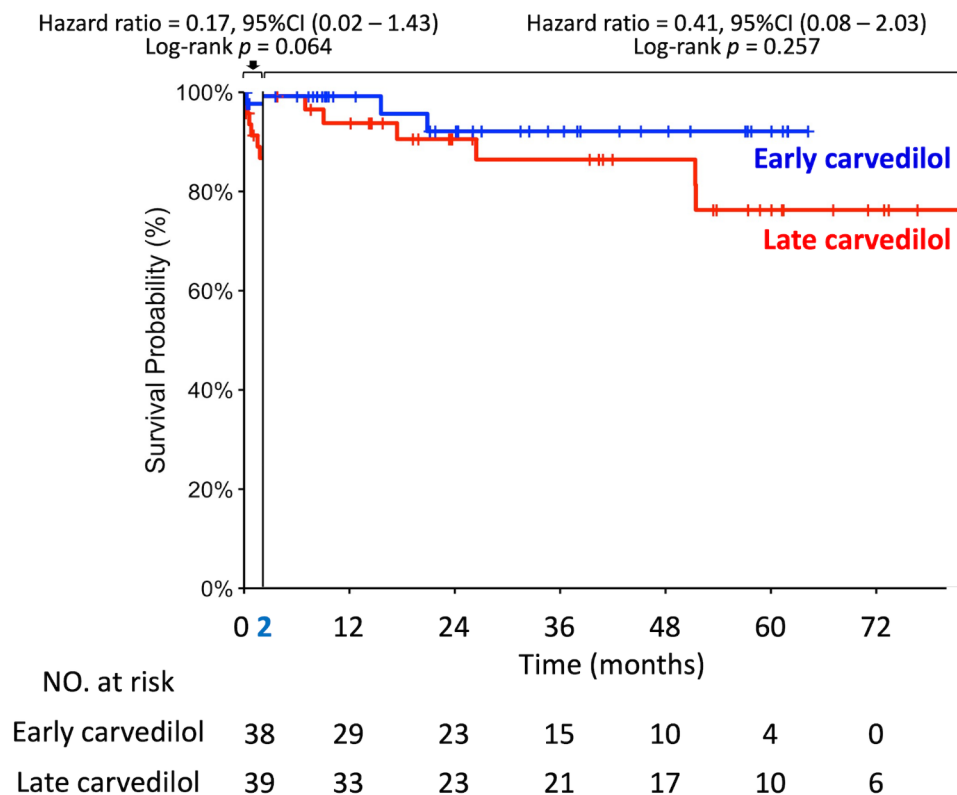
Fig. 3 Landmark analysis for all-cause death in early versus late carvedilol groups in the propensity score matched population using the cutoff point of 60 days. All-cause mortality tended to be lower in the early carvedilol group in the first 60 days though did not reach statistical significance, but was more similar between the 2 groups thereafter. CI, confidence interval

group among the low risk population [12]. Another trial showed similar results [28]. Subsequently, the Clopidegrel and Metoprolol in Myocardial Infarction (COMMIT) trial comprising 45,852 subjects with follow-up for up to 28 days showed no difference in overall mortality, but found increased risk of cardiogenic shock associated with early intravenous metoprolol administration [11]. Subgroup analysis revealed that hemodynamically stable patients experienced survival benefit from early intravenous metoprolol. In the era of thrombolysis, results of these 3 trials were not able to support routine intravenous beta-blocker administration.

Among studies performed during the primary PCI era, the non-blinded, non-placebo-controlled METO-CARD-CNIC trial, which recruited 260 relatively stable anterior ST-segment elevation MI patients who underwent primary PCI, showed that intravenous metoprolol before reperfusion was associated with smaller infarct size measured by cardiac magnetic resonance imaging at 5–7 days, higher left ventricular ejection fraction persisting for 6 months, and fewer heart failure admission, but no difference in overall survival during a median follow-up period of 2 years [13, 25]. The recent EARLY-BAMI trial comprising of 683 relatively low risk acute MI patients did not demonstrate differences in either infarct

size measured by cardiac magnetic resonance at 30 days or 1-year incidence of cardiac death, non-fatal re-infarction, and target vessel revascularization [14, 29]. Notably, in the EARLY-BAMI trial, the primary endpoint (infarct size measured by cardiac magnetic resonance) was only assessed in 55% of randomized patient [14]. Due to the lack of consistency in the current scientific literature, early intravenous beta-blocker injection received class IIa recommendation for ST-segment elevation MI in both the ACC/AHA and ESC guidelines [3, 5].

