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CORONARY

# Early Invasive Strategy Based on the Time of Symptom Onset of Non-ST-Segment Elevation Myocardial Infarction

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## ABSTRACT

**BACKGROUND** A limitation of the current guidelines regarding the timing of invasive coronary angiography for patients with non-ST-segment elevation acute coronary syndrome is the randomization time. To date, no study has reported the clinical outcomes of invasive strategy timing on the basis of the time of symptom onset.

**OBJECTIVES** The aim of this study was to investigate the effect of invasive strategy timing from the time of symptom onset on the 3-year clinical outcomes of patients with non-ST-segment elevation myocardial infarction (NSTEMI).

**METHODS** Among 13,104 patients from the Korea Acute Myocardial Infarction Registry-National Institutes of Health, 5,856 patients with NSTE myocardial infarction were evaluated. The patients were categorized according to symptom-to-catheter (StC) time (<48 or ≥48 hours). The primary outcome was 3-year all-cause mortality.

**RESULTS** Overall, 3,919 patients (66.9%) were classified into the StC time <48 hours group. This group had lower all-cause mortality than the group with StC time ≥48 hours (7.3% vs 13.4%; $P < 0.001$). The lower risk for all-cause mortality in the group with StC time <48 hours group was consistent in all subgroups. Notably, emergency medical service use (HR: 0.31; 95% CI: 0.19-0.52) showed a lower risk for all-cause mortality than no emergency medical service use (HR: 0.54; 95% CI: 0.46-0.65; $P$ value for interaction = 0.008).

**CONCLUSIONS** An early invasive strategy on the basis of StC time was associated with a decreased risk for all-cause mortality in patients with NSTEMI. Because the study was based on a prospective registry, the results should be considered hypothesis generating, highlighting the need for further research. (iCReaT Study No. C110016)
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The clinical outcomes of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) have rapidly improved over the past 2 decades.[1] Such improvements are attributed to advancements in medical facilities, the development of new devices, and the rapid initiation of invasive procedures, particularly in patients with non-ST-segment elevation myocardial infarction (NSTEMI). Among patients with NSTEMI, those who underwent percutaneous coronary intervention (PCI) within 72 hours were shown to have an approximately 3-fold lower 6-month mortality rate than patients who did not.[1]

The optimal timing of invasive coronary angiography (ICA) and revascularization in patients with NSTE-ACS has received increasing interest. Several randomized clinical trials and meta-analyses have demonstrated that an early invasive strategy does not reduce adverse clinical outcomes compared with a delayed invasive strategy in all patients with NSTE-ACS.[2-5] However, a limitation of the interpretation of such studies is that the calculated time to ICA is based on the randomization time. That is, few studies have reported the effect of optimal timing of an invasive strategy on the basis of symptom onset on the clinical outcomes of patients with NSTEMI.[2-6] In addition, no large-scale study has addressed long-term clinical outcomes according to the timing of an invasive strategy on the basis of the time of symptom onset in patients with NSTEMI. Thus, the current recommendation may not completely reflect real-world practice in patients with NSTEMI. However, real-world evidence of the highest quality can provide insightful clues regarding the uncertain gaps between randomized clinical trials and real-world practice.[7]

We aimed to investigate the effect of invasive strategy timing on the basis of the time of symptom onset on the 3-year clinical outcomes of patients with NSTEMI using an all-comers, nationwide, multicenter, prospective myocardial infarction (MI) registry.

## METHODS

**STUDY PROTOCOLS.** The data used in this study were obtained from the nationwide, multicenter, prospective KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health) registry. The KAMIR-NIH registry included multiple centers in South Korea and was supported by a grant from the Korea Centers for Disease Control and Prevention from November 2011 to December 2015 and did not feature any exclusion criteria. Detailed study protocols have been published previously.[8] The protocol of the KAMIR-NIH registry was approved by the ethics committee at each participating center and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent upon enrollment. All data were collected by independent clinical research coordinators, using a web-based case report form in the Internet-Based Clinical Research and Trial Management System, a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (Internet-Based Clinical Research and Trial Management System Study No. C110016; cris.nih.go.kr identifier KCT0000863).

**STUDY POPULATION AND DEFINITION.** The KAMIR-NIH registry enrolled 13,104 patients between November 2011 and December 2015 and analyzed 3-year clinical outcomes. After excluding 6,326 patients who were diagnosed with ST-segment elevation MI, 169 who did not undergo coronary angiography, 698 who had very high risk (cardiogenic shock, acute heart failure [HF], life-threatening arrhythmia, or ST-segment depression >1 mm in 6 leads plus ST-segment elevation in leads aVR and/or $V_1$),[9] and 55 who were lost to follow-up, we ultimately investigated 5,856 patients with NSTEMI (**Figure 1**).

The study population was categorized according to the time between symptom onset and ICA as those with a symptom-to-catheter (StC) time of <48 hours and those with an StC time of ≥48 hours (Supplemental Figure S1). Symptom onset time was defined as an index time of onset of the last sustained chest pain.

The diagnosis of NSTEMI was based on the criteria of the fourth universal definition of MI.[10] The patients' GRACE (Global Registry of Acute Coronary Events) risk scores (on a scale of 1-372, with higher scores indicating greater risk) were derived from readily available hospital admission records.[11] Definitions of other baseline covariates have been described in detail previously.[8]

Patients were managed according to current guidelines.[12] The selection of the mode of revascularization (PCI or coronary artery bypass surgery) was based on patient characteristics and preferences, the extent of disease, the presence or absence of coexisting illnesses, and the level of left ventricular function.

