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Optimal timing of revascularization for patients with non-ST segment elevation myocardial infarction and severe left ventricular dysfunction

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Abstract

Optimal timing of revascularization for patients who presented with non-ST segment elevation myocardial infarction (NSTEMI) and severe left ventricular (LV) dysfunction is unclear. A total of 386 NSTEMI patients with severe LV dysfunction from the nationwide, multicenter, and prospective Korea Acute Myocardial Infarction Registry V (KAMIR-V) were enrolled. Severe LV dysfunction was defined as LV ejection fraction ≤ 35%. Patients with cardiogenic shock were excluded. Patients were stratified into two groups: PCI within 24 hours (early invasive group) and PCI over 24 hours (selective invasive group). Primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) including all-cause death, non-fatal MI, repeat revascularization, and stroke at 12 months after index procedure. Early invasive group showed higher incidence of in-hospital death (9.4% vs 3.3%, $P = .036$) and cardiogenic shock (11.5% vs 4.6%, $P = .030$) after PCI. Early invasive group also showed higher maximum troponin I level during admission (27.7 ± 44.8 ng/mL vs 14.9 ± 24.6 ng/mL, $P = .001$), compared with the selective invasive group. Early invasive group had an increased risk of 12-month MACCE, compared with selective invasive group (25.6% vs 17.1%; adjusted HR = 2.10, 95% CI 1.17–3.77, $P = .006$). Among NSTEMI patients with severe LV dysfunction, the early invasive strategy did not improve the clinical outcomes. This data supports that an individualized approach may benefit high-risk NSTEMI patients rather than a routine invasive approach.

Abbreviations: CI = confidence interval, D2BT = door-to-balloon time, GRACE = Global Registry of Acute Coronary Events, HR = hazard ratio, KAMIR = Korea Acute Myocardial Infarction Registry, LVEF = left ventricular ejection fraction, MACCE = major adverse cardiovascular and cerebrovascular event, PCI = percutaneous coronary intervention, RCT = randomized clinical trials.

Keywords: acute myocardial infarction, echocardiography, left ventricular ejection fraction, percutaneous coronary intervention, prognosis

YS and SHL contributed equally to this work.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Author's Summary

Using nationwide, multicenter, and prospective Korea Acute Myocardial Infarction Registry V, this study assessed the clinical benefit and outcomes of early invasive strategy of percutaneous coronary intervention for NSTEMI patients with severe LV dysfunction. Among NSTEMI patients with severe LV dysfunction (LVEF ≤ 35%), an early invasive strategy within 24 hours did not improve their clinical outcomes, compared to a selective invasive strategy. These findings suggest that an individualized approach based on physician judgement can benefit high-risk NSTEMI patients.

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Key message

1. This analysis of KAMIR-V (Korea Acute Myocardial Infarction Registry V) is first to assess the optimal revascularization timing for NSTEMI patients considering left ventricular ejection fraction.
2. Early invasive strategy did not improved clinical outcomes in NSTEMI patients with severe LV dysfunction.
3. Individualized approach based on physician judgement can benefit high-risk NSTEMI patients.

1. Introduction

Although there was remarkable improvement in clinical outcomes for patients with non-ST segment elevation myocardial infarction (NSTEMI) for several decades, recent data has suggested no more improvements in contemporary practice.[1,2] One of the plausible explanations of this phenomenon is that the heterogenic nature and course of NSTEMI, which interfere with appropriate treatment. In contrast to ST segment elevation myocardial infarction, NSTEMI usually exhibits Thrombolysis In Myocardial Infarction flow preservation at the culprit artery and responds well to initial medical treatment.[3] Several randomized clinical trials have provided inconclusive results,[4–8] suggesting that an early invasive strategy for NSTEMI patients should not be routinely used without considering the clinical context.

Although the early invasive approach for high-risk NSTEMI patients has been associated with favorable outcomes,[9] the real-world data demonstrated that high-risk NSTEMI patients did not undergo the early invasive approach.[10] Current guidelines continue to recommend the early invasive strategy (within 24 hours) for NSTEMI patients with high-risk clinical characteristics, including recurrent/refractory chest pain, hemodynamic instability, acute heart failure, cardiogenic shock, and high Global Registry of Acute Coronary Events (GRACE) score (>140).[11–14] However, most of these criteria supporting an early invasive strategy were established based on clinical findings rather than objective evidence.

Transthoracic echocardiography is a useful noninvasive tool for evaluating the etiologies of non-coronary diseases such as aortic dissection and pulmonary thromboembolism in patients with acute chest pain.[13] It can assess regional wall motion abnormalities and left ventricular ejection fraction (LVEF),[15] making it an essential adjunct to high-sensitive cardiac troponin assays in terms of differentiating type 2 myocardial infarction.[16,17] NSTEMI patients with severe LV dysfunction (LVEF ≤ 35%) are particularly vulnerable to periprocedural events during percutaneous coronary intervention (PCI), but the optimal timing of intervention in this population has not been established.