In real-world clinical practice, physicians may be reluctant to intravenously administer beta-blockers to acute MI patients during an early stage because of underlying risks, lack of clear evidence, and uncertain diagnosis in some cases. Thus, there is a need to expand the evidence regarding the role of early initiation of oral beta-blockers. Currently, there is no clear evidence indicating the potential benefits of initiating oral beta-blockers within the first 24 h or later in patients with acute MI who underwent primary PCI, though authoritative guidelines suggest initiation within 24 h [5, 6]. One previous report from a prospective cohort study compromising 664 ST-segment elevation MI patients showed reductions in both all-cause and cardiovascular mortality in patients administered bisoprolol 2.5 mg orally within 30 min

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compared with administration later than 24 h after onset [30]. However, only 59% of patients included in the study underwent primary PCI, which does not represent the current practices in acute MI management. Furthermore, the feasibility of giving a patient oral beta-blocker within the first 30 min remains questionable. In another recent prospective multi-center cohort study conducted in France, early use of beta-blocker, which was defined as within 48 h of admission, was shown to be associated with reduced 30-day mortality [31]. However, the patient profiles did not reflect the current practice: approximately 30% subjects underwent thrombolysis, 30% did not receive any reperfusion therapy, leaving only less than 40% patients who had primary PCI [31].

A possible explanation for the survival benefit of early administration of an oral beta-blocker observed in this study might be the restriction of infarct size and preservation of ventricular systolic function, as suggested by the METOCARD-CNIC trial [13]. Recent clinical research and experimental animal models suggest that early initiation of beta-blocker may lead to early suppression of post MI inflammatory response, and a resultant preventive effect of ventricular remodeling [32–34].

Limitations

It is important to acknowledge certain limitations of this study. First, data on the duration of oral beta-blocker use after discharge were not available. There have been data suggesting that continuation of beta-blocker beyond discharge or beyond 1 year is of no additional benefit [35], which still remains debatable [10]. Second, due to inherent limitation of non-randomized studies, we cannot rule out a potential effect of unadjusted confounding. However, our approach to address confounding using propensity score matching effectively balanced a large number of suspected confounding baseline characteristics between the comparison group. We believe residual confounding, if any, should have had only minimal influence on the results. Third, the sample size was modest in size which may have affected the statistical power in the evaluation of the more rare outcomes, such as in-hospital mortality. This may have led to the inconsistent results that we observed between the multivariable regression and propensity score matching approach. Large-scale randomized controlled trials would help further clarify whether early initiation of oral beta-blockers is beneficial. Finally, the present study focused on oral carvedilol as this was the type administered to the majority of the study population. Due to possible differences across beta-blocker types, further studies are need to evaluate whether the observed benefit apply to those as well.

Conclusions

In summary, we were able to observe that initiation of oral carvedilol within the first 24 h was associated with reduction in all-cause mortality among acute MI patients who underwent primary PCI. Survival benefit of initiating oral beta-blockers within 24 h indicated by the present results supports the recommendations in current guidelines that oral beta-blockers be initiated in the first 24 h unless contraindicated [5, 6].

Abbreviations

MI	Myocardial infarction
PCI	Percutaneous coronary intervention
ACC	American College of Cardiology
AHA	American Heart Association
ESC	European Society of Cardiology
CABG	Coronary artery bypass grafting
MACE	Major adverse cardiac event
HR	Hazard ratio
CI	Confidence interval

Declarations

Ethics approval and consent to participate
The institutional review board of St. Luke's International University approved the study protocol (No. 16-J010). All patients provided informed consent under an opt-out policy.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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