**CLINICAL OUTCOMES.** An extended description of the statistical analysis is presented in the Supplemental Appendix. The primary endpoint of the

**ABBREVIATIONS AND ACRONYMS**

**CKD** = chronic kidney disease

**DtC** = door-to-catheter

**EMS** = emergency medical services

**HF** = heart failure

**ICA** = invasive coronary angiography

**MI** = myocardial infarction

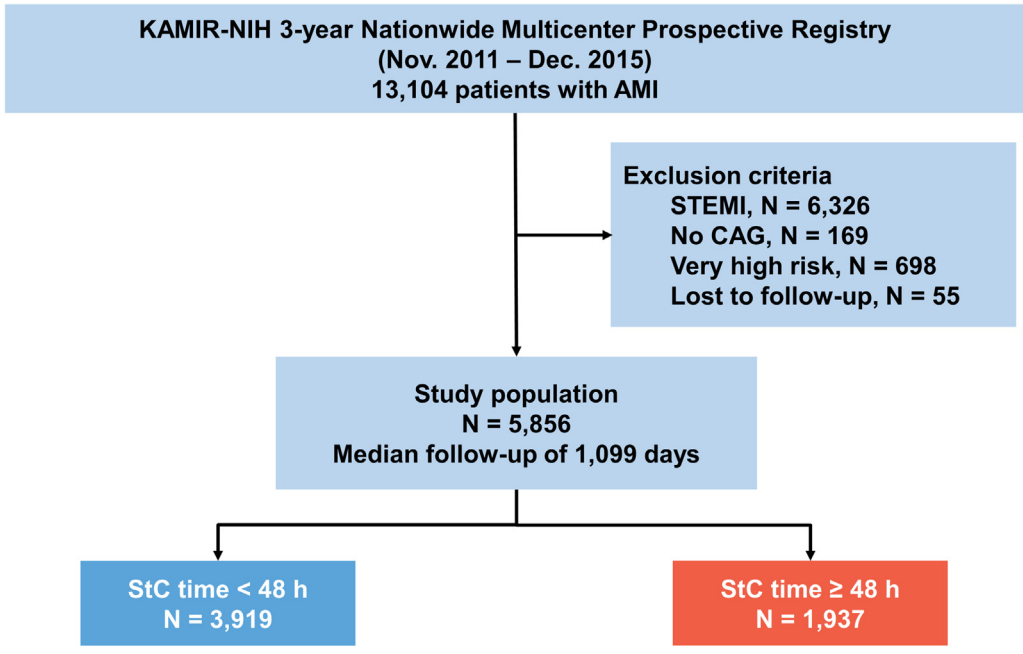
**NSTE-ACS** = non-ST-segment elevation acute coronary syndrome

**NSTEMI** = non-ST-segment elevation myocardial infarction

**PCI** = percutaneous coronary intervention

**StC** = symptom-to-catheter

**FIGURE 1** Study Flowchart




The data used in this study were derived from the nationwide, multicenter, prospective KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health) registry. AMI = acute myocardial infarction; CAG = coronary angiography; StC = symptom-to-catheter; STEMI = ST-segment elevation myocardial infarction.

present study was 3-year all-cause mortality. The secondary endpoint was 3-year composite outcomes, which included all-cause mortality, recurrent MI, or hospitalization for HF. All deaths were considered cardiac deaths unless an undisputed noncardiac cause was present. Recurrent MI was defined as the occurrence of cardiogenic chest pain accompanied by changes on 12-lead electrocardiography (new ST-segment elevation or newly developed left bundle branch block) or an increase in cardiac marker levels (cardiac troponin) above the upper limit of normal, and periprocedural MI was not included as a clinical outcome. Hospitalization for HF was defined as rehospitalization with New York Heart Association functional class III or IV symptoms with reduced left ventricular ejection fraction on echocardiography. According to the Academic Research Consortium definitions,[13] repeated revascularizations were defined as the need for clinically driven revascularization that occurred after discharge.

## STATISTICAL ANALYSES

An extended description of the statistical analysis is presented in the Supplemental Appendix.

Continuous variables were analyzed using descriptive methods depending on their distribution, corroborated using the Shapiro-Wilk test. Variables with normal distributions are expressed as mean ± SD. Otherwise, median (IQR) are used. Considering the normality of each quantitative variable, an analysis with independent 2-sample Student's *t*-tests or Mann-Whitney *U* tests was performed. Discrete variables are expressed as frequencies and percentages. We measured the Kaplan-Meier curves of the primary and secondary outcomes according to an StC time of <48 hours and an StC time of ≥48 hours.

As differences in baseline characteristics could significantly affect outcomes, sensitivity analyses were performed to adjust for confounding factors as much as possible. First, we used a Cox proportional hazards regression model (with adjustment for covariates) to assess clinical outcomes. Variables in the multivariate analysis were selected if they were significantly different between the 2 groups ($P < 0.05$) or had predictive values (Supplemental Appendix). Second, we performed propensity score matching between groups. Propensity scores were obtained from logistic regression with covariates of demographics, procedural characteristics, and

medication at discharge. Missing values of the covariates were imputed using multiple imputations to ensure that propensity scores could be calculated for all patients. We used nearest neighbor matching with a caliper size of 0.1 multiplied by the SD for linearly transformed propensity scores (logit transformation).[14] Propensity score matching yielding 1,846 patients in the group with StC time <48 hours matched with 1,846 control subjects in the group with StC time ≥48 hours. The standardized mean difference after propensity score matching was ≤10% across all matched covariates. This finding demonstrates successful balance achievement between the comparison groups (Supplemental Table S1). Third, we performed inverse probability weighting adjustment. The inverse of the propensity score of all variables was assessed using the proportional hazards regression model.

To determine the continuous association between StC time and clinical outcomes, we used a restrictive cubic spline model to graphically display the HRs representing the association of StC time and response. Shaded areas around the curves depict 95% CIs, and solid lines represent HRs for estimates obtained from a regression of restricted cubic splines (6 knots: 0, 24, 48, 72, 96, and 120 hours). The multivariate Cox proportional hazards model for adjusted variables was used as described earlier.

To identify predictors of delayed ICA (StC time ≥48 hours), we performed univariate and multivariate logistic regression analyses. The multivariable Cox regression model was performed on the basis of 24-hour door-to-catheter (DtC) time to investigate the difference in clinical outcomes by DtC time.

All analyses were 2 tailed, and a $P$ value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using the R version 3.6.0 (R Foundation for Statistical Computing).

