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Original article

Early versus delayed invasive strategy in patients with non-ST-elevation acute coronary syndrome and concomitant congestive heart failure

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ABSTRACTS

Background: Although there are guidelines that recommend an early invasive strategy in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) and concomitant congestive heart failure (CHF), optimal timing of the invasive strategy remains controversial.
Methods: Among 2045 patients who were admitted owing to NSTE-ACS or CHF, 300 presented with NSTE-ACS and concomitant CHF. Of the 300 patients, we enrolled 160 patients for whom coronary angiography (CAG) during their hospital stay was planned at the time of admission; 64 of these patients were classified into the early invasive group (<24 h) and 96 were classified to the delayed invasive group (≥24 h). We evaluated the primary outcome which was defined as a composite of cardiac mortality, life-threatening arrhythmia, and non-fatal myocardial infarction (MI).
Results: The median time between presentation and CAG was 2 h in the early invasive group and 240 h in the delayed group. During follow-up, the primary outcome was significantly lower in the early invasive group [hazard ratio (HR), 0.52; 95% confidence interval (CI), 0.30–0.87; $p = 0.01$]. After the adjustment of confounding factors, the primary outcome was significantly less frequent (HR, 0.44; 95% CI, 0.23–0.78; $p = 0.004$) in the early invasive group compared to the delayed invasive group.
Conclusions: The early invasive strategy was associated with a lower risk of the composite primary outcome in the long-term follow-up of patients with NSTE-ACS and concomitant CHF.

Introduction

Coronary angiography (CAG) confirms the diagnosis, aids in risk stratification, and helps decide the treatment strategy of non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Early CAG is recommended for those who present with concomitant acute heart failure on the basis of expert opinion [1,2]; the results of meta-analyses, which investigated early vs. delayed invasive strategy for NSTE-ACS, are inconsistent on mortality and myocardial infarction (MI) [3–6].

Approximately, one-quarter of patients with NSTE-ACS present with signs of congestive heart failure (CHF), and CHF has shown to be an independent predictor of in-hospital mortality in patients with NSTE-ACS [7–9]. Therefore, guidelines recommend the immediate invasive strategy in patients with NSTE-ACS concomitant with CHF [10]. However, in clinical practice, emergent CAG is not frequently conducted [11] because many of the patients with NSTE-ACS and concomitant CHF are likely to have high-risk features, such as advanced age, renal insufficiency, and respiratory

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failure, which could be exacerbated by increased burden of catheterization [8,12]. Until now, the optimal timing of the invasive procedure for this subset of patients remains unknown.

Therefore, the purpose of this study was to investigate whether the early invasive strategy improves the long-term outcomes of patients with NSTE-ACS and concomitant CHF.

Materials and methods

Study population

This observational cohort study was conducted at Ogaki Municipal Hospital from January 2012 to August 2015. Patients were eligible for enrollment if they presented with both NSTE-ACS and concomitant CHF, and plans to undergo CAG during the hospital stay were determined at the time of admission. NSTE-ASC was defined as ST-segment changes on electrocardiography (ECG) indicating ischemia [ST-segment depression or transient elevation ($\geq$1 mm) in at least two contiguous leads] or positive biomarkers indicating myocardial necrosis [troponin I $\geq$ 0.1 ng/ml or creatine phosphokinase-myocardial band (CK-MB) above the upper limit of normal]. CHF was diagnosed on the basis of Framingham heart failure criteria [13]. Supplemental Table 1 shows the criteria for diagnosis of CHF. CHF was diagnosed if at least two major criteria or one major and two minor criteria were present. Minor criteria were acceptable only if they did not result from another medical condition, such as chronic lung disease, cirrhosis, and the nephrotic syndrome. The major exclusion criteria were as follows: acute ST-segment elevation of $\geq$1 mV for 20 min, cardiogenic shock, severe systemic illness, severe valvular disease, and unsuitability for catheterization (i.e. patient with severe dementia, high frailty, who did not agree catheterization, and other conditions). The indication for revascularization was based on established European, US, and Japanese guidelines [14,15]. This study was approved by the research review board of Ogaki Municipal Hospital. Moreover, this study was conducted in accordance with the principles of the Helsinki Declaration. All patients consented to their participation in this study.

Follow-up, outcome and definitions

For the present investigation, the longest time frame possible for follow-up was considered for analysis. The primary outcome was a composite of cardiac mortality, life-threatening arrhythmia, and non-fatal MI.

Demographic, angiographic, and procedural data were collected from hospital charts and hospital databases. Follow-up data were obtained from hospital charts and by contacting the patients on the telephone.