Therefore, this study sought to evaluate the clinical benefit and outcomes of an early invasive strategy for NSTEMI patients with severe LV dysfunction.

2. Methods

2.1. Study design and participants

The study population was derived from the Korea Acute Myocardial Infarction Registry-V (KAMIR-V), a nationwide, multicenter, observational prospective study, endorsed by the Korean Society of Myocardial Infarction. Patients with acute myocardial infarction were consecutively enrolled in 39 tertiary university hospitals from January 2016 to December 2020. Detailed study protocols have been published elsewhere.[18]

Among 15,628 patients, we selected 7058 NSTEMI patients who underwent PCI for the current analysis (Fig. 1). We excluded the patients who were not eligible for the current analysis: presented with cardiogenic shock (n = 134); lacked data regarding baseline profiles (n = 230), echocardiography (n = 318), or door-to-balloon time (D2BT) (n = 279); or were lost to follow-up (n = 346). According to the LVEF, patients were stratified into 3 groups: LVEF > 50% (preserved LV systolic function, n = 4139), LVEF 35 to 50% (mild to moderate LV systolic dysfunction, n = 1226), and LVEF ≤ 35% (severe LV systolic dysfunction, n = 386). Subsequently, 386 NSTEMI patients with severe LV dysfunction were classified into 2 groups according to the D2BT: those with early invasive group (D2BT ≤ 24 hours, n = 234) and selective invasive group (D2BT > 24 hours, n = 152).

The ethics committee at each participating center approved the KAMIR-V protocol, which was conducted in accordance with the principles of the Declaration of Helsinki. All enrolled patients, or an informed relative on behalf of clinically incapacitated patients, provided written informed consent.

2.2. Patient management, data collection, and follow-up

Baseline characteristics, including demographics, risk factors, and vital signs, were recorded at the time of presentation. During hospitalization, coronary angiography findings, detailed PCI information, and discharge medications lists were collected. Patient management was performed in accordance with standard clinical guidelines valid during the enrollment period.[11,12] However, the final choices for treatment strategy; type, diameter, and length of stents; and medications used were made based on the treating physician's preferences. All patients were prescribed aspirin indefinitely plus clopidogrel or other potent antiplatelet agents (such as prasugrel or ticagrelor) for at least 1 year, unless a clear reason for discontinuing the dual antiplatelet therapy was present.

NSTEMI was defined as the presence of ischemic symptoms with cardiac troponin elevation > 99th percentile of the upper reference value, with an increase or decrease in the value on serial assessments and the absence of ST segment elevation on 12-lead electrocardiography.[19] All patients were recommended to undergo transthoracic echocardiography during the periprocedural period using commercially available ultrasound systems, and the mean time from presentation to echocardiography was 3.8 days. LV systolic function was evaluated in accordance with ASE/EACVI recommendations.[20,21] Attending physicians collected data with the assistance of trained clinical research coordinators at each site. Data collection and management were performed using an electronic web-based case report form that had been established by the central coordinating site (Chonnam National University Hospital, Gwangju, South Korea).

2.3. Outcome measures

The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), a composite of all-cause death, spontaneous non-fatal myocardial infarction, any repeat revascularization (target lesion, target vessel, or non-target vessel revascularization), and stroke, at 12 months after enrollment. All deaths were regarded as cardiac unless a definite non-cardiac cause was established. If patients were unavailable to visit each hospital, outcome data were obtained from hospital electronic medical records and/or telephone interviews. All events were centrally adjudicated by the committee composed of interventional cardiologists blinded to the baseline characteristics.

2.4. Statistical analysis

All discrete or categorical variables are expressed as counts and/or percentages. Continuous variables are expressed as means and standard deviations or medians and 25% to 75% interquartile ranges, according to their distribution. The normality of continuous variables was assessed using the Shapiro–Wilk test and visual Q-Q plot inspection. Discrete or categorical variables

