Research Article

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Invasive versus conservative strategy in consecutive patients aged 80 years or older with non-ST-segment elevation myocardial infarction: a retrospective study in China

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Abstract

Objective   To investigate whether the very elderly patients with non-ST-segment elevation myocardial infarction (NSTEMI) will benefit from an invasive strategy versus a conservative strategy. **Methods**   190 consecutive patients aged 80 years or older with NSTEMI were included in the retrospective study from September 2014 to August 2017, of which 69 patients received conservative strategy and 121 patients received invasive strategy. The primary outcome was death. Multivariate Cox regression models were used to assess the statistical association between strategies and mortality. The survival probability was further analyzed. **Results**   The primary outcome occurred in 17.4% patients in the invasive group and in 42.0% patients in the conservative group ($P = 0.0002$). The readmission rate in the invasive group (14.9%) was higher than that in the conservative group (7.2%). Creatinine level (OR = 1.01, 95% CI: 0.10–1.03, $P = 0.05$) and use of diuretic (OR = 3.65, 95% CI: 1.56–8.53, $P = 0.003$) were independent influential factors for invasive strategy. HRs for multivariate Cox regression models were 3.45 (95% CI: 1.77–6.75, $P = 0.0003$), 3.02 (95% CI: 1.52–6.01, $P = 0.0017$), 2.93 (95% CI: 1. 46–5.86, $P = 0.0024$) and 2.47 (95% CI: 1.20–5.07, $P = 0.0137$). Compared with the patients received invasive strategy, the conservative group had remarkably reduced survival probability with time since treatment ($P < 0.001$). **Conclusions**   An invasive strategy is superior to a conservative strategy in reducing mortality of patients aged 80 years or older with NSTEMI. Our results suggest that an invasive strategy is more suitable for the very elderly patients with NSTEMI in China.

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Keywords: Conservative strategy; Death; Invasive strategy; Non-ST-segment elevation myocardial infarction

1   Introduction

The very elderly patients, who are aged 80 years or older, are a heterogeneous group due to their frailty, decline in cognition and function, complex coronary artery disease with greater ischemic burden and comorbidities.[1,2] They constitute a rapidly increasing subgroup of patients with acute coronary syndrome (ACS), where non-ST-segment elevation myocardial infarction (NSTEMI) is a common manifestation of ACS and a common cause of hospitalization for patients aged 80 years or older.

However, patients aged 80 years or older at high risk of recurrent events are less likely to receive invasive therapy than younger patients.[3] Although these patients should be treated differently compared with younger patients, the European Society of Cardiology (ESC)[4] or American Heart Association/American College of Cardiology (AHA/ACC)[5] guidelines failed to recommend a specific invasive strategy to manage NSTEMI to distinguish between elderly and younger patients. Additionally, evidences from expert consensus and large randomized controlled trials have shown that the effects of revascularization in patients aged 80 years or older are scarce versus medical treatment. This makes daily optimum management strategy decision-making of these elderly patients more complex and proper sub-analysis of its benefits and disadvantages is more uncertain. The After Eighty study impressively supported an invasive strategy in octogenarians with NSTEMI or unstable angina from 16 hospitals in the South-East Health Region of Norway.[6] To our knowledge, no previous study reported the optimum

management strategy in this population of NSTEMI patients aged 80 years or older in China. This retrospective study, therefore, was carried out to investigate whether patients aged 80 years or older with NSTEMI could benefit from an invasive strategy versus a conservative strategy in China.

2 Methods

2.1 Patients

A total of 190 consecutive very elderly patients with NSTEMI, aged 80 years or older, were eligible for inclusion in this retrospective study from September 2014 to August 2017 in Fuwai Hospital, Beijing, China. NSTEMI was defined by typical ischemia symptoms, elevated level of cardiac troponin-I or creatine kinase-MB and no evidence of ST-segment elevation in electrocardiogram. We excluded patients with continuing chest pain, hemodynamic instability, persistent hemorrhage, short life expectancy (< 12 months) due to chronic obstructive pulmonary disease or disseminated malignant disease, substantial mental disorder or other ischaemic symptoms. Hypertension was defined as taking an antihypertensive medication without regard to the actual measurement of blood pressure, or having a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was defined as active use of an antidiabetic agent, or fasting plasma glucose level ≥ 7.0 mmol/L or casual plasma glucose level ≥ 11.1 mmol/L. The need for informed consent was waived due to the retrospective nature of the study.

2.2 Procedures

The invasive strategy included early coronary angiography with immediate assessment for ad-hoc percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or optimum medical therapy, while the conservative strategy was only optimum medical therapy. Early coronary angiography was defined as the coronary angiography was performed < 24 h from admission.

Patients in the invasive group underwent coronary angiography. Coronary angiography was performed in compliance with the standard local practice and existing clinical practice guidelines by experienced cardiologists. In patients who were eligible for percutaneous revascularization, PCI was performed under the same settings. CABG should be performed as soon as possible if it was recommended as means of revascularization. Coronary angiography was reviewed by at least two invasive cardiologists until consensus was reached before identifying revascularization strategy for each patient.