Invasive strategy was defined as CAG during the hospital stay that was scheduled at the time of admission. Patients were stratified into 2 groups according to the timing of CAG: early ($<$24 h) or delayed ($\geq$24 h). The timing of invasive strategy was at the discretion of each attending physician. Life-threatening arrhythmia was defined as sustained ventricular tachycardia (VT), ventricular fibrillation, and asystole. Cardiac death was defined as death resulting from an acute myocardial infarction, fatal arrhythmia, and progression of heart failure. Taking into consideration the presence or absence of elevated CK-MB at baseline, the timing of occurrence, and the association of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), MI was diagnosed on the basis of acuity (Supplemental Table 2) [16]. Stent thrombosis was defined according to the academic research consortium definitions [17]. Acute kidney injury (AKI) was defined as an absolute increase in serum creatinine at least 0.3 mg/dl within 48 h or by a 50% increase in serum creatinine from baseline within seven days [18]. Bleeding complications were counted according to the thrombolysis in myocardial infarction (TIMI) major or minor criteria [19]. No-reflow is defined as slow-flow in the affected vessel (TIMI flow $\leq$2) and lack of contrast uptake blush by the subtended myocardium without angiographic evidence of mechanical vessel obstruction [20,21].

Statistical analysis

Continuous variables are summarized as means and standard deviation or median and interquartile range (IQR), and categorical variables are shown as numbers and proportions. Continuous variables were compared using Student's *t*-test or Wilcoxon rank-sum test based on their distributions. Categorical variables were compared with chi-squared tests.

Outcomes based on time to first event were assessed using comparison of Kaplan–Meier-based cumulative incidence rate with the log-rank test. On-treatment analysis was used for the complication of invasive procedure. We calculated the hazard ratio (HR) and 95% confidence intervals (CI) using Cox's proportional hazards regression analysis. When performing multivariate Cox's proportional hazards regression analysis, we used bypass-graft flow volume $\geq$10 ml/min as a substitute for the final TIMI 3 flow grade in CABG patients.

A propensity score indicating the predicted probability of early invasive strategy that was conditional on the observed covariates was calculated from the logistic equation for each patient. The following variables were included in the logistic regression model to calculate the propensity score: age, sex, prior history of CHF, the Global Registry of Acute Coronary Events (GRACE) risk score, baseline serum albumin levels, and estimated glomerular filtration rate. The C-statistic was 0.66, and the Hosmer–Lemeshow test *p*-value was 0.33. We performed rigorous adjustment for significant differences in the baseline characteristics of patients matched by propensity score. Clinical outcomes in the matched population were analyzed by Kaplan–Meier curve with the log-rank test and Cox proportional hazards regression. We performed explorative sub group analysis between those aged $<$75 and $\geq$75 years old, those with and without chronic kidney disease (CKD), and those with and without severe respiratory failure. Because all the patients suffered from some degree of respiratory failure due to CHF, we defined severe respiratory failure as those who required mechanical ventilation with intubation or non-invasive positive pressure ventilation.

All statistical analyses were performed using JMP software version 13.1 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). A *p*-value of $<$0.05 was considered statistically significant.

Results

Characteristics of study population

Among 2045 patients who were admitted owing to NSTE-ACS or CHF during the study period, we identified 300 eligible subjects who presented with NSTE-ACS and concomitant CHF. Of those 300 patients, 140 were excluded because they were unsuitable for catheterization. Finally, we enrolled 160 patients who were treated with invasive strategy. Of those 160 patients, CAG was planned at an early time-point ($<$24 h) in 64 patients and at a delayed time-point ($\geq$24 h) in 96 patients (Fig. 1). Clinical characteristics of the recruited patients are summarized in Table 1. The mean age was 74.5 years, 58.8% of the patients were male, 77.0% of patients had elevated troponin at presentation, 94.4% of patients had ST deviation on ECG at presentation, and the mean GRACE risk score

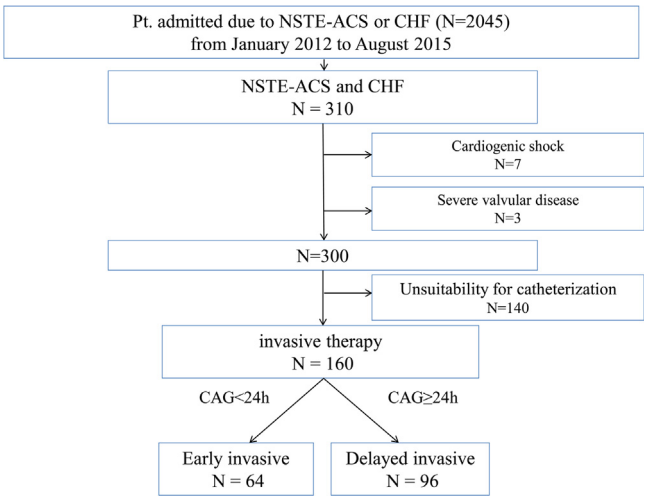

Fig. 1. Flowchart detailing the study design. Pt., patient; CHF, congestive heart failure; NSTE-ACS, non-ST elevation acute coronary syndrome; CAG, coronary angiography.

was 227 points in all patients. The prevalence of prior MI and prior CHF were more frequent in the delayed invasive group; GRACE risk score was similar between the two groups. Both serum CK-MB levels at arrival and peak CK-MB levels were slightly higher in the early invasive group.

