Original Article

Long-term Prognosis of Patients with Acute non-ST-segment Elevation Myocardial Infarction undergoing Different Treatment Strategies

Bo Zhang[1], Da-Peng Shen[2], Xu-Chen Zhou[1], Jun Liu[1], Rong-Chong Huang[1], Yan-E Wang[1], Ai-Ming Chen[3], Ye-Ran Zhu[1], Hao Zhu[1]

[1]Department of Cardiology, First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116011, China
[2]Department of Cardiology, Fuxin Center Hospital, Fuxin, Liaoning 123000, China
[3]Department of Cardiology, Dalian Jinzhou First People's Hospital, Dalian, Liaoning 116100, China

Bo Zhang and Da-Peng Shen contributed equally to this work.

Abstract

Background: In cardiology, it is controversial whether different therapy strategies influence prognosis after acute coronary syndrome. We examined and compared the long-term outcomes of invasive and conservative strategies in patients with non-ST-segment elevation myocardial infarction (NSTEMI) and characterized the patients selected for an invasive approach.

Methods: A total of 976 patients with acute NSTEMI were collected from December 2006 to October 2012 in the First Affiliated Hospital of Dalian Medical University Hospital. They are divided into conservative strategy (586 patients) and invasive strategy (390 patients) group. Unified follow-up questionnaire was performed by telephone contact (cut-off date was November, 2013). The long-term clinical events were analyzed and related to the different treatment strategies.

Results: The median follow-up time was 29 months. Mortality was 28.7% ($n = 168$) in the conservative group and 2.1% ($n = 8$) in the invasive management at long-term clinical follow-up. The secondary endpoint (the composite endpoint) was 59.0% ($n = 346$) in the conservative group and 30.3% ($n = 118$) in the invasive management. Multivariate analysis showed that patients in the conservative group had higher all-cause mortality rates than those who had the invasive management (adjusted risk ratio [*RR*] = 7.795; 95% confidence interval [*CI*]: 3.796–16.006, $P < 0.001$), and the similar result was also seen in the secondary endpoint (adjusted *RR* = 2.102; 95% *CI*: 1.694–2.610, $P < 0.001$). In the subgroup analysis according to each Thrombolysis in Myocardial Infarction risk score (TRS), log-rank analysis showed lower mortality and secondary endpoint rates in the invasive group with the intermediate and high-risk patients (TRS 3–7).

Conclusions: An invasive strategy could improve long-term outcomes for NSTEMI patients, especially for intermediate and high-risk ones (TRS 3–7).

Key words: Invasive Strategy; Long-term Outcome; Non-ST-segment Elevation Myocardial Infarction; Thrombolysis in Myocardial Infarction Risk Score

Introduction

Worldwide, more than 4 million people each year are estimated to have a non-ST-segment elevation myocardial infarction (NSTEMI), and long-term mortality is higher in patients with non-ST-elevation acute coronary syndrome (ACS) than in those with ST-elevation ACS.[1,2] In clinical practice, for patients who present with non-ST-elevation ACS, different therapeutic strategies may significantly affect short and long-term outcomes.[3] The influence of different therapy strategies on mortality after non-ST-elevation ACS is still a matter of controversy.[3-8] To our knowledge, few studies have evaluated the long-term outcomes (>2 years) of invasive and conservative strategies in patients with acute NSTEMI in China. With the development of modern percutaneous coronary intervention (PCI) technology, we aimed to determine the long-term prognosis and disparities for NSTEMI patients in the real-world setting of different therapeutic strategies in the current era.

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Methods

Patient population

This was a retrospective study that was approved by the Ethics Committee of Dalian Medical University. From December

Address for correspondence: Dr. Hao Zhu, Department of Cardiology, First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116011, China
E-Mail: drzhuhao@163.com