## RESULTS

**BASELINE CHARACTERISTICS.** Among 13,104 patients with acute MI, 5,856 patients with NSTEMI (StC time <48 hours, n = 3,919 [66.9%]; StC time ≥48 hours, n = 1,937 [33.1%]) were analyzed in this study (**Figure 1, Table 1**). The mean age of the patients was 64.2 ± 12.2 years, and 72% were male. The group with StC time <48 hours had a higher prevalence of typical chest pain (88.1% vs 78.0%; $P < 0.001$), a higher prevalence of previous chest pain before the index time of symptom onset (31.1% vs 28.0%; $P = 0.019$), a lower rate of Killip class 3 (5.3% vs 10.6%; $P < 0.001$), and lower GRACE risk scores (median 116 [IQR: 94-139] vs 128 [IQR: 103-151]; $P < 0.001$) than the group with StC time ≥48 hours. Regarding comorbidities, the group with StC time <48 hours had lower prevalence of hypertension, diabetes, chronic kidney disease (CKD), history of MI, and cardiovascular accident but had higher left ventricular ejection fractions than the group with StC time ≥48 hours. Regarding the extent of coronary disease, 5.6% of patients had left main coronary artery disease. No differences were found in revascularization strategy (PCI or coronary artery bypass surgery) between the 2 groups. In periprocedural outcomes, acute kidney injury did not differ between the 2 groups, and a higher prevalence of new HF (0% vs 0.7%; $P < 0.001$) was reported in the group with StC time <48 hours. With regard to

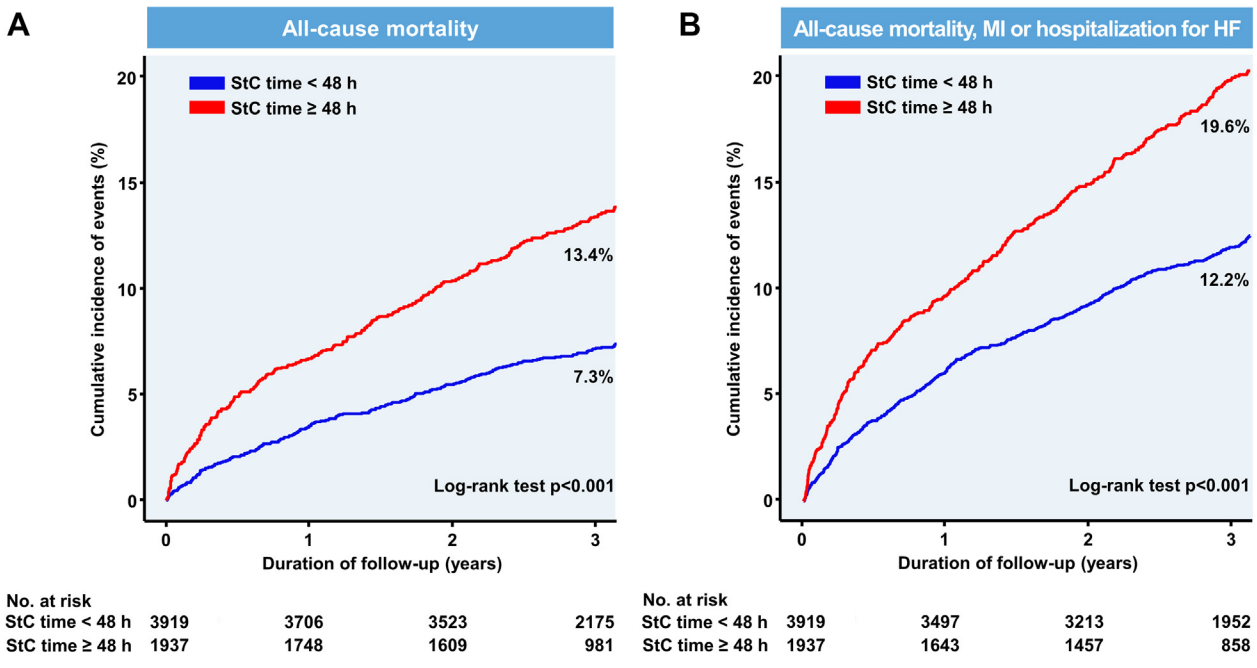
**TABLE 1 Baseline Clinical Characteristics**

| | Total (N = 5,856) | StC Time <48 h (n = 3,919) | StC Time ≥48 h (n = 1,937) | *P* Value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, y | 64.2 ± 12.2 | 63.1 ± 12.1 | 66.4 ± 12.2 | <0.001 |
| Male | 4,216 (72.0) | 2,892 (73.8) | 1,324 (68.4) | <0.001 |
| Body mass index, kg/m$^2$ | 24.0 (22.0-26.0) | 24.1 (22.1-26.1) | 23.8 (21.8-26.0) | 0.006 |
| On admission | | | | |
| Typical chest pain | 4,962 (84.7) | 3,451 (88.1) | 1,511 (78.0) | <0.001 |
| Previous chest pain[a] | 1,760 (30.1) | 1,217 (31.1) | 543 (28.0) | 0.019 |
| Dyspnea | 1,372 (23.4) | 754 (19.2) | 618 (31.9) | <0.001 |
| Killip class 3 | 412 (7.0) | 207 (5.3) | 205 (10.6) | <0.001 |
| Initial Q wave on ECG | 452 (7.7) | 280 (7.1) | 172 (8.9) | 0.022 |
| ST-segment deviation | 1,702 (29.1) | 1,137 (29.0) | 565 (29.2) | 0.926 |
| GRACE score | 119 (97-143) | 116 (94-139) | 128 (103-151) | <0.001 |
| First medical contact | | | | <0.001 |
| EMS | 603 (10.3) | 471 (12.0) | 132 (6.8) | |
| Non-PCI center | 3,038 (51.9) | 2,023 (51.6) | 1,015 (52.4) | |
| PCI center | 2,215 (37.8) | 1,425 (36.4) | 790 (40.8) | |
| Process of care index | | | | |
| Symptom-to-door time, h | 7.0 (2.4-24.0) | 4.4 (1.9-10.1) | 48.0 (11.9-98.0) | <0.001 |
| Door-to-catheter time, h | 13.7 (4.1-24.9) | 9.6 (3.2-17.6) | 28.8 (11.1-60.3) | <0.001 |
| Symptom-to-catheter time, h | 26.9 (13.7-63.2) | 17.5 (9.5-27.0) | 90.8 (63.5-157.1) | <0.001 |
| Cardiovascular risk factors | | | | |
| Hypertension | 3,171 (54.1) | 2,052 (52.4) | 1,119 (57.8) | <0.001 |
| Diabetes mellitus | 1,762 (30.1) | 1,104 (28.2) | 658 (34.0) | <0.001 |
| Dyslipidemia | 724 (12.4) | 492 (12.6) | 232 (12.0) | 0.556 |
| Chronic kidney disease | 1,060 (18.1) | 585 (14.9) | 475 (24.5) | <0.001 |
| History of MI | 519 (8.9) | 338 (8.6) | 181 (9.3) | 0.388 |
| History of PCI | 375 (6.4) | 257 (6.6) | 118 (6.1) | 0.530 |
| History of CVA | 452 (7.7) | 282 (7.2) | 170 (8.8) | 0.037 |
| Familial history | 405 (6.9) | 301 (7.7) | 104 (5.4) | 0.001 |
| LVEF | 56.0 (49.0-62.0) | 56.0 (50.0-62.0) | 55.0 (47.0-61.0) | <0.001 |

Values are mean ± SD, n (%), or median (interquartile range). [a]Previous chest pain before the index time of symptom onset.