Aspirin and clopidogrel were used for antiplatelet treatment, but a few patients received ticagrelor in the two groups. Statin, β-receptor-blocking agent, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and diuretic were administrated when needed. The patients' baseline characteristics, medical history, medications at discharge and prognosis conditions were collected and compared between patients received invasive and conservative strategies.

2.3 Primary and secondary outcomes

The primary outcome was the composite of death, and death was defined as death from any cause. The secondary outcomes were readmission and complications including angina pectoris, heart failure (HF), atrial fibrillation, acute myocardial infarction, and cerebral infarction. Either primary or secondary outcomes in-hospital was immediately recorded. Follow-up was telephone follow-up, and the last follow-up was in August 2018. If deaths or adverse events occurred at regular telephone follow-up prior to August 2018, then the outcomes were recorded.

2.4 Statistical analysis

All statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Continuous variables distributed normally were expressed as mean ± SD, and normal distribution data were compared between the two groups using the Student t-test. Skewed distribution measurement data were expressed as medians and quartiles, and skewed distribution data were compared using the Mann-Whitney U-test. Categorical data were expressed as numbers and percentages and the Chi-square test was used for comparing categorical data between the two strategy groups. Univariate and multivariate analyses were applied to confirm the independent influential factors for invasive strategy group. Variables with $P < 0.10$ in univariate analysis were included for further multivariate analysis. Unadjusted and adjusted multivariate Cox regression models were established to assess the association of the two strategy groups with the occurrence of clinical endpoints. Model 1 was unadjusted model, Model 2 was adjusted for age and gender, and Model 3 was adjusted for age, gender, hypertension, diabetes, hyperlipemia and anemia. Model 4 was adjusted for age, gender, hypertension, diabetes, hyperlipemia, anemia, previous myocardial infarction, previous CABG, III degree atrioventricular block and renal insufficiency. Kaplan-Meier curve was plotted to depict survival probability and statistical differences were performed using the log rank test. The statistical significance was considered as a two-tailed $P < 0.05$.

3 Results

3.1 Patients

As shown in Table 1, a total of 190 patients aged 80 years or older diagnosed with NSTEMI were enrolled in this study. The candidates for inclusion were divided to the conservative group (69 patients) and the invasive group (121 patients). There was no significance in mean age

Table 1. Baseline characteristics.

Characteristic	Total (*n* = 190)	Conservative strategy group (*n* = 69)	Invasive strategy group (*n* = 121)	*P*-value
Age				0.0032
< 85 yrs	137 (72.1%)	41 (59.4%)	96 (79.3%)	
≥ 85 yrs	53 (27.9%)	28 (40.6%)	25 (20.7%)	
Sex				0.3392
Male	107 (56.3%)	42 (60.9%)	65 (53.7%)	
Female	83 (43.7%)	27 (39.1%)	56 (46.3%)	
BMI	23.7 ± 4.5	23.8 ± 4.3	23.7 ± 4.7	0.237
Medical history				
Previous myocardial infarction	64 (33.7%)	36 (52.2%)	28 (23.1%)	< 0.0001
Previous stenting	44 (23.2%)	15 (21.7%)	29 (24.0%)	0.7263
Previous CABG	14 (7.4%)	10 (14.5%)	4 (3.3%)	0.0045
Valvular heart disease	27 (14.2%)	11 (15.9%)	16 (13.2%)	0.6057
Atrial fibrillation	46 (24.2%)	18 (26.1%)	28 (23.1%)	0.6484
III degree atrioventricular block	5 (2.6%)	5 (7.2%)	0	0.0027
Hypertension	154 (81.1%)	59 (85.5%)	95 (78.5%)	0.2367
Diabetes	94 (49.5%)	39 (56.5%)	55 (45.5%)	0.1423
Hyperlipidaemia	182 (95.6%)	67 (97.1%)	115 (95.0%)	0.4965
Renal insufficiency	46 (24.2%)	28 (40.6%)	18 (14.9%)	< 0.0001
Previous cerebral infarction	36 (18.9%)	17 (24.6%)	19 (15.7%)	0.1307
Cerebral hemorrhage	2 (1%)	1 (1.4%)	1 (0.8%)	0.6858
Digestive disease	62 (32.6%)	18 (26.1%)	44 (36.4%)	0.1462
Gastrointestinal hemorrhage	7 (3.7%)	2 (2.9%)	5 (4.1%)	0.6642
Anaemia	32 (16.8%)	19 (27.5%)	13 (10.7%)	0.0029.
Peripheral arterial disease	21 (11.1%)	7 (10.1%)	14 (11.6%)	0.7632
Respiratory disease	30 (15.8%)	14 (20.3%)	16 (13.2%)	0.1989
Creatinine, mg/dL	89.0 (74.0, 109.6)	97.2 (80.9, 133.1)	86.0 (71.1, 101.5)	0.0005
Systolic pressure, mmHg	139.9 ± 23.6	139.1 ± 25.5	140.4 ± 22.6	0.7261
Diastolic pressure, mmHg	73.0 ± 13.7	70.4 ± 13.9	74.4 ± 13.4	0.0516
Heart rate, beats per min	76.5 (66.0, 90.0)	80.0 (67.0, 90.0)	74.0 (66.0, 86.0)	0.0638
GRACE score	172.5 ± 15.1	177.2 ± 16.2	169.9 ± 13.8	0.0012
Lesion branches				
1	1 (0.5%)	0	1 (0.8%)	NA
2	17 (8.9%)	0	17 (14.0%)	NA
3	31 (16.3%)	0	31 (25.6%)	NA
4	72 (37.9%)	0	72 (59.5%)	NA
Left main coronary artery	20 (10.5%)	0	20 (100.0%)	NA
EF				0.0191
< 50%	50 (26.3%)	25 (36.2%)	25 (20.7%)	
≥ 50%	140 (73.7%)	44 (63.8%)	96 (79.3%)	
Killip class				0.0037
I	120 (63.2%)	32 (46.4%)	88 (72.7%)	0.001
II	50 (26.3%)	27 (39.1%)	23 (19.0%)	
III	15 (7.9%)	8 (11.6%)	7 (5.8%)	0.696
IV	5 (2.6%)	2 (2.9%)	3 (2.5%)	