2006 to December 2012, the study included 1194 consecutive patients survived NSTEMI and discharged from the Cardiology Department of the First Affiliated Hospital of Dalian Medical University. We recorded patient characteristics, the treatment process, and adverse events during the patients' hospital stay. The Thrombolysis in Myocardial Infarction (TIMI) risk score (TRS) was calculated from the initial clinical history, electrocardiogram (ECG), and laboratory values collected on admission. A retrospective calculation of the TRS was made for each patient.[9] Unified follow-up questionnaire was performed by outpatient or telephone contact from November 1, 2013 to November 30, 2013. We excluded patients with coronary artery bypass grafting (CABG) on admission ($n = 37$; 3.1%) and those lost to follow-up ($n = 181$; 15.2%). The final study population included 976 NSTEMI patients. Data quality was checked by the project director. NSTEMI diagnosis was defined as ECG ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin I ≥ 1 μg/L in our laboratory) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or angina equivalent). Exclusion criteria: PCI-related myocardial infarction or CABG related myocardial infarction; other diseases affecting the long-term prognosis including other serious heart diseases (severe primary cardiomyopathy, valvular heart diseases, and congenital heart diseases), severe liver dysfunction (liver cirrhosis), kidney dysfunction (serum creatinine [Scr] ≥443 μmol/L), severe infection, and malignant tumor.

Treatment strategy

The invasive group contained patients who underwent PCI during hospitalization; in contrast, the conservative group contained patients who did not receive PCI during hospitalization.

Endpoints

The primary endpoint was death from any cause. The secondary endpoint was a composite of death, myocardial reinfarction, recurrent angina or New York Heart Association Class IV heart failure.

Clinical definition

Hypercholesterolemia was defined as a history of hypercholesterolemia and use of lipid-lowering agents or levels of total cholesterol ≥6.22 mmol/L or low-density lipoprotein cholesterol ≥4.14 mmol/L. Myocardial reinfarction was based on the recurrence of chest pain, new ECG changes indicative of ischemia, and an increase in creatine kinase (CK), CK-MB, or troponin I that was 50% or higher than the previous value. Recurrent angina was defined as clinical features of angina with ischemic change in ECG findings or related symptoms only released by anti-ischemic agents but not satisfying the diagnostic standard of myocardial infarction.

Statistical analysis

For statistical analyses, we used SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Continuous data were described with mean ± standard deviation (SD) and categorical data with median and interquartile range (25th to 75th). For comparisons between two groups of continuous data, we used *t*-tests and for comparisons of categorical data we used Chi-square tests. The data were censored with a closing date of November 30, 2013. The cumulative event-free survival curves were estimated and plotted on the Kaplan–Meier estimator and differences were analyzed with a log-rank test. We controlled for confounding effects by performing multivariate Cox regression analyses for the primary and secondary endpoints. The regression model was adjusted for the patient's demographics (gender and age), medical history (hypertension diabetes, Hypercholesterolemia, smoking, etc), hospital-related characteristics and therapies. We calculated risk ratios (*RR*s) and 95% confidence intervals (95% *CI*s) and considered $P < 0.05$ to represent statistical significance.

Results

Patients' characteristics

A total of 976 patients were enrolled in the study, which involved 390 (40%) in the invasive group. Patients in the invasive group were younger and were more likely to be males, with a history of smoking, prior PCI, family history of coronary heart disease, ST-segment change, a history of taking aspirin within 1-week prior to admission and higher ejection fraction; less likely to have hypertension, a Killip class ≥ 2. There were higher N-terminal pro-brain natriuretic peptide (NT-proBNP), Scr and serum uric acid (UA) levels in the conservative group. There was no difference in Cardiac troponin I (the highest values during hospitalization) and TIMI score between the two groups [Table 1].

Clinical performance measures

There was no difference in β-blocker, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker and calcium antagonists therapies between the two groups. However, there was more use of aspirin, clopidogrel, statin, and LMWH in the interventional therapy group and more use of diuretics in the conservative group [Table 2].

Endpoint events

The median follow-up time was 29 months (interquartile range: 18–51 months). There was no difference between the two groups in follow-up time (median 31 months vs. 28 months, $P = 0.166$). Mortality was 28.7% ($n = 168$) in the conservative group and 2.1% ($n = 8$) in the invasive one, crude *RR* for conservative group 14.93 (95% *CI*: 7.35–30.63, $P < 0.001$). The secondary endpoint was 59.0% ($n = 346$) in the conservative group and 30.3% ($n = 118$) in the invasive one, crude *RR* for conservative group 2.43 (95% *CI*: 1.97–2.99, $P < 0.001$) [Figure 1]. After multivariable adjustment, patients in the conservative group had higher mortality rates than in the invasive one (adjusted $RR = 7.795$; 95% *CI*: 3.796–16.006, $P < 0.001$). The similar result was also seen in the secondary endpoint (adjusted $RR = 2.102$; 95% *CI*: 1.694–2.610, $P < 0.001$).