As reference, clinical characteristics of excluded 140 patients are summarized in Supplemental Table 3.

Coronary angiographical and procedural characteristics

The angiographic and procedural characteristics are shown in Table 2. Briefly, the median time to CAG was 2 h in the early invasive group and 240 h in the delayed invasive group. Patients in the early invasive group were more likely to have a culprit of left main (LM) lesion, had more acute thrombotic occlusion, and they were more likely to have a higher chance of intra-aortic balloon pumping. On the other hand, the delayed invasive group had more triple-vessel disease (TVD). Three patients in the early invasive group and fourteen patients in the delayed invasive group did not undergo either PCI or CABG after CAG. In those patients, four patients had unsuitable anatomy for revascularization, three patients had no evidence of significant stenosis on major epicardial artery, three patients did not undergo revascularization at the discretion of physician, two patients rejected PCI, two patients rejected CABG, two patients died before the day of planned CABG, and one patient did not undergo PCI because of CKD.

Outcome in early and delayed invasive group

Median length of follow-up was 1236 (IQR = 844, 1619) days with 98.1% follow-up rate. In the delayed invasive group, urgent CAG before 24 h was necessary in nine patients. Of them, eight patients crossed over due to re-MI and corresponding elevation of CK and CK-MB levels after admission; however, there was no TIMI 0/1 flow grade in those patients. The other one patient crossed over owing to hemodynamical instability. Urgent CAG after 24 h was necessary in 13 patients in the delayed invasive group before the improvement of CHF. The indication of urgent CAG was as follows: life-threatening arrhythmia in seven patients, recurrent exacerbation of CHF in two, refractory angina in one, and hemodynamical instability in one.

On Kaplan–Meier event-free survival analysis, the early invasive group was associated with a lower risk of primary outcome than the delayed invasive group (HR, 0.52; 95% CI, 0.30–0.87; $p = 0.01$) (Fig. 2A). On landmark analysis, the incidence of the primary outcome during the 14 days was lower in the early invasive group than the delayed invasive group (HR, 0.19; 95% CI, 0.03–0.67; $p = 0.01$); the primary outcome was numerically lower in early invasive group after 14 days (HR, 0.66; 95% CI, 0.36–1.7; $p = 0.15$) (Fig. 2B). After adjusting for confounding factors, early invasive strategy was significantly associated with lower incidence of primary outcome (HR, 0.44; 95% CI, 0.23–0.78; $p = 0.004$) (Table 3). Final TIMI 3 flow grade was also associated with a lower incidence of the primary outcome; higher GRACE risk score was a predictor of adverse outcome. The length of stay was similar between the early and delayed invasive group [median, 24.5 days, IQR (16–31) in the early invasive group; 22 days, IQR (16.3–32.8) in the delayed invasive group; $p = 0.97$], even excluding patients discharged due to death [median, 24.5 days, IQR (16–31); 22 days, IQR (17–32.5); $p = 0.89$].

In propensity score matched cohort, the early invasive group was associated with a lower risk of primary outcome than the delayed invasive group (HR, 0.56; 95% CI, 0.30–0.99; $p = 0.05$) (Fig. 2C). On landmark analysis, the incidence of the primary outcome during the 14 days was lower in the early invasive group than the delayed invasive group (HR, 0.14; 95% CI, 0.007–0.77; $p = 0.02$); however, the incidence of the primary outcome after 14 days was not significantly different between the two groups (HR, 0.68; 95% CI, 0.36–1.27; $p = 0.23$) (Fig. 2D). After adjusting for culprit lesions, TVD, and final TIMI3 flow grade, early invasive strategy was significantly associated with lower incidence of primary outcome (HR, 0.45; 95% CI, 0.22–0.87; $p = 0.02$).

Explorative subgroup analyses revealed significant between-group differences with respect to severe respiratory failure. The early invasive strategy was more efficient than the delayed invasive strategy in patients with severe respiratory failure; however, the benefit of early invasive strategy was not observed in those without severe respiratory failure. There was no significant between-group difference with respect to those aged <75 or ≥ 75 years old, and the presence or absence of CKD (Fig. 3).

As reference, clinical outcome of the excluded 140 patients is shown in Supplemental Figure 1.

Complications of invasive procedure

Table 4 shows the incidence of procedure complications. AKI and bleeding complications occurred more frequently in the early invasive strategy group. As shown in Table 2, the total amount of contrast media was not different between the two groups. After adjusting contrast media volume, the incidence of AKI was higher in the early invasive group (odds ratio, 3.08; 95% CI, 1.21–7.89; $p = 0.02$).

Discussion

In this study, we compared between the early and delayed invasive strategy used among the patients with NSTE-ACS and concomitant CHF on long-term outcome. Our study focused on the patients that presented with NSTE-ACS and concomitant CHF. Furthermore, we provided precise data of angiography in these specific patients. The main findings of our study were as follows:

1) After adjustment for confounding factors, early invasive therapy was associated with lower incidence of primary outcome (cardiac mortality, life-threatening arrhythmia, and non-fatal MI).
2) However, the risk of bleeding complications and AKI were higher in the early invasive group.