CVA = cerebrovascular accident; ECG = electrocardiography; EMS = emergency medical services; GRACE = Global Registry of Acute Coronary Events; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; StC = symptom-to-catheter.

**FIGURE 2 Cumulative Incidence of Primary and Secondary Endpoints**




Kaplan-Meier curves show the rates of **(A)** 3-year all-cause mortality and **(B)** the 3-year composite of all-cause death, myocardial infarction (MI), or hospitalization for heart failure (HF) between the group with symptom-to-catheter (StC) time <48 hours and the group with StC time ≥48 hours among patients with non-ST-segment elevation MI.

discharge medications, patients were treated with fair compliance to contemporary guidelines for medical treatment, including dual antiplatelet therapy (92.4%), beta-blockers (81.6%), renin-angiotensin-aldosterone system inhibitors (79.0%), and statins (93.1%).

**CLINICAL OUTCOMES.** The median follow-up duration was 1,099 days (IQR: 1,057-1,130 days). The primary endpoint (all-cause mortality) occurred in 7.3% of patients in the group with StC time <48 hours compared with 13.4% of those in the group with StC time ≥48 hours (3-year adjusted HR: 0.76; 95% CI: 0.64-0.91; $P = 0.002$) (**Figure 2A, Table 2**). The secondary endpoint (a composite of all-cause mortality, recurrent MI, or hospitalization for HF) occurred in 12.2% of patients in the group with StC time <48 hours group compared with 19.6% of those in the group with StC time ≥48 hours (3-year adjusted HR: 0.84; 95% CI: 0.73-0.96; $P = 0.015$) (**Figure 2B, Table 3**).

In the individual clinical outcomes, the group with StC time <48 hours had better clinical outcomes of cardiac death and hospitalization for HF. No differences were found in recurrent MI and any revascularization between the 2 groups. These results were consistently observed in divided groups according to the StC median time as well as both propensity score matching and inverse probability weight adjustment for baseline characteristics and confounding factors (Supplemental Tables S1 to S7, Supplemental Figures S2 to S4).

The continuous association of StC time and risk for the primary and secondary endpoints showed a shorter StC time (reference 48 hours), and lower adjusted HR reduction was observed (**Figure 3**). No differences were observed in primary and secondary endpoints in patients regarding invasive strategy timing within 24 hours on the basis of DtC time (all-cause death: 3-year adjusted HR: 0.98; 95% CI: 0.82-1.18; $P = 0.846$) (Supplemental Table S8).

**ALL-CAUSE MORTALITY ACCORDING TO SUBGROUP ANALYSIS.** Subgroup analysis was performed for age, sex, typical chest pain, dyspnea, ST-segment deviation, use of emergency medical services (EMS), hypertension, diabetes mellitus, CKD, left ventricular dysfunction, GRACE risk score, and PCI (**Figure 4**). The lower risk for all-cause mortality in the group with StC time <48 hours was consistent in all subgroups. Notably, EMS use (HR: 0.31; 95% CI: 0.19-0.52)

showed a lower risk for all-cause mortality than no EMS use (HR: 0.54; 95% CI: 0.46-0.65; *P* for interaction = 0.008). Patients without CKD (HR: 0.56; 95% CI: 0.44-0.72) had a lower risk for all-cause mortality than those with CKD (HR: 0.70; 95% CI: 0.55-0.88; *P* for interaction = 0.027).

**INDEPENDENT PREDICTORS OF DELAYED ICA IN PATIENTS WITH NSTEMI.** Multivariate logistic regression analysis on the basis of baseline characteristics revealed that older age (75 years or older), symptom presentation with atypical chest pain, dyspnea, no use of EMS, no ST-segment deviation, CKD, and GRACE score >140 were associated with delayed ICA (Supplemental Table S9).

**TABLE 2 Baseline Procedure and Discharge Medication Characteristics**

| | Total (N = 5,856) | StC Time <48 h (n = 3,919) | StC Time ≥48 h (n = 1,937) | *P* Value |
|---|---|---|---|---|
| Extent of coronary disease | | | | |
| Left main coronary artery | 330 (5.6) | 185 (4.7) | 145 (7.5) | <0.001 |
| Number of vessels involved | | | | <0.001 |
| 0 | 409 (7.0) | 301 (7.7) | 108 (5.6) | |
| 1 | 2,622 (44.8) | 1,825 (46.6) | 797 (41.1) | |
| 2 | 1,684 (28.8) | 1,105 (28.2) | 579 (29.9) | |
| 3 | 1,141 (19.5) | 688 (17.6) | 453 (23.4) | |
| ACC/AHA type B2/C lesion | 4,212 (71.9) | 2,827 (72.1) | 1,385 (71.5) | 0.634 |
| Pre-PCI TIMI flow grade 0 | 1,422 (24.3) | 1,030 (26.3) | 392 (20.2) | <0.001 |
| Procedural characteristics | | | | |
| Transradial approach | 2,632 (44.9) | 1,759 (44.9) | 873 (45.1) | 0.915 |
| CAG result | | | | 0.706 |
| PCI | 5,024 (85.8) | 3,358 (85.7) | 1,666 (86.0) | |
| No PCI | 832 (14.2) | 561 (14.3) | 271 (14.0) | |
| Periprocedural outcomes | | | | |
| Acute kidney injury | 21 (0.4) | 11 (0.3) | 10 (0.5) | 0.240 |
| New heart failure | 14 (0.2) | 1 (0) | 13 (0.7) | <0.001 |
| CABG | 90 (1.5) | 53 (1.4) | 37 (1.9) | 0.129 |
| Medication at discharge | | | | |
| Dual antiplatelet agent | 5,413 (92.4) | 3,604 (92.0) | 1,809 (93.4) | 0.058 |
| Aspirin | 5,685 (97.1) | 3,804 (97.1) | 1,881 (97.1) | 0.992 |
| $P2Y_{12}$ inhibitor | 5,484 (93.6) | 3,652 (93.2) | 1,832 (94.6) | 0.046 |
| RAAS inhibitor | 4,624 (79.0) | 3,127 (79.8) | 1,497 (77.3) | 0.029 |
| Beta-blocker | 4,781 (81.6) | 3,218 (82.1) | 1,563 (80.7) | 0.199 |
| Statin | 5,454 (93.1) | 3,669 (93.6) | 1,785 (92.2) | 0.042 |

Values are n (%).