In the subgroup analysis according to each TRS, log-rank analysis showed lower mortality and secondary endpoint

Table 1: Baseline characteristics of patients with acute non-ST-segment elevation myocardial infarction

Characteristics	Invasive (n = 390)	Conservative (n = 586)	P
Male (n (%))	287 (73.6)	330 (56.3)	<0.001
Age (years, mean ± SD)	64.5 ± 10.9	71.0 ± 12.0	<0.001
Prior CHD (n (%))	230 (59.0)	343 (58.5)	0.891
Prior PCI (n (%))	65 (16.7)	61 (10.4)	0.004
Prior CABG (n (%))	12 (3.1)	16 (2.7)	0.751
Hypertension (n (%))	240 (61.5)	434 (74.1)	<0.001
Diabetes (n (%))	136 (34.9)	234 (39.9)	0.111
Smoking history (n (%))	159 (40.8)	175 (29.9)	<0.001
Family history (n (%))	66 (16.9)	66 (11.3)	0.011
Hypercholesterolemia (n (%))	91 (23.3)	135 (23.0)	0.915
Aspirin consumption (n (%))	62 (15.9)	61 (10.4)	0.011
ST segment depression (n (%))	306 (78.5)	419 (71.5)	0.015
TIMI score (n (%))			0.073
0–2	40 (10.3)	68 (11.6)	
3–4	248 (63.6)	330 (56.3)	
5–7	102 (26.2)	188 (32.1)	
Scr (μmol/L, mean ± SD)	75.79 ± 33.93	103.75 ± 81.18	<0.001
UA (μmol/L, mean ± SD)	322.96 ± 99.63	362.37 ± 121.12	<0.001
BNP (pg/ml, mean ± SD)	594.79 ± 179.99	1831.69 ± 248.13	0.005
CRP (mg/L, mean ± SD)	13.00 ± 2.05	16.70 ± 1.08	0.083
LVDd (mm, mean ± SD)	48.00 ± 5.17	49.35 ± 6.35	0.001
EF (%, mean ± SD)	54.51 ± 7.45	52.06 ± 9.35	<0.001
CK (U/L, mean ± SD)	386.14 ± 27.67	389.79 ± 24.45	0.923
CK-MB (μg/L, mean ± SD)	50.01 ± 18.94	31.34 ± 3.36	0.242
Tpn-I (μg/L, mean ± SD)	13.98 ± 2.17	15.69 ± 2.37	0.615

CHD: Coronary heart disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; TIMI score: Thrombolysis in Myocardial Infarction (TIMI: Low risk 0-2; Intermediate risk 3-4; High-risk 5-7); Scr: Serum creatinine; UA: Uric acid; BNP: Brain natriuretic peptide; CRP: C-reactive peptide; LVDd: Left ventricular end-diastolic diameter; EF: Ejection fraction; CK: Creatine kinase; CK-MB: Creatine kinase-MB; Tpn-I: Troponin-I; Aspirin consumption: aspirin consumption in the previous 7 days; SD: Standard deviation.

Table 2: Concomitant drug therapy during hospitalization (n (%))

Drugs	Interventional (n = 390)	Conservative (n = 586)	P
Aspirin	387 (99.2)	564 (96.2)	0.007
Clopidogrel	385 (98.7)	541 (92.3)	<0.001
LMWH	374 (95.9)	486 (82.9)	<0.001
Statins	379 (97.2)	546 (93.2)	0.006
β-blocker	317 (81.3)	446 (76.1)	0.055
ACEI/ARB	288 (73.8)	423 (72.2)	0.567
CCB	119 (30.5)	207 (35.3)	0.119
Diuretics	57 (14.6)	208 (35.5)	0.001

LWWH: Low molecular weight heparin; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium antagonists.

rates in the invasive group with the intermediate and high-risk patients (TRS 3–7). However, for patients in the low-risk group (TRS 0–2), there was no significant difference in the long-term outcomes between the two groups [Table 3 and Figure 1].