Table 1
Baseline patient clinical characteristics and medication at discharge.

Patients: *n*	All patients			Propensity-matched patients		
	Early (*n* = 64)	Delayed (*n* = 96)	*p*-Value	Early (*n* = 60)	Delayed (*n* = 60)	*p*-Value
Clinical baseline characteristics						
Mean (SD) age (years)	74.9 (12.0)	74.1 (10.4)	0.65	74.4 (12.0)	74.3 (11.2)	0.94
Male sex	35 (54.7%)	59 (61.5%)	0.39	34 (56.7%)	36 (60.0%)	0.71
Diabetes mellitus	39 (60.9%)	57 (59.4%)	0.84	37 (61.7%)	34 (56.7%)	0.58
Hypertension	45 (71.4%)	64 (66.7%)	0.53	44 (74.6%)	40 (66.7%)	0.34
Dyslipidemia	37 (57.8%)	60 (62.5%)	0.55	35 (58.3%)	38 (63.3%)	0.57
Smoking history	32 (50.0%)	54 (56.3%)	0.44	30 (50.0%)	31 (51.7%)	0.86
Prior myocardial infarction	10 (15.6%)	29 (30.2%)	0.03	9 (15.0%)	13 (21.7%)	0.35
Prior heart failure	4 (6.3%)	27 (28.1%)	0.0003	4 (6.7%)	4 (6.7%)	1.0
Prior PCI	15 (23.4%)	33 (34.4%)	0.14	14 (23.3%)	15 (25.0%)	0.83
Prior CABG	5 (7.8%)	13 (13.5%)	0.25	4 (6.7%)	6 (10.0%)	0.51
Liver disease	3 (4.7%)	3 (3.1%)	0.61	2 (3.3%)	1 (1.7%)	0.56
Lung disease	6 (9.4%)	8 (8.3%)	0.82	6 (10.0%)	5 (8.3%)	0.75
eGFR (ml/min/1.73 m^2)	51.1 (25.5)	44.5 (23.9)	0.10	48.8 (23.5)	48.2 (22.3)	0.88
Albumin (g/dl)	3.69 (0.50)	3.73 (0.51)	0.58	3.73 (0.49)	3.70 (0.49)	0.77
Hemoglobin (g/dl)	11.8 (2.3)	12.2 (2.4)	0.36	11.9 (2.4)	12.4 (2.6)	0.28
Serum Na (mEquiv./l)	135.3 (13.1)	137.6 (3.6)	0.11	135.7 (13.3)	137.8 (3.4)	0.23
BNP (pg/ml)	735 [417, 1293]	899 [524, 1603]	0.12	735 [406, 1347]	941 [530, 1757]	0.08
CK at arrival	173 [101, 311]	135 [84, 223]	0.06	173 [101, 273]	149 [106, 235]	0.60
CK-MB at arrival	17 [12, 26]	14 [9, 20]	0.01	17 [12, 26]	14 [10, 21]	0.11
Peak CK	416 [171, 1100]	195 [104,425]	0.001	416 [173, 1147]	198 [128, 375]	0.004
Peak CK-MB	32 [16, 111]	16 [11, 30]	<0.0001	32 [27, 114]	11 [11, 31]	0.0002
hs-CRP (mg/l)	6.5 [2.7, 22.0]	6.1 [2.2, 18.3]	0.55	5.6 [2.7, 22.0]	7.7 [1.8, 23.9]	0.91
Systolic BP (mmHg)	138 [121, 157]	143 [123, 163]	0.18	138 [122, 165]	141 [122, 162]	0.47
HR (bpm)	96 [77, 115]	99 [84, 117]	0.37	97 [77, 117]	98 [86, 114]	0.52
LVEF (%)	47.2 (11.3)	43.7 (14.8)	0.11	47.5 (11.6)	43.6 (13.8)	0.10
LVDd (mm)	54.8 (6.7)	55.5 (7.5)	0.57	54.9 (6.9)	54.9 (7.7)	0.86
Killip class			0.73			1.0
2	10 (15.6%)	17 (17.7%)		10 (16.7%)	10 (16.7%)	
3	54 (84.4%)	79 (82.3%)		50 (83.3%)	50 (83.3%)	
GRACE risk score	226 (38.4)	228 (36.8)	0.81	225 (36.6)	225 (39.5)	0.95
Elevated troponin[a]	42/53 (79.3%)	62/82 (75.6%)	0.62	38/49 (77.6%)	41/50 (82.0%)	0.58
ST deviation	60 (93.7%)	91 (94.8%)	0.78	56 (93.3%)	56 (93.3%)	1.0
Mechanical ventilation	9 (14.1%)	10 (10.4%)	0.49	8 (13.3%)	5 (8.3%)	0.38
NPPV	17 (26.6%)	27 (28.1%)	0.83	17 (28.3%)	14 (23.3%)	0.53
Medication						
Aspirin	62 (96.9%)	91 (94.8%)	0.52	58 (96.7%)	59 (98.3%)	0.56
Thienopyridine	53 (82.8%)	73 (76.0%)	0.30	50 (83.3%)	47 (78.3%)	0.49
Oral anticoagulant	11 (17.2%)	20 (20.8%)	0.57	10 (16.7%)	13 (21.7%)	0.49
Statin	59 (92.2%)	81 (84.4%)	0.13	55 (91.7%)	52 (86.7%)	0.38
Pimobendan	2 (3.1%)	5 (5.2%)	0.52	2 (3.3%)	1 (1.7%)	0.56
Loop diuretics	43 (67.2%)	80 (83.3%)	0.02	40 (66.7%)	50 (83.3%)	0.04
Mineralocorticoid receptor antagonist	26 (40.6%)	42 (43.8%)	0.70	23 (38.3%)	29 (48.3%)	0.27
Thiazide	4 (6.3%)	7 (7.3%)	0.80	3 (5.0%)	3 (5.0%)	1.0
Tolvaptan	2 (3.1%)	8 (8.3%)	0.16	2 (3.3%)	6 (10.0%)	0.14
ACE-I/ARB	45 (70.3%)	67 (69.8%)	0.94	41 (68.3%)	42 (70.0%)	0.84
Beta-blocker	44 (68.8%)	67 (69.8%)	0.89	41 (68.3%)	42 (70.0%)	0.84
Calcium channel blocker	22 (34.4%)	30 (31.3%)	0.68	22 (36.7%)	21 (35.0%)	0.85