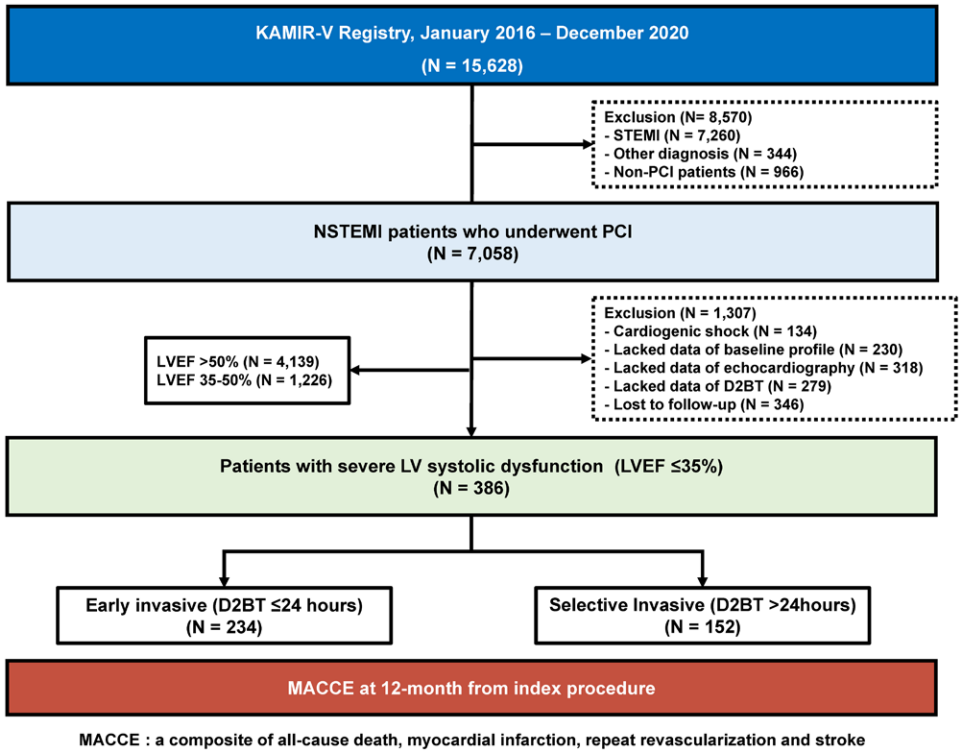

Figure 1. Study flow. D2BT = door-to-balloon time, KAMIR = Korea Acute Myocardial Infarction Registry, LVEF = left ventricular ejection fraction, MACCE = major adverse cardiac and cerebrovascular event, NSTEMI = non-ST segment elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST segment elevation myocardial infarction.

were analyzed using the chi-squared test or Fisher's exact test. Continuous variables were analyzed using unpaired *t*-test or the Mann–Whitney rank-sum test, according to their distribution. For multiple group comparisons, one-way analysis of variance was used. post hoc analyses were not performed.

Cumulative incidence of events at 12 months was calculated on the basis of Kaplan–Meier censoring estimates, then compared clinical outcomes among groups using log-rank tests. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using univariable and multivariable Cox proportional hazard models. Proportional hazards assumptions for the models were assessed by the log-minus-log plot and the Schoenfeld residuals. All Cox models fulfilled the proportional hazards assumptions. All covariates with $P < .10$ on univariable analyses were included in the multivariable model. The final model for prediction of 12-month MACCEs was constructed using a backward elimination method based on the Akaike information criterion. The final model included the covariates of treatment strategy (early invasive vs selective invasive), age, sex, hypertension, diabetes mellitus, chronic kidney disease, LVEF, and GRACE score. Propensity score matching at one-to-one ratio was additionally used to overcome selection bias of observational non-randomized studies. Standardized mean difference of all covariates (age, sex, hypertension, diabetes mellitus, chronic kidney disease, LVEF, and GRACE score) were less than 0.05.

All analyses were two-tailed, and *P* values < .05 were considered statistically significant. Statistical analyses were performed using SPSS 25.0 for Windows (SPSS-PC, Chicago) and R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

NSTEMI patients with severe LV systolic dysfunction (LVEF ≤ 35%) were older; had higher GRACE score; and higher rates of hypertension, diabetes mellitus, chronic kidney disease, previous heart failure, and stroke than NSTEMI patients with mild to moderate LV systolic dysfunction (LVEF 35–50%) or preserved LV systolic function (LVEF > 50%) (Table S1, Supplemental Digital Content, http://links.lww.com/MD/M794). Among NSTEMI patients with severe LV systolic dysfunction, 234 (60.6%) underwent the early invasive strategy and 152 (39.4%) underwent the selective invasive strategy (Table 1). The mean age of the study population was 69.5 ± 11.8 years, and 67.4% of the patients were men. The mean GRACE score was 169.7 ± 47.4, and the mean LVEF was 28.9 ± 5.3%. Other baseline characteristics (e.g., age, sex, GRACE score, comorbidities, and echocardiographic findings) were similar in both groups. The maximum troponin I level during the index hospitalization was higher among patients in the early invasive strategy group than among patients in the selective invasive strategy group (27.7 ± 44.8 ng/mL vs 14.9 ± 24.6 ng/mL, $P = .001$).