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft; CAG = coronary angiography; RAAS = renin-angiotensin-aldosterone system; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

## DISCUSSION

In this study we investigated 3-year clinical outcomes among patients with NSTEMI regarding invasive strategy timing on the basis of the time of symptom onset. The main findings of the present study are as follows. First, to the best of our knowledge, the present study is the first observation of long-term clinical outcomes according to early invasive strategy on the basis of symptom onset among patients with NSTEMI. Regarding StC time, the group with StC time <48 hours had lower 3-year all-cause mortality than the group with StC time ≥48 hours (**Central Illustration**). Second, in the subgroup analysis, the lower mortality rate of the group with StC time <48 hours was consistent regardless of the subcategory variables. Notably, EMS use and no CKD were associated with a lower risk for all-cause mortality than no EMS use and CKD, respectively.

The patients enrolled in this study were diagnosed with NSTEMI. Thus, an early invasive strategy is recommended according to the NSTE-ACS guideline.[9] However, similar to the findings of previous studies, no difference was found in all-cause mortality in patients regarding invasive strategy timing within 24 hours on the basis of DtC time.[2-5] In the present study, we observed that the group with StC time <48 hours had lower 3-year all-cause mortality than the group with StC time ≥48 hours. This suggests that total ischemic time should be considered an important factor in reducing all-cause mortality in patients with NSTEMI. This hypothesis could be supported by the results of the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) study, which registered all comers with NSTEMI among 40,494 consecutive PCI-treated patients.[15] In the SWEDEHEART study, despite an unclear method of time calculation, early PCI was associated with a lower risk for 1-year all-cause mortality.

Recent guidelines recommend that an early invasive strategy is not superior to a delayed invasive strategy concerning composite clinical outcomes in patients with NSTE-ACS according to various randomized clinical trials that investigated the optimal timing of ICA and revascularization in patients with NSTE-ACS.[16-18] According to the TIMACS (Early Versus Delayed Timing of Intervention in Patients With Acute Coronary Syndromes) trial, VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) trial, and some meta-analyses, patients with NSTE-ACS with GRACE risk scores of >140 benefited from the early invasive strategy, in terms of clinical outcomes, compared with those with GRACE risk scores of ≤140.[2,4,5] Thus, current guidelines recommend an early invasive strategy in patients with NSTE-ACS with at least 1 of the high-risk criteria: GRACE risk score > 140, established NSTEMI, and dynamic ST/T change (Class 1, Level of Evidence: A).[18] However, even with the early invasive strategy in patients with high-risk NSTE-ACS, no difference was shown in all-cause

**TABLE 3 Comparison of 3-Year Clinical Outcomes According to StC Time**

| | Total (N = 5,856) | StC Time <48 h (n = 3,919) | StC Time ≥48 h (n = 1,937) | Unadjusted | | Multivariable Adjusted[a] | | Propensity Score Matched | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| All-cause mortality | 544 (9.3) | 285 (7.3) | 259 (13.4) | 0.52 (0.44-0.61) | <0.001 | 0.76 (0.64-0.91) | 0.002 | 0.72 (0.59-0.87) | 0.001 |
| CV mortality | 320 (5.5) | 166 (4.2) | 154 (8.0) | 0.51 (0.41-0.64) | <0.001 | 0.77 (0.62-0.97) | 0.026 | 0.74 (0.58-0.94) | 0.014 |
| Recurrent MI | 242 (4.1) | 147 (3.8) | 95 (4.9) | 0.73 (0.56-0.94) | 0.016 | 0.91 (0.70-1.18) | 0.474 | 0.93 (0.70-1.25) | 0.651 |
| Hospitalization for HF | 236 (4.0) | 115 (2.9) | 121 (6.2) | 0.45 (0.35-0.58) | <0.001 | 0.70 (0.54-0.91) | 0.008 | 0.69 (0.52-0.92) | 0.013 |
| Any revascularization | 523 (8.9) | 338 (8.6) | 185 (9.6) | 0.87 (0.72-1.04) | 0.114 | 0.91 (0.76-1.09) | 0.311 | 0.93 (0.75-1.14) | 0.482 |
| Definite/probable ST | 29 (0.5) | 15 (0.4) | 14 (0.7) | 0.51 (0.24-1.05) | 0.066 | 0.58 (0.27-1.23) | 0.152 | 0.70 (0.31-1.57) | 0.384 |
| All-cause mortality, recurrent MI, or hospitalization for HF | 859 (14.7) | 479 (12.2) | 380 (19.6) | 0.59 (0.52-0.68) | <0.001 | 0.84 (0.73-0.96) | 0.015 | 0.83 (0.71-0.97) | 0.020 |

Values are n (%, cumulative incidence). [a]Adjusted variables: age ≥75 years, sex, body mass index, Killip class 3, initial Q wave, ST-segment deviation, GRACE (Global Registry of Acute Coronary Events) risk score >140, hypertension, diabetes mellitus, chronic kidney disease, previous history of MI, cerebrovascular disease, LVEF <50%, left main or multivessel disease, and discharge medication comprising renin-angiotensin-aldosterone system inhibitors and statins.