Values are the mean ± standard deviation (SD), *n* (%), or median (interquartile range) as appropriate.
PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; Na, sodium concentration; BNP, brain natriuretic peptide; CK, creatine kinase; CK-MB creatine kinase-myocardial band; hs-CRP, high sensitivity-C reactive protein; BP, blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; NPPV, non-invasive positive pressure ventilation; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a] Elevated troponin was counted only in available patients.

3) Seven patients in the delayed invasive group developed life-threatening arrhythmia and were resuscitated from cardiac arrest during medical therapy for CHF.
4) On angiographic findings, many of those patients revealed advanced coronary artery disease, such as LM lesion, TVD, and chronic total occlusion.

Our findings, which showed improved outcome after early invasive strategy, offers an important message because clinicians tend to avoid the early invasive procedure in patients with severe status due to clinical evidence of CHF [7–9], even in current practice [11], concerning procedural complications. Previous observational studies revealed that patients who presented with NSTE-ACS and concomitant CHF were older and had more co-morbidities, such as decreased renal function or diabetes mellitus, which lead to conservative treatment [7,8]. Accordingly, those patients with NSTE-ACS and concomitant CHF had much higher incidence of in-hospital and mid-term (6 months) mortality as compared to those with NSTE-ACS and no CHF [8,9,22–24]. However, there have been limited data investigating the long-term outcome of this subset of patients. The present study demonstrated the long-term outcome of this specific patient group.

The mechanisms linking early invasive strategy and lower incidence of primary outcome might be complicated and multifactorial. Although a causal link between delayed invasive strategy and adverse outcome has not been established, there are several potential mechanisms: (1) lower rates of recurrent MI in

Table 2
Angiographic and procedural characteristics.