3.2. Procedural findings, medications, complications, and in-hospital outcomes

Table 1 shows the management strategies for NSTEMI patients, including procedural findings and medications. The mean D2BT value in the early invasive strategy group was 542.4 ± 453.7 min, whereas it was 4566.2 ± 2978.7 min in the selective invasive strategy group. Both patient groups exhibited rates of multivessel disease (early invasive group, 77.4% vs selective invasive group, 74.3%; $P = .775$), and approximately half of the patients underwent multivessel PCIs (early invasive group, 45.7% vs selective invasive group, 52.6%; $P = .222$). There were no significant differences in the rate of drug-eluting stent use, stent diameter, total stent length, and number of implanted stents between both groups.

During admission, the early invasive strategy group showed a higher rate of in-hospital death compared with patients in the selective invasive strategy group (9.4% vs 3.3%, $P = .036$)

(Table 2). Cardiogenic shock occurred more frequently in the early invasive strategy group than in the selective invasive strategy group (11.5% vs 4.6%, $P = .030$). There were no significant differences in the rates of acute decompensated heart failure (16.7% vs 23.0%, $P = .156$), bleeding (4.3% vs 2.6%, $P = .572$), and acute kidney injury (2.6% vs 1.3%) according to the treatment strategy.

Prescribed discharge medications were similar in both groups, with the exception of antiplatelet agents (Table 1). The potent $P2Y_{12}$ inhibitor was more frequently used in the early invasive strategy group than in the selective invasive strategy group (36.8% vs 22.4%, $P = .004$). Conversely, clopidogrel was more frequently used in the selective invasive strategy group than in the selective invasive strategy group (76.3% vs 58.1%, $P < .001$).

3.3. Clinical outcomes and prognostic implications of treatment strategy

NSTEMI patients with severe LV systolic dysfunction showed significantly higher risk of 12-month MACCE than those with mild to moderate LV systolic dysfunction or preserved LV systolic function (22.3% vs 10.1% vs 5.8%, $P < .001$) (Table S2, Supplemental Digital Content, http://links.lww.com/MD/M795 and Figure S1, Supplemental Digital Content, http://links.lww.com/MD/M792). Furthermore, the early invasive strategy was associated with higher risks of 30-day (11.5% vs 3.9%, $P = .016$) and 12-month (25.6% vs 17.1%, $P = .036$) MACCEs than the selective invasive strategy among NSTEMI patients with severe LV systolic dysfunction (Table 3, Figure 2). The early invasive strategy showed higher risks of 12-month (29.6% vs 17.1%, $P = .015$) MACCEs even after propensity score matching among NSTEMI patients with severe LV systolic dysfunction than the selective invasive strategy (Tables S3 and S4, Supplemental Digital Content, http://links.lww.com/MD/M796, http://links.lww.com/MD/M797 and Figure 3).

Multivariable analysis indicated that the early invasive strategy was an independent predictor of 12-month MACCEs among NSTEMI patients with severe LV systolic dysfunction (adjusted HR 2.10, 95% CI 1.17–3.77, $P = .006$) (Table 4). The

Table 1

Baseline characteristics of study population.