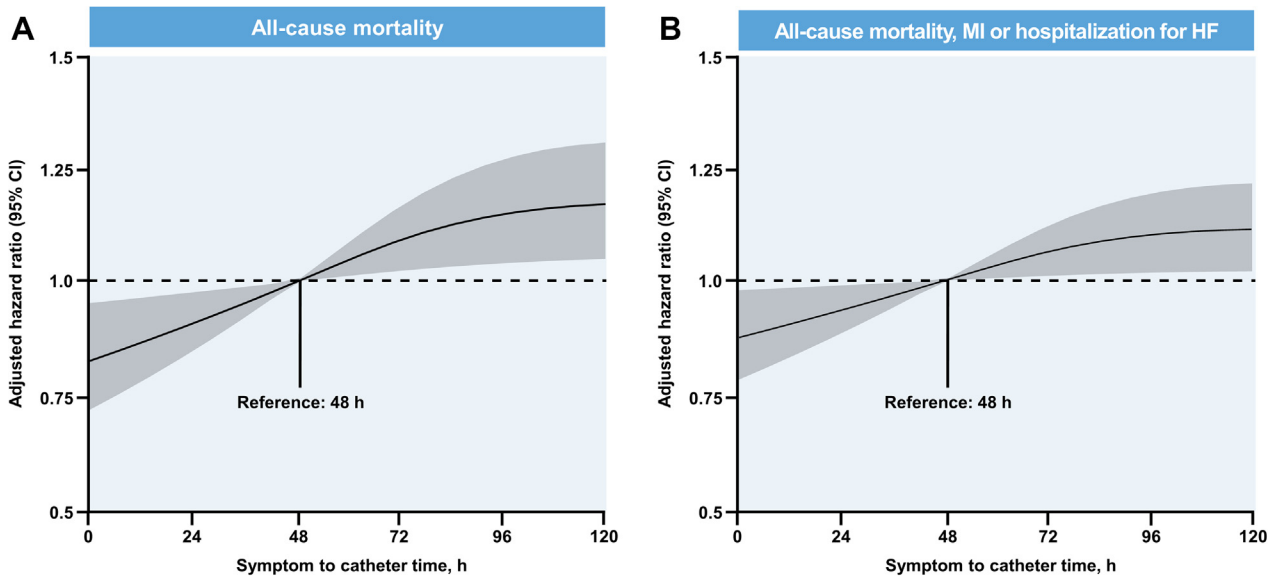
CV = cardiovascular; ST = stent thrombosis; other abbreviations as in Table 1.

mortality.[2,4,5,16,17,19] Only 1 meta-analysis demonstrated that an early invasive strategy had a beneficial trend for all-cause mortality and significantly reduced the composite endpoint in patients with NSTE-ACS but increased the rate of revascularization.[20] Moreover, in the RIDDLE-NSTEMI (Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non ST-Segment Elevation Myocardial Infarction) trial, which reported clinical outcomes according to ICA timing among patients with NSTEMI, the median time of ICA in the delayed group was 61 hours.[21] Despite the violation of current guidelines that permit ICA after 24 hours for the delayed group, no difference was noted in 3-year mortality between the immediate intervention and delayed intervention groups.[15]

These discrepancies in clinical outcomes among patients with NSTE-ACS classified as high risk could be explained as a limitation of the randomized clinical trials, that is, the definition of an early invasive strategy that ICA within 24 hours is not from the time of symptom onset but from the hospitalization time or randomization time. To reduce confounding, most studies, including the TIMACS trial, enrolled patients who had symptoms within 24 hours.[2,4] However, in real-world practice, a considerable number of patients had delayed hospitalization after symptom onset. Compared with previous randomized controlled trials among patients with NSTE-ACS, the difference in mortality between the previous trials and the present study may be explained by the fact that the previous trials did not consider an important factor, symptom duration. Recently, Cha et al[22] reported association between delayed hospitalization and clinical outcomes in patients with NSTEMI. In a 3-year follow-up study, the proportion of patients with NSTEMI with delayed hospitalization (arrived at the hospital 24 hours after symptom onset) was 27.9%. A 1.6-fold increase in mortality was observed in the delayed hospitalization group compared with patients who arrived at the hospital within 24 hours. In this context, similar to patients with ST-segment elevation MI,[23] StC time may be suggested as a predictor of clinical outcomes among patients with NSTEMI rather than DtC time. This study suggests the necessity of reducing myocardial ischemic time by minimizing symptom duration to improve clinical outcomes for patients with NSTEMI, as for those with ST-segment elevation MI. However, the present study was not randomized; therefore, the results should be considered hypothesis generating, highlighting the need for further research.

In a subgroup analysis, this study consistently showed that all-cause mortality was lower in the group with StC time <48 hours than in the group with StC time ≥48 hours. Notably, these results were based on the all-comers registry, except for patients with very high risk. To the best of our knowledge, this study is the first large-scale observation to show an association between an early invasive strategy on the basis of the symptom onset time and all-cause mortality in patients with NSTEMI. In particular, the group with StC time <48 hours had a relatively lower risk for mortality among those without CKD than those with CKD (*P* for interaction = 0.027). This suggests that patients with NSTEMI with CKD may have an increased possibility of delayed ICA because of the effect of comorbidities. Moreover, group with StC time <48 hours had a relatively lower risk for mortality among patients who used EMS than those who

**FIGURE 3** **Continuous Association of StC Time and Primary and Secondary Endpoints**




The continuous association of StC time and risk for the **(A)** the primary and **(B)** secondary endpoints showed shorter StC time (reference 48 hours) and a lower adjusted HR reduction. **Shaded areas** around the curves depict 95% CIs, and **solid lines** represents HRs for estimates obtained from a regression of restricted cubic splines (6 knots: 0, 24, 48, 72, 96, and 120 hours). Abbreviations as in Figure 2.

did not use EMS (*P* for interaction = 0.008), which may emphasize the importance of using EMS for NSTEMI. Meanwhile, concerning the GRACE risk score, both high-risk and low- to intermediate-risk groups showed a reduced risk for mortality in the group with StC time <48 hours with borderline significant interaction (*P* for interaction = 0.087).

We investigated the predictors that affect delayed ICA in terms of patient characteristics. In multivariable logistic analysis, older age, the presence of nonspecific symptoms such as atypical chest pain and dyspnea, no use of EMS, no ST-segment deviation, CKD, and GRACE risk score >140 were independent predictors of delayed ICA. Consistent with previous studies,[18,22] patients with nonspecific symptoms, older age, or not using EMS may tend to underestimate their symptoms; that is, StC time may be prolonged in these patients. No ST-segment deviation on electrocardiography and CKD were predictors of delayed ICA. These observations may explain the fact that relatively stable signs on electrocardiography and the need for prehydration before using contrast agent may affect physicians' decisions regarding ICA in real-world practice. Moreover, GRACE risk score >140 conferred a higher risk for delayed ICA. In other words, this observation showed the need for an early invasive strategy for patients with NSTEMI to reduce adverse clinical outcomes, which was consistent with recent guidelines.[16-18]

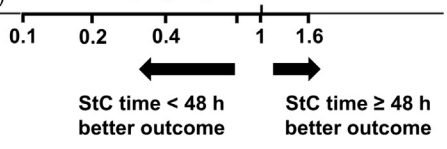
**STUDY LIMITATIONS.** First, this study had an inherent limitation because nonrandomized, prospective, observational registry data were used in the analysis. Despite the adjustments made to minimize bias with extensive sensitivity analyses for different baseline characteristics and measured or unmeasured confounders, the possibility of physician-generated selection bias in the treatment strategy is inevitable.