Patients: *n*	All patients			Propensity-matched patients		
	Early (*n* = 64)	Delayed (*n* = 96)	*p*-Value	Early (*n* = 60)	Delayed (*n* = 60)	*p*-Value
Time to CAG (h)	2 [1.5, 3.5]	240 [120,399]	<0.0001	2 [1.5, 3.5]	264 [168,384]	<0.0001
Culprit lesion			0.03			0.03
RCA	14 (21.9%)	28 (29.2%)		13 (21.7%)	20 (33.3%)	
LMT	10 (15.6%)	2 (2.1%)		9 (15.0%)	0 (0.0%)	
LAD	17 (26.6%)	27 (28.1%)		17 (28.3%)	21 (35.0%)	
LCx	12 (18.8%)	15 (15.6%)		11 (18.3%)	6 (10.0%)	
Bypass graft	2 (3.1%)	6 (6.3%)		2 (3.3%)	1 (1.7%)	
Unknown	9 (14.1%)	16 (16.7%)		8 (13.3%)	11 (18.3%)	
Baseline TIMI flow			0.27			0.56
0–1	14 (21.9%)	13 (13.7%)		13 (21.7%)	9 (15.0%)	
2	18 (28.1%)	36 (37.9%)		16 (26.7%)	20 (33.3%)	
3	32 (50.0%)	46 (48.4%)		31 (51.7%)	31 (51.7%)	
Collateral (Rentrop 3)	9 (14.1%)	12 (12.5%)	0.78	9 (15.0%)	8 (13.3%)	0.79
Total occlusion without good collateral	7 (10.9%)	1 (1.0%)	0.004	6 (10.0%)	0 (0.0%)	0.01
Extent of coronary disease						
LMT lesion	26 (40.6%)	23 (24.0%)	0.03	24 (40.0%)	15 (25.0%)	0.08
No. of vessel involved			0.16			0.50
1	5 (7.8%)	8 (8.3%)		5 (8.3%)	7 (11.7%)	
2	21 (32.8%)	18 (18.8%)		20 (33.3%)	14 (23.3%)	
3	38 (59.4%)	70 (72.9%)		35 (58.3%)	39 (65.0%)	
CTO	37 (57.8%)	40 (42.1%)	0.05	34 (56.7%)	24 (40.0%)	0.07
Interventions			0.04			0.32
PCI	52 (81.3%)	76 (79.2%)		49 (81.7%)	48 (80.0%)	
CABG	9 (14.1%)	6 (6.3%)		8 (13.3%)	5 (8.3%)	
IABP	29 (45.3%)	18 (18.8%)	0.003	28 (46.7%)	9 (15.0%)	0.002
Final TIMI flow[a]			0.35			0.52
0–1	0 (0.0%)	1 (1.1%)		0 (0.0%)	1 (1.8%)	
2	8 (12.7%)	7 (7.6%)		7 (11.9%)	5 (8.8%)	
3	55 (87.3%)	84 (91.3%)		52 (88.1%)	51 (89.5%)	
Stent no.	2 [1, 3.75]	2 [1, 3]	0.58	2 [1, 3.5]	2 [1, 3]	0.97
Stent length (mm)	52 [29, 88]	56 [24.5, 84]	0.43	52 [30, 87]	56 [29, 91.5]	0.87
Minimum stent diameter (mm)	2.5 [2.5, 3]	2.5 [2.25, 3]	0.43	2.5 [2.5, 3]	2.5 [2.25, 3]	0.89
DES	45 (86.5%)	67 (88.2%)	0.79	42 (85.7%)	43 (89.6%)	0.56
2nd Generation DES	44 (84.6%)	63 (82.9%)	0.80	41 (83.7%)	42 (87.5%)	0.59
Contrast media (ml)	157.5 [110, 225]	165 [85, 250]	0.93	167.5 [110, 225]	185 [85, 265]	0.51

Values are the mean ± standard deviation (SD), *n* (%), or median (interquartile range) as appropriate.
CAG, coronary angiography; RCA, right coronary artery; LMT, left main trunk artery; LAD, left anterior descending artery; LCx, left circumflex artery; TIMI, thrombolysis in myocardial infarction; CTO, chronic total occlusion; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pumping; DES, drug-eluting stent.
[a] Final TIMI flow grade was counted only in patients undergoing PCI.

the pre-catheterization period in patients in early invasive group, (2) prevention of subsequent heart failure because of avoidance of the earlier myocardial injury, (3) electronical instability because of myocardial injury in delayed invasive groups, or (4) recurrent exacerbation of CHF and hemodynamical instability in patients with decreased cardiac function. Notably, seven patients in the delayed invasive group developed life-threatening arrhythmia and were resuscitated from cardiac arrest during medical therapy for CHF. Early invasive strategy seemed to be associated with avoidance of the consequences of earlier myocardial injury that lead to subsequent arrhythmic events [25].

On multivariate Cox regression hazard analysis, early invasive strategy was associated with lower risk of the primary outcome. The results of the previous studies, regarding the optimal timing of invasive strategy for NSTE-ACS, are inconsistent on the hard outcomes (death or MI) [26–29]. Recently, the results of a large-scale randomized clinical trial (RCT) (VERDICT trial) were published [30]. Although the VERDICT trial was different from the TIMACS trial [31] in the timing of invasive strategy, components of the primary outcome, and the duration of follow-up, the main result of the two large-scale RCTs was similar. Both did not observe any difference in all-cause mortality in the overall patients; only the high-risk patients, defined as GRACE score >140, benefited from early invasive strategy. The results of the meta-analyses were also inconsistent with the outcomes, such as mortality and non-fatal MI [4–6]. Early invasive strategy seemed to be associated with lower events in high-risk patients only [6]. The present study demonstrated superiority of the early invasive strategy to the delayed invasive strategy, even though the number of patients was small. It may be attributed to the very high-risk nature of patients who presented with NSTE-ACS and concomitant CHF: the mean GRACE score in the present study was approximately 230. The result of the present study enhances the guideline recommendation of immediate invasive strategy in patients with NSTE-ACS and concomitant CHF.

It is worthy of mention that the early invasive strategy exerted benefit for patients with severe respiratory failure but not for those without severe respiratory failure. The precise mechanism as to how the early invasive therapy achieved benefit only for those with severe respiratory failure remained uncertain; however, the early invasive strategy also achieved more benefits for patients with CKD than those without CKD, suggesting the possibility that the early invasive strategy may achieve more benefits for higher risk patients. However, given the exploratory nature of this subgroup analysis, further dedicated randomized control studies with large sample sizes are warranted.