	Overall population (N = 386)	Early invasive strategy (N = 234)	Selective invasive strategy (N = 152)	*P* value
Age, yr	69.5 ± 11.8	69.2 ± 12.0	69.9 ± 11.6	.558
Men, n (%)	260 (67.4)	160 (68.4)	100 (65.8)	.676
Body mass index, kg/m^2	23.3 ± 3.5	23.3 ± 3.5	23.4 ± 3.6	.884
GRACE score	169.7 ± 47.4	168.0 ± 50.0	172.4 ± 43.1	.383
Door to balloon time, minute	2126.4 ± 2734.7	542.4 ± 453.7	4566.2 ± 2978.7	<.001
Risk factors, n (%)				
Hypertension	234 (60.6)	141 (60.3)	93 (61.2)	.940
Diabetes mellitus	175 (45.3)	101 (43.2)	74 (48.7)	.337
Dyslipidemia	67 (17.4)	44 (18.8)	23 (15.1)	.428
Current smoker	92 (23.8)	59 (25.2)	33 (21.7)	.557
Chronic kidney disease	68 (17.6)	36 (15.4)	32 (21.1)	.197
Previous heart failure	37 (9.,6)	20 (8.5)	17 (11.2)	.495
Previous stroke	39 (10.1)	21 (9.0)	18 (11.8)	.459
Laboratory and Echocardiographic findings				
Hemoglobin, g/dL	12.4 ± 2.3	12.6 ± 2.2	12.2 ± 2.5	.123
Creatinine, mg/dL	1.9 ± 2.2	1.8 ± 2.3	1.9 ± 2.0	.667
Maximum Troponin I, ng/mL	22.6 ± 38.5	27.7 ± 44.8	14.9 ± 24.6	.001
proBNP, pg/mL	5795.0 [2141.5-15189.5]	5334.0 [1635.4-15539.5]	6696.0 [2781.0-14119.5]	.229
LV ejection fraction, %	28.9 ± 5.3	29.2 ± 5.0	28.3 ± 5.7	.100
LVEDD, mm	57.0 [52.1-62.1]	56.2 [52.0-61.8]	58.0 [53.0-63.6]	.126
LVESD, mm	47.0 [40.5-52.2]	46.0 [39.3-51.5]	48.2 [42.0-54.0]	.009
Procedural characteristics				
Multivessel disease, n (%)	294 (76.2)	181 (77.4)	113 (74.3)	.775
Multivessel PCI, n (%)	187 (48.4)	107 (45.7)	80 (52.6)	.222
Lesion location, n (%)				.207
Left main coronary artery	29 (7.5)	15 (6.4)	14 (9.2)	
Left anterior descending artery	187 (48.4)	107 (45.7)	80 (52.6)	
Left circumflex artery	80 (20.7)	50 (21.4)	30 (19.7)	
Right coronary artery	90 (23.3)	62 (26.5)	28 (18.4)	
Treatment method, n (%)				.230
Drug-eluting stent	363 (94.0)	218 (93.2)	145 (95.4)	
Others	23 (6.0)	16 (6.8)	7 (4.6)	
Stent diameter, mm	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.4	.922
Total stent length, mm	31.3 ± 16.8	30.0 ± 16.0	33.2 ± 17.9	.057
Number of stents	1.2 ± 0.6	1.2 ± 0.6	1.3 ± 0.6	.276
Discharge medications, n (%)				
Aspirin	380 (98.4)	230 (98.3)	150 (98.7)	1.000
Clopidogrel	286 (74.1)	157 (67.1)	129 (84.9)	<.001
Potent $P2Y_{12}$ inhibitor	120 (31.1)	86 (36.8)	34 (22.4)	.004
Beta blocker	277 (71.8)	174 (74.4)	103 (67.8)	.197
RAAS blocker	267 (69.2)	166 (70.9)	101 (66.4)	.412
Statin	340 (88.1)	210 (89.7)	130 (85.5)	.276

Values are expressed as mean ± standard deviation, median [interquartile range], or number (%).

GRACE = Global Registry of Acute Coronary Events, LV = left ventricular, LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter, PCI = percutaneous coronary intervention, proBNP = Pro-B-type natriuretic peptide, RAAS = renin-angiotensin-aldosterone system.

prognostic implication of the treatment strategy was not evident for NSTEMI patients with mild to moderate LV systolic dysfunction (adjusted HR 0.95, 95% CI 0.65–1.37, $P = .766$) or preserved LV systolic function (adjusted HR 1.10, 95% CI 0.83–1.46, $P = .514$) (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/M793).

4. Discussion

In this real-world data analysis, we explored the optimal timing of revascularization for NSTEMI patients with severe LV systolic dysfunction (LVEF ≤ 35%). The major findings were as follows: NSTEMI patients exhibited distinct clinical profiles and outcomes according to LV systolic function, and the patients with severe LV systolic dysfunction had high-risk features, requiring an early invasive strategy in accordance with current guidelines; only 60% of NSTEMI patients with severe LV systolic dysfunction were managed with an early invasive strategy; use of the early invasive strategy for severe LV systolic dysfunction was associated with increased risks of in-hospital mortality, 30-day MACCEs, and 12-month MACCEs, compared to use of the selective invasive strategy; and there was the differential prognostic implication of PCI timing that it was only evident for the patients with severe LV systolic dysfunction not for the patients with mild to moderate LV systolic dysfunction or preserved LV systolic function.

4.1. Current status of optimal timing of PCI for NSTEMI

The Timing of Intervention in Acute Coronary Syndromes (TIMACS) and Very Early versus Deferred Invasive Evaluation Using Computerized Tomography (VERDICT) trials were 2 major randomized clinical trials evaluated the appropriate timing of invasive coronary angiography in NSTEMI patients. The TIMACS trial enrolled 3031 NSTEMI patients and compared routine early intervention (invasive coronary angiography ≤ 24 hours) to delayed intervention (invasive coronary angiography ≥ 36 hours).[4] The VERDICT trial enrolled 2147 NSTEMI patients and compared early invasive care (invasive coronary angiography ≤ 12 hours) to standard invasive care (invasive coronary angiography within 48–72 hours).[7] Although both trials did not demonstrated a clinical benefit for an early invasive strategy in the overall population, the pre-specified subgroup analyses in both trials showed that the early invasive strategy was beneficial for high-risk patients with GRACE score > 140 (TIMACS trial: HR 0.65, 95% CI 0.48–0.89; VERDICT trial: HR 0.81, 95% CI 0.67–1.00).[4,7]

The Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients (RIDDLE-NSTEMI) trial enrolled 323 NSTEMI patients and demonstrated that immediate invasive strategy (<2 hours) was significantly associated with lower rates of death or new MI compared with delayed invasive strategy (2–72 hours) (6.8% vs 18.8%; HR 0.34, 95% CI 0.17–0.67, $P = .002$).[6] The Early or Delayed Revascularization for Intermediate and High-Risk Non ST-Elevation Acute Coronary Syndromes (EARLY) trial enrolled 741 high-risk NSTEMI patients, and assessed the clinical benefit of very early invasive strategy (within 2 hours), compared to a delayed invasive strategy (12–72 hours).[8] In this study, the very early invasive strategy was associated with a significant reduction in ischemic events than the delayed invasive strategy (4.4% vs 21.3%; HR 0.20, 95% CI 0.11–0.34, $P < .001$).

Based on those results, current guidelines recommend a different timing of invasive strategy for NSTEMI patients according to their clinical profiles. The most recent guideline has recommended the immediate invasive strategy within 2 hours for NSTEMI patients with very high risk, including cardiogenic shock, refractory chest pain, or electrical instability.[13] An early invasive strategy within 24 hours has been suggested for high-risk patients (GRACE score > 140). A selective invasive strategy has been suggested for other NSTEMI patients with low risk.[11–14] However, these recommendations did not consider cardiac function, which could be an important determinant of periprocedural, short-term, or long-term events.

Table 2

Post-procedural outcomes and complications.

	Overall (N = 386)	Early invasive strategy (N = 234)	Selective invasive strategy (N = 152)	*P* value
In-hospital death, n (%)	27 (7.0)	22 (9.4)	5 (3.3)	0.036
Cardiac arrest, n (%)	47 (12.2)	34 (14.5)	13 (8.6)	0.111
Cardiogenic shock, n (%)	34 (8.8)	27 (11.5)	7 (4.6)	0.030
Acute decompensated heart failure, n (%)	39 (10.1)	39 (16.7)	35 (23.0)	0.156
Bleeding complications, n (%)	14 (3.6)	10 (4.3)	4 (2.6)	0.572
Acute kidney injury, n (%)	8 (2.1)	6 (2.6)	2 (1.3)	0.634

Table 3

Clinical outcomes according to the treatment strategy at 12-month.

	Overall (N = 386)	Early invasive strategy (N = 234)	Selective invasive strategy (N = 152)	*P* value
30-day outcome				
MACCE*, n (%)	33 (8.5)	27 (11.5)	6 (3.9)	.016
All-cause death, n (%)	28 (7.3)	24 (10.3)	4 (2.6)	.009
Cardiac death, n (%)	24 (6.2)	21 (9.0)	3 (2.0)	.010
Myocardial infarction, n (%)	2 (0.5)	2 (0.9)	0 (0.0)	.676
Repeat revascularization, n (%)	0 (0)	0 (0)	0 (0)	1.000
Stroke, n (%)	4 (1.0)	2 (0.9)	2 (1.3)	1.000
Re-hospitalization due to heart failure, n (%)	7 (1.8)	5 (2.1)	2 (1.3)	.841
12-month outcome				
MACCE*, n (%)	86 (22.3)	60 (25.6)	26 (17.1)	.036
All-cause death, n (%)	56 (14.5)	40 (17.1)	16 (10.5)	.061
Cardiac death, n (%)	37 (9.6)	27 (11.5)	10 (6.6)	.080
Myocardial infarction, n (%)	13 (3.4)	8 (3.4)	5 (3.3)	.831
Repeat revascularization, n (%)	17 (4.4)	11 (4.7)	6 (3.9)	.595
Stroke, n (%)	11 (2.8)	5 (2.1)	6 (3.9)	.365
Re-hospitalization due to heart failure, n (%)	31 (8.0)	16 (6.8)	15 (9.9)	.379

Data are expressed as the cumulative incidence of clinical outcomes and the number of events.
Cumulative incidences of clinical outcomes represent Kaplan–Meier estimates during 12 months.
P values were used for the log-rank test in the survival analysis.
MACCE = major adverse cardiac and cerebrovascular events.
*A composite of all-cause death, myocardial infarction, repeat revascularization, and stroke.

4.2. Clinical role of echocardiography for NSTEMI patients

Many clinical conditions associated with chest pain and troponin elevation must be considered in patients with suspected NSTEMI.[13] Moreover, high-sensitivity troponin levels may indicate non-coronary troponin release mechanisms.[19] noninvasive detection of myocardial ischemia or wall motion abnormalities may establish the presence of coronary artery disease. Echocardiography is a useful noninvasive bedside test for NSTEMI patients that can be easily adopted and provides information regarding cardiac function.[15,22] It has been well known that both the LV systolic and diastolic functions have been associated with clinical outcomes after PCI in NSTEMI patients.[22] NSTEMI patients with preexisting impaired cardiac function may display exacerbated symptoms, such as pulmonary edema or cardiogenic shock, after acute myocardial ischemic insults. Moreover, invasive procedures (e.g., contrast injection and balloon occlusion of coronary arteries) during PCI can induce ischemia. Therefore, the objective cardiac function parameters provided by echocardiography can be useful in determining the optimal timing of invasive strategy for NSTEMI patients, along with the recommended clinical profiles.