Discussion

Acute coronary syndrome has been categorized into unstable angina, NSTEMI and ST-segment elevation myocardial infarction.[10] ST-elevation ACS represents an increasingly frequent cause of hospital admission, as it is the most frequent presentation of coronary instability in patients with prior cardiac events or coronary revascularizations.[11] So far, an increasing number of studies have demonstrated that an invasive treatment strategy rather than a conservative approach improves the outcomes of non-ST-elevation ACS patients, and the two guidelines recommended an invasive approach for the higher-risk ST-elevation ACS patients,[10,12] however, some studies showed an invasive strategy could not provide comparable benefits of all-cause mortality and long-term survival when compared to conservative therapy.[3,4,7,8] Our results showed that invasive strategy is still the most effective treatment to reduce long-term complications in NSTEMI patients.[5,6,10,12]

In our study, patients in the invasive therapy group were younger and were more likely to have higher Ejection Fraction and lower NT-proBNP, Scr and serum UA levels, but less likely to have a Killip class ≥ 2. These results indicated more comorbidities and higher baseline risk in a conservative group that could lead to worse outcomes. According to *Heart Association Task Force on practice guidelines*,[10] medical therapy remains a cornerstone in managing patients with non-ST-elevation ACS. In our study, patients in the conservative group received less evidence-based medical therapy than those underwent the invasive management, including the use of aspirin, clopidogrel, statin, and LMWH, which should be considered as another main reason for worse primary and secondary endpoints. Our main finding in this study assessing the long-term impact of the invasive strategy demonstrated a sustained advantage for invasive management in the subsequent primary or secondary endpoints. After adjustment for confounding factors including the above comorbidities, baseline risk, and evidence-based medical care, the trend toward decreased all-cause mortality or the secondary endpoint in patients with an invasive strategy was still observed. This is almost consistent with the findings from the recent meta-analysis,[5] particularly in term of reduced long-term mortality rates, but is in disagreement with those of the randomized Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial.[13,14]

To avoid other diseases affecting the long-term prognosis, the admission criteria excluded patients with other serious diseases. Previous studies showed cardiac troponin I (the highest values during hospitalization), C-reactive protein, and TIMI score might be better discriminator of patients of ACS who remain at high-risk,[9,15,16] however, these markers have no difference in between the two groups. For most patients