Second, ICA timing for the patients in this multicenter registry was at the operator's discretion in the individual institutions. Thus, our registry had a probability of healthy candidate bias regarding ICA timing, which should be clarified in a randomized controlled trial to support the hypothesis. However, the KAMIR-NIH registry used standardized definitions for all collected variables and is regulated and monitored by the National Institutes of Health.[8]

Third, compared with the group with StC time <48 hours, the DtC time of the group with StC time >48 hours was longer, which may have affected clinical outcomes. There was little evidence of optimal timing

**FIGURE 4** Exploratory Subgroup Analysis

| | StC time < 48 h | StC time ≥ 48 h | Hazard Ratio (95% CI) | Hazard Ratio (95% CI) | *P* Value for interaction |
|---|---|---|---|---|---|
| Age < 75 years | 143/3167 (4.5%) | 131/1374 (9.5%) | 0.46 (0.36 – 0.58) | | 0.522 |
| Age ≥ 75 years | 142/752 (18.9%) | 128/563 (22.7%) | 0.79 (0.63 – 1.00) | | |
| Male | 181/2892 (6.3%) | 164/1324 (12.4%) | 0.48 (0.39 – 0.60) | | 0.666 |
| Female | 104/1027 (10.1%) | 95/613 (15.5%) | 0.63 (0.47 – 0.83) | | |
| Typical chest pain | 200/3451 (5.8%) | 148/1511 (9.8%) | 0.57 (0.46 – 0.71) | | 0.063 |
| Atypical chest pain | 85/468 (18.2%) | 111/426 (26.1%) | 0.67 (0.50 – 0.88) | | |
| Dyspnea | 89/754 (11.8%) | 113/618 (18.3%) | 0.61 (0.46 – 0.81) | | 0.379 |
| No dyspnea | 196/3165 (6.2%) | 146/1319 (11.1%) | 0.54 (0.44 – 0.67) | | |
| ST segment deviation | 104/1137 (9.1%) | 85/565 (15.0%) | 0.57 (0.43 – 0.77) | | 0.875 |
| No ST segment deviation | 181/2782 (6.5%) | 174/1372 (12.7%) | 0.49 (0.40 – 0.60) | | |
| Use of EMS | 33/471 (7.0%) | 27/132 (20.5%) | 0.31 (0.19 – 0.52) | | 0.008 |
| No use of EMS | 252/3448 (7.3%) | 232/1805 (12.9%) | 0.54 (0.46 – 0.65) | | |
| Hypertension | 191/2052 (9.3%) | 171/1119 (15.3%) | 0.58 (0.47 – 0.71) | | 0.877 |
| No hypertension | 94/1867 (5.0%) | 88/818 (10.8%) | 0.44 (0.33 – 0.59) | | |
| Diabetes mellitus | 118/1104 (10.7%) | 125/658 (19.0%) | 0.53 (0.41 – 0.68) | | 0.283 |
| No diabetes mellitus | 167/2815 (5.9%) | 134/1279 (10.5%) | 0.54 (0.43 – 0.68) | | |
| CKD | 133/585 (22.7%) | 144/475 (30.3%) | 0.70 (0.55 – 0.88) | | 0.027 |
| No CKD | 152/3334 (4.6%) | 115/1462 (7.9%) | 0.56 (0.44 – 0.72) | | |
| LV dysfunction (EF < 50%) | 138/910 (15.2%) | 133/591 (22.5%) | 0.64 (0.50 – 0.81) | | 0.106 |
| No LV dysfunction | 147/3009 (4.9%) | 126/1346 (9.4%) | 0.50 (0.40 – 0.64) | | |
| GRACE score ≤ 140 | 104/3032 (3.4%) | 80/1255 (6.4%) | 0.53 (0.39 – 0.71) | | 0.087 |
| GRACE score > 140 | 181/887 (20.4%) | 179/682 (26.2%) | 0.64 (0.50 – 0.81) | | |
| PCI | 221/3358 (6.6%) | 190/1666 (11.4%) | 0.55 (0.46 – 0.67) | | 0.232 |
| No PCI | 64/561 (11.4%) | 69/271 (25.5%) | 0.41 (0.29 – 0.58) | | |