4.3. Early invasive strategy for NSTEMI patients with severe LV systolic dysfunction

The rationale for an early invasive strategy was that restoration of coronary flow results in recovery of cardiac function, followed by improvements in clinical outcomes. However, our results

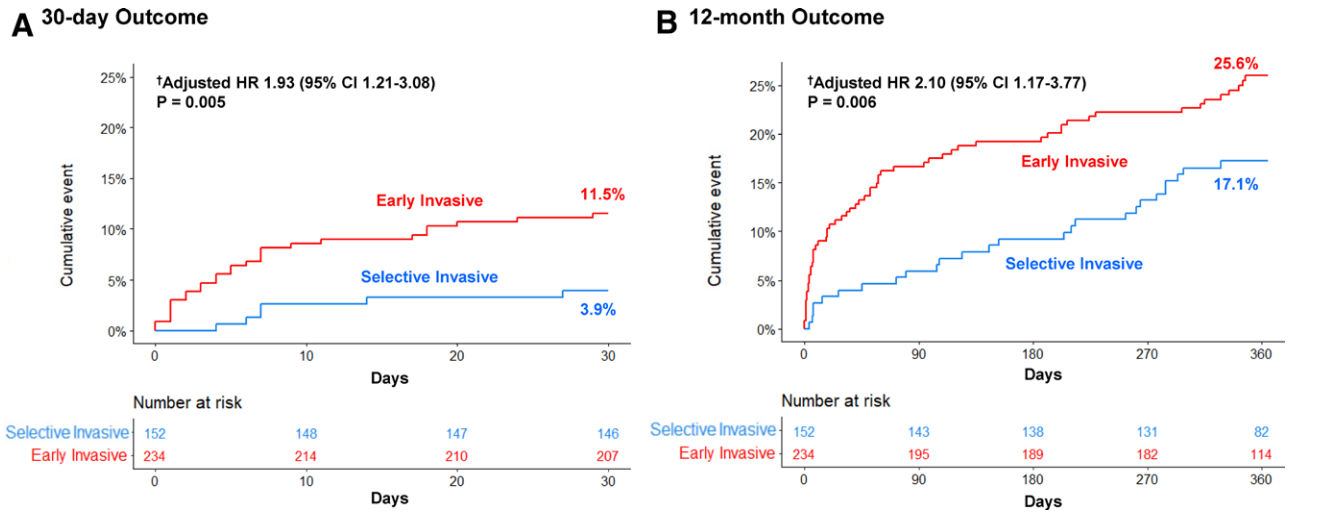

Figure 2. Comparison of MACCE According to Treatment Strategy. Comparison of cumulative incidence and Kaplan–Meier curves of 30-day (A) and 12-month (B) outcomes after early invasive (≤24 hours) or selective (>24 hours) invasive strategies. †Adjusted for age, sex, hypertension, diabetes mellitus, chronic kidney disease, GRACE score, and left ventricular ejection fraction. CI = confidence interval, GRACE = Global Registry of Acute Coronary Events, HR = hazard ratio, MACCE = major adverse cardiac and cerebrovascular event.