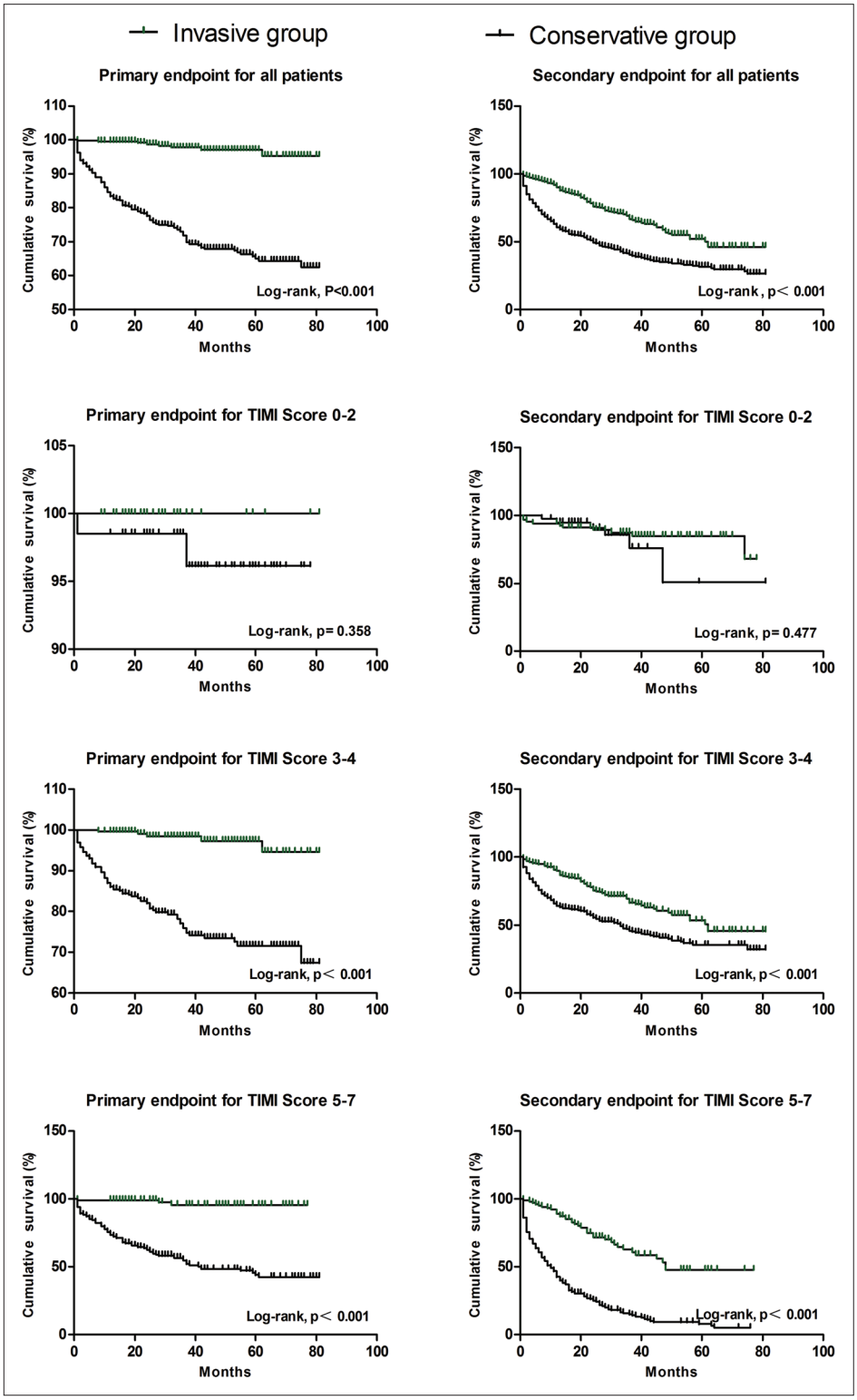

Figure 1: Kaplan–Meier curves for primary and secondary endpoints.

Table 3: The long-term outcomes according to TRS (*n* (%))

TRS	The primary endpoint		*P*	The secondary endpoint		*P*
	Invasive	Conservative		Invasive	Conservative	
0–2 (*n* = 108)	0 (0)	2 (2.9)	0.358	6 (15.0)	10 (14.7)	0.477
3–5 (*n* = 578)	5 (2.0)	76 (23.0)	<0.001	76 (30.6)	172 (52.1)	<0.001
6–7 (*n* = 290)	3 (2.9)	90 (47.9)	<0.001	36 (35.3)	164 (87.2)	<0.001

TIMI: Thrombolysis in Myocardial Infarction; TRS: TIMI risk score.

who stabilized after an ACS, in-hospital coronary intervention was not associated with reduced risk compared with medical therapy.[6] The Korea Acute Myocardial Infarction Registry indicated early invasive (within 48 h) rather than late invasive treatment improved 1-year clinical outcomes in patients with high TRS (≥5 points).[17] However, in the FIR database of patients presenting with ST-elevation ACS, the timing of angiography was not related to 5-year cardiovascular mortality or myocardial infarction.[8] The present study did not focus on the optimal timing of PCI during hospitalization and showed lower mortality and secondary endpoint rates in the intermediate and high groups (TRS 3–7) from the studied population of NSTEMI patients suggesting that we should focus on a "treatment-risk paradox" in clinical practice where most interventions are performed in lower risk patients.[18,19] However, the ICTUS showed that an early invasive strategy was not better than an early conservative strategy, even for the higher risk patients, on the short-term and long-term clinical follow-up.[13,14] Hence, the heterogeneity of different results clearly calls for clinical investigation.

In previous trials, ST-elevation ACS patients in the conservative group also received invasive therapy during the index hospitalization when medical therapy failed or if substantial residual ischemia was documented.[3,20,21] A major strength of this study is that we strictly distinguished or defined between conservative and invasive strategies during hospitalization. We performed the present retrospective study to analyze the benefits between invasive and conservative strategies for NSTEMI patients and had no "crossover" from conservative treatment to PCI during hospitalization and eliminated the interference from the two therapies with one another, and reflected real-life setting in NSTEMI prevalence and outcome. Different from the majority of trials, patients with unstable angina were not enrolled in our study which could exclude possible residual confounding by different ST-elevation ACS diseases.

Several limitations exist in this study. This was a single-center and observational uncontrolled study. The samples were restricted to patients discharged from our hospital with a successful follow-up, which may have resulted in selection biases and conclusions with limited generalizability. There was a tendency for cardiologists to perform conservative treatment for high-risk patients which might have affected the final results. Finally, this study cannot exclude possible residual confounding by other measured and/or unmeasured factors including the treatment decisions of patients when NSTEMI occurred, which is an important source of prognosis.

In conclusion, our findings suggested that an invasive strategy could improve long-term outcomes for NSTEMI patients, especially for intermediate and high-risk ones (TRS 3–7).

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