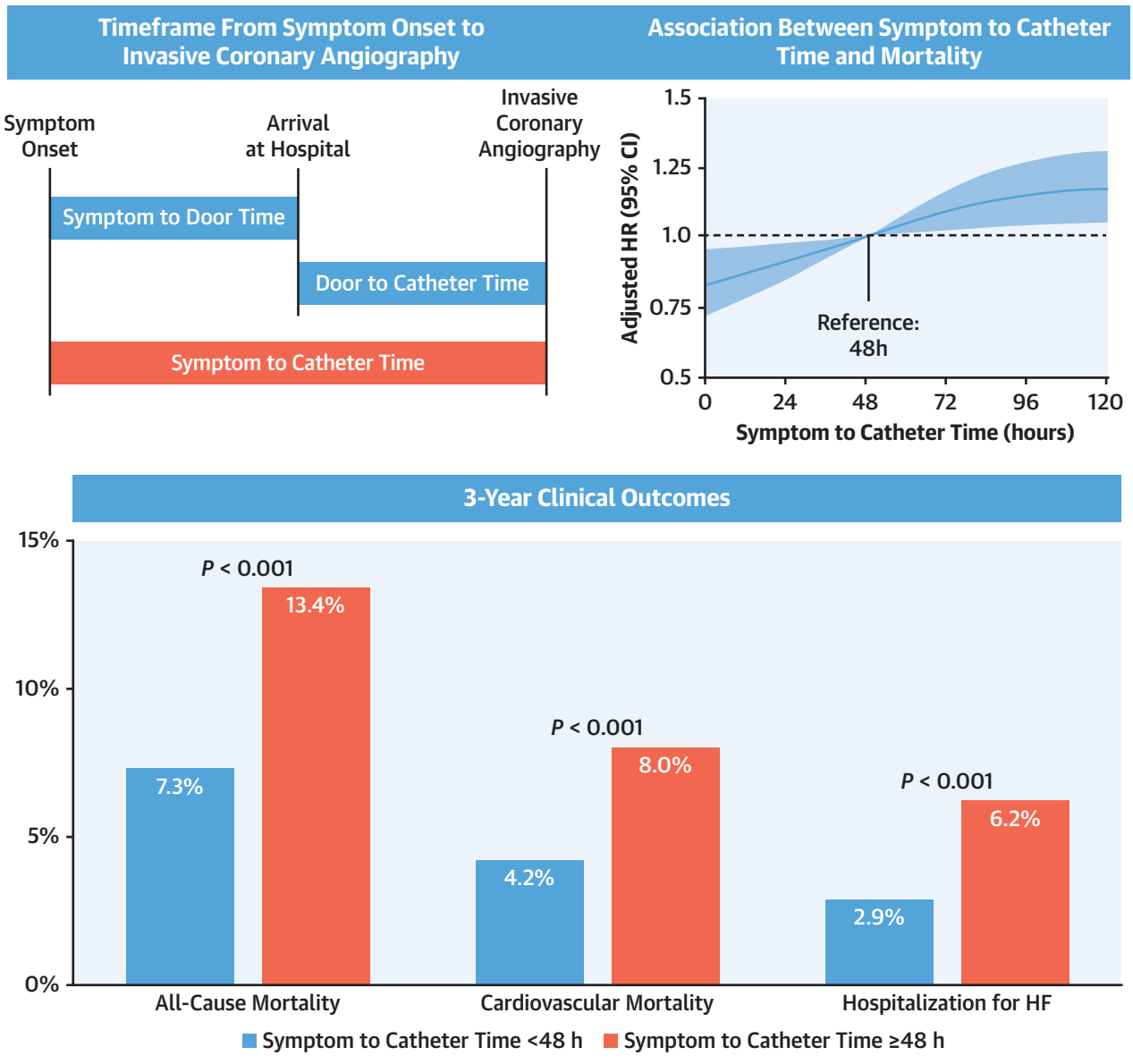



Values are event n/N (%) unless otherwise indicated. CKD = chronic kidney disease; EF = ejection fraction; EMS = emergency medical services; GRACE = Global Registry of Acute Coronary Events; LV = left ventricular; PCI = percutaneous coronary intervention; StC = symptom-to-catheter.

of invasive strategy in patients with delayed hospitalization. The current guidelines recommend that PCI not be performed in patients who have totally occluded infarct arteries >24 hours after symptom onset.[18,19,24] However, there is no study on optimal invasive strategy timing for patients with suspected recent MI, such as initial Q-wave MI in patients with NSTE-ACS. Expert consensus recommends implementing ICA for those patients at an appropriate time on the basis of individual risk.[25] In context, the present study suggests the necessity of education about rapid contact with medical services on the basis of symptom onset time for patients suspected of having NSTE-ACS to prevent poor clinical outcomes.

Fourth, as the present registry data did not collect bleeding events, which might affect worse clinical outcomes, the results should be interpreted with caution.

**CENTRAL ILLUSTRATION** **The 3-Year Outcomes in Patients With NSTEMI According to Symptom to Catheter Time From the KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health) Registry (N = 5,856)**

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**(Top left)** Schema for the time frame from symptom onset to invasive coronary angiography. **(Top right)** The continuous association of symptom to catheter (StC) time and risk for mortality showed that shorter StC time (reference 48 hours) was associated with lower adjusted HR reduction. **(Bottom)** The 3-year clinical outcomes between StC times of <48 and ≥48 hours.

Finally, in the present study, an StC time of 48 hours was established as the cutoff. The current guideline defines an early invasive strategy for high-risk patients with NSTE-ACS as conducting ICA within 24 hours after hospitalization. And most supporting randomized controlled trials for an early invasive strategy enrolled only patients who had symptoms within 24 hours. As there was no study of

patients with NSTE-ACS regarding StC time, the present study set an StC time of 48 hours defined as an early invasive strategy on the basis of the summation of the symptom-to-door time 24 h and DtC time 24 h. The optimal timing from symptoms to ICA was not completely elucidated in patients with NSTEMI, stressing the importance of rapid recourse to health services in case of suspected symptoms of acute coronary syndrome. In context, although our result should be interpreted with caution, the present study emphasizes that reducing both the patient factor (symptom-to-door time) and the intervention factor (DtC time) in an early invasive strategy in patients with NSTEMI may have a better mortality benefit. And this study provides a clue to the optimal timing of ICA for patients with NSTEMI in real-world practice. The results should be considered hypothesis generating, highlighting the need for further randomized clinical trials.

## CONCLUSIONS

In this nationwide, multicenter, prospective registry, an early invasive strategy on the basis of StC time was associated with a decreased risk for all-cause mortality in patients with NSTEMI. Because the study was based on a prospective registry, the results should be considered hypothesis generating, highlighting the need for further research.

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## PERSPECTIVES

**WHAT IS KNOWN?** The current guideline defines an early invasive strategy for high-risk patients with NSTE-ACS as conducting ICA within 24 hours after hospitalization. And most supporting randomized controlled trials for an early invasive strategy enrolled only patients who had symptoms within 24 hours. To date, no study has reported the clinical outcomes of invasive strategy timing on the basis of the time of symptom onset.

**WHAT IS NEW?** In a prospective nationwide Korean registry, an early invasive strategy based on StC time improved all-cause mortality in patients with NSTEMI. These results were consistent regardless of subcategory variables.

**WHAT IS NEXT?** As there are currently no large-scale studies or in-progress randomized clinical trials on clinical outcomes according to invasive strategy timing for patients with NSTEMI, the present study provides a clue regarding the optimal timing of ICA for patients with NSTEMI.

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**KEY WORDS** all-cause mortality, invasive coronary angiography, myocardial infarction, symptom onset

**APPENDIX** For supplemental methods, tables, and figures, please see the online version of this paper.