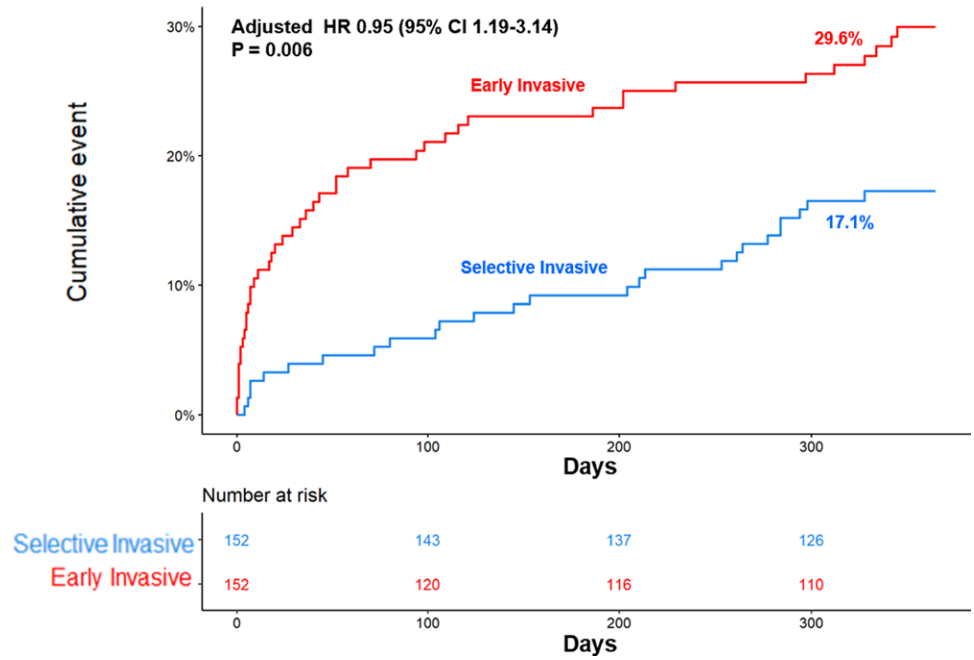

Figure 3. Comparison of MACCE at 12-Month According to Treatment Strategy after Propensity Score Matching. Comparison of cumulative incidence and Kaplan–Meier curves of 12-month outcomes after early invasive (≤24 hours) or selective (>24 hours) invasive strategies. CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiac and cerebrovascular event.

Table 4

Multivariable analysis for predicting MACCE at 12-month.

	Unadjusted		Multivariable-adjusted*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment strategy (Early invasive vs Selective)	1.85 (1.11–3.11)	.018	2.10 (1.17–3.77)	.006
Chronic kidney disease	2.16 (1.36–3.45)	<.001	2.40 (1.28–4.49)	.012
Diabetes mellitus	1.76 (1.15–2.70)	.009	1.77 (1.00–3.13)	.049
Age (every 1 increase)	1.01 (0.99–1.02)	.538	1.04 (1.01–1.08)	.008
Hypertension	1.67 (1.05–2.67)	.030	1.02 (0.53–1.96)	.963
GRACE score (every 1 increase)	1.01 (1.00–1.01)	.006	1.01 (1.00–1.01)	.083
LVEF (every 1% increase)	0.95 (0.92–0.99)	.021	0.93 (0.89–0.97)	.002
Male	0.89 (0.57–1.39)	.612	0.92 (0.53–1.61)	.781

CI = confidence interval, GRACE = Global Registry of Acute Coronary Events, HR = hazard ratio, LVEF = left ventricular ejection fraction, MACCE = Major adverse cardiac and cerebrovascular events.

*A multivariable Cox model was fitted using all variables with $P < .10$ on univariable analyses. Final model was constructed using backward elimination method based on the Akaike information criterion.

suggest that this strategy is associated with approximately 2-fold increases in the risks of adverse events in both short- and long-term follow-up periods, compared to a selective invasive strategy. Notably, the early invasive strategy for NSTEMI patients with severe LV systolic dysfunction was associated with 3-fold increases in the risks of periprocedural cardiogenic shock and in-hospital mortality. Conversely, the early invasive strategy was not significantly associated with poor prognoses for NSTEMI patients with LVEF > 35%. Coronary flows are usually maintained during NSTEMI, and anti-ischemic therapy could relieve myocardial ischemia. Additionally, heart failure management for those patients led to improvements in myocardial oxygenation and resolution of myocardial demand-supply mismatch. In contrast, the invasive approach caused additional myocardial ischemia, and it was harmful to vulnerable patients with severe LV systolic dysfunction during acute NSTEMI. Our results suggest that the optimal timing of invasive procedures should be individualized, and routine early invasive strategies should be avoided for patients with severe LV systolic dysfunction. This data has also provided evidence that LVEF is a key decision factor regarding the timing of invasive approaches, although current guidelines do not consider the role of echocardiography.

4.4. Study limitations

There were several limitations in the present analysis. First, although the study population was derived from a prospective, multicenter, and nationwide observational study with a large sample size, there was a risk of selection bias. Second, the LV diastolic function also has been known to be associated with clinical outcomes. However, there was no available data on diastolic function, we could not elucidate its clinical role Considering their interrelated nature, systolic function presumably reflects a substantial proportion of diastolic function. Third, the 12-month follow-up period after PCI for NSTEMI may be an insufficient duration to determine the long-term prognostic significance of an early invasive strategy. KAMIR-V study researchers plan to record follow-up data for up to 3 years, allowing further evaluation of the long-term prognostic impact of optimal timing.

5. Conclusions

Echocardiography facilitates the assessment of LVEF in NSTEMI patients, but current guidelines have not considered its role in determining the optimal timing of invasive approaches. Among NSTEMI patients with severe LV dysfunction (LVEF ≤ 35%), an early invasive strategy within 24 hours did not improve their clinical outcomes, compared to a selective invasive strategy. These findings suggest that an individualized approach based on physician judgement can benefit high-risk NSTEMI patients.

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