Bleeding and AKI were higher in the early invasive group. Although the meta-analysis of RCTs demonstrated that both early and delayed strategies were associated with similar rates of major

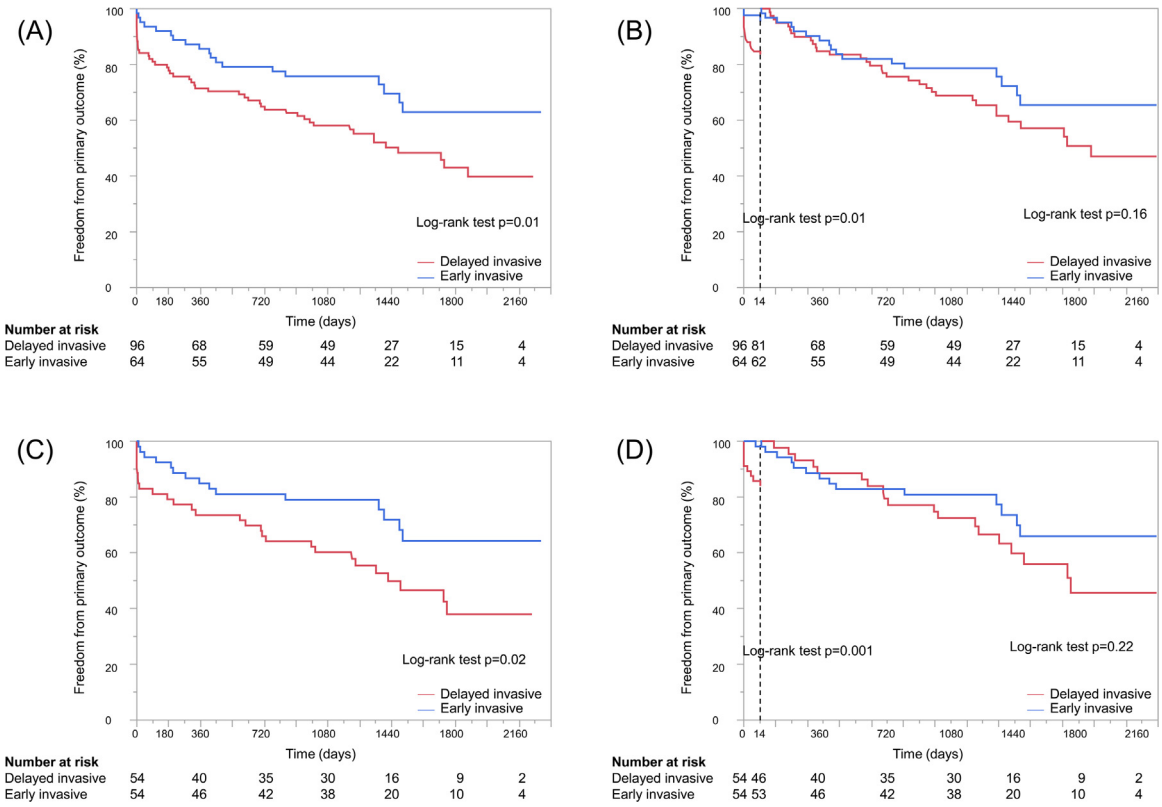

Fig. 2. Freedom from the primary outcome (composite of cardiac mortality, life-threatening arrhythmia, and non-fatal myocardial infarction) between early and delayed invasive treatment groups. Panels A and C show the survival curve of freedom form the primary outcome between the early and delayed invasive treatment groups of all patients and propensity-matched patients, respectively. Panels B and D show the landmark analysis before and after 14 days of the survival curve of freedom form the primary outcome between the early and delayed invasive treatment groups of all patients and propensity-matched patients, respectively.

Table 3
Predictors of primary outcome.

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Early invasive	0.52	0.30–0.87	0.01	0.44	0.23–0.78	0.004
Age	1.04	1.02–1.07	0.001	1.02	1.00–1.06	0.07
Male sex	1.08	0.67–1.78	0.75			
Diabetes mellitus	1.16	0.71–1.93	0.55			
Hypertension	1.42	0.83–2.53	0.20			
Prior myocardial infarction	1.29	0.74–2.15	0.36			
Prior heart failure	1.99	1.12–3.36	0.02	1.69	0.93–2.93	0.08
Prior PCI	1.94	1.18–3.13	0.01	1.65	0.99–2.73	0.05
Prior CABG	1.61	0.77–3.01	0.19			
eGFR (ml/min/1.73 m^2)	0.99	0.98–1.00	0.08			
Albumin (g/dl)	0.63	0.39–1.00	0.05			
Hemoglobin (g/dl)	0.93	0.84–1.03	0.18			
Serum Na (mEquiv./l)	1.00	0.98–1.05	0.79			
BNP (pg/ml)	0.99	0.99–1.00	0.26			
LVEF (%)	0.99	0.98–1.01	0.66			
GRACE risk score	1.01	1.01–1.02	0.0002	1.01	1.00–1.02	0.02
Statin	0.90	0.47–1.96	0.78			
ACE-I/ARB	0.61	0.37–1.00	0.05			
Beta-blocker	0.76	0.46–1.28	0.29			
IABP	1.61	0.95–2.68	0.08			
LMT lesion	0.89	0.51–1.48	0.66			
TVD	1.10	0.66–1.90	0.72			
Final TIMI 3	0.39	0.22–0.77	0.01	0.34	0.18–0.69	0.004

HR, hazard ratio; CI, confidence interval; Early invasive, early invasive therapy (<24 h); PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; Na, sodium concentration; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IABP, intra-aortic balloon pumping; LMT, left main trunk; TVD, triple vessel disease; TIMI, thrombolysis in myocardial infarction.

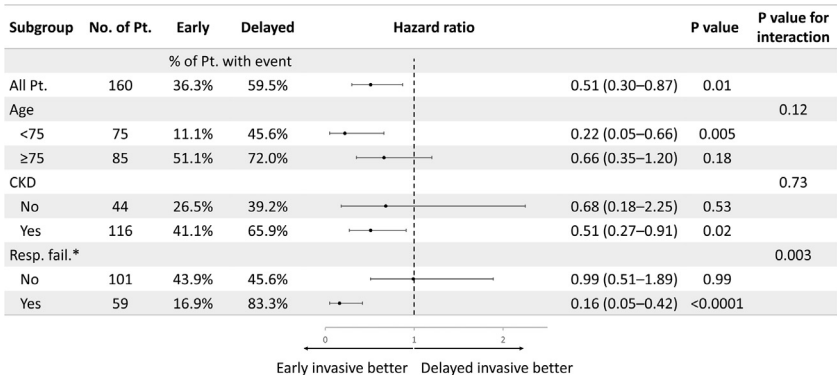

Fig. 3. Subgroup analysis for primary outcome. Explorative subgroup analyses revealed significant between-group differences with respect to severe respiratory failure; no significant between-group difference with respect to age <75 or ≥75 years old, and the presence or absence of chronic kidney disease. * Severe respiratory failure was defined as those who required mechanical ventilation with intubation or non-invasive positive pressure ventilation. No., number; Pt., patient; CKD, chronic kidney disease; Resp. fail, respiratory failure.

Table 4
Complication between early and delayed invasive strategy.

Patients: *n*	Early (*n* = 66)	Delayed (*n* = 94)	*p*-Value
Acute kidney injury	15 (19.5)	7 (8.4)	0.04
Coronary perforation	2 (2.6%)	1 (1.2%)	0.51
No-reflow	9 (14.1%)	6 (9.4%)	0.41
Bleeding	17 (22.1%)	1 (1.2%)	<0.0001

Values are the mean ± standard deviation (SD), *n* (%).

bleeding, the meta-analysis of observational studies suggested potential harm of major bleeding with early intervention [4]. Unlike what was mentioned in the RCTs, it is likely that the incidence of bleeding complications is higher in the early invasive strategy in real-world practice. Recent evidence suggested that relatively mild injury of kidney function is a predictor of serious clinical consequences [32–35]. Therefore, extreme care in preventing AKI should be taken in early invasive strategy under the condition of CHF [36]. Nevertheless, the risk of death greatly outweighed the risk of kidney injury following acute coronary syndrome [37]; early invasive strategy should not be hesitated even among CKD patients.

Study limitations

This study had several limitations. First, it was performed at a single medical center and followed a non-randomized, retrospective study design. There was a limited number of patients enrolled in this study. Second, we could not distinguish if some of the patients with decompensated CHF and renal insufficiency had troponin increases that were not specifically related to an ACS or myocardial necrosis. Moreover, symptoms may overlap between ischemia and CHF. Third, the timing of invasive strategy was at the discretion of the attending physician. Therefore, there may exist selection bias between the two groups. More severe patients should be enrolled in the early invasive group. In fact, both serum CK-MB levels at arrival and maximum CK-MB levels were higher in the early invasive group. However, we think that this point seemed to be a disadvantage for the early invasive strategy and did not exaggerate the efficacy of early invasive strategy.

Conclusion

In this study, early invasive strategy was associated with a lower risk of the primary outcome of cardiac mortality, life-threatening arrhythmia, and non-fatal MI in the long-term follow-up of patients with NSTE-ACS and concomitant CHF. Early invasive strategy should not be hesitated even among patients with more co-morbidities.

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Conflict of interest

H.I. received lecture fees from Astellas Pharma Inc., Bayer Pharmaceutical Co., Ltd., Daiichi-Sankyo Pharma Inc., and MSD K. K. T.M. received lecture fees from Bayer Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Pfizer Japan Inc., Sanofi-Aventis K. K., and Takeda Pharmaceutical Co., Ltd. T.M. received unrestricted research grant for Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-Aventis K. K., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd. For the remaining authors none were declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.03.006.

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