Data are presented as means ± SD or *n* (%) or median (interquartile range). BMI: body mass index; CABG: coronary artery bypass graft; EF: left ventricular ejection fraction.

between the conservative group and the invasive group. While the number of patients aged < 85 years accounting for 72.1% was more than the number of patients aged ≥ 85 years accounting for 27.9% in the study ($P = 0.0032$). Medical history was similar between the two groups except for previous myocardial infarction ($P < 0.0001$), previous CABG ($P = 0.0045$), III degree atrioventricular block ($P = 0.0027$), renal insufficiency ($P < 0.0001$) and anaemia ($P = 0.0029$). Remarkable differences in creatinine level ($P = 0.0005$), GRACE score ($P = 0.0012$), left ventricular ejection fraction ($P = 0.0191$) and Killip class ($P = 0.0037$) were observed.

3.2   Medical treatment at discharge

As summarized in Table 2, medical treatment at discharge including clopidogrel, β-blocker and ACEI/ARB was similar between the two strategy groups. Patients were given dual antiplatelet including aspirin and clopidogrel. 100% patients in the invasive group and 89.9% patients in the conservative group took aspirin ($P = 0.0526$), as well as 90.9% patients received invasive strategy and 89.9% patients received conservative strategy took clopidogrel ($P = 0.8144$), respectively. The use of statins was much more frequent in the invasive group (97.5% *vs.* 89.9%, $P = 0.0229$), whereas diuretic was used more commonly in the conservative group (27.3% *vs.* 59.4%, $P < 0.0001$).

3.3   Outcomes and complications

The primary endpoint (death) occurred in 21 (17.4%) patients received invasive strategy and in 29 (42.0%) patients received conservative management ($P = 0.0002$) (Table 3). Six (5.0%) patients in the invasive group and one (1.4%) in the conservative group both had angina pectoris. Three (2.5%) patients in the invasive group and two (2.9%) patients in the conservative group had HF. The invasive group had one (0.8%) atrial fibrillation, one (0.8%) acute myocardial infarction and one (0.8%) cerebral infarction, whereas the conservative group had none of these complications. Patients had a higher readmission rate (14.9%) in the invasive group compared with the conservative group (7.2%) (Table 3).

3.4   Independent influential factors for invasive strategy

Variables with $P < 0.1$ from univariate analysis were further analyzed. Multivariate analysis showed that the level of creatinine (OR = 1.01, 95% CI: 0.10–1.03, $P = 0.05$) and use of diuretic (OR = 3.65, 95% CI: 1.56–8.53, $P = 0.003$) were independent influential factors for invasive strategy (Table 4).

Table 2.   Medical treatment at discharge.

Medical treatment	Total (*n* = 190)	Conservative strategy group (*n* = 69)	Invasive strategy group (*n* = 121)	*P*-value
Aspirin	179 (94.2%)	62 (89.9%)	121 (100.0%)	0.0526
Clopidogrel	172 (90.5%)	62 (89.9%)	110 (90.9%)	0.8114
Statins	180 (94.7%)	62 (89.9%)	118 (97.5%)	0.0229
β-blocker	156 (82.1%)	54 (78.3%)	102 (84.3%)	0.2965
ACEI/ARB	96 (50.5%)	33 (47.8%)	63 (52.1%)	0.5740
Diuretic	74 (38.9%)	41 (59.4%)	33 (27.3%)	< 0.0001

Data are presented as *n* (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 3.   Clinical outcomes and complications.

Outcome and complication	Total (*n* = 190)	Conservative strategy group (*n* = 69)	Invasive strategy group (*n* = 121)	*P*-value
Death	50 (26.3%)	29 (42.0%)	21 (17.4%)	0.0002
Complications				
Angina pectoris	7 (3.7%)	1 (1.4%)	6 (5.0%)	0.2168
Heart failure	5 (2.6%)	2 (2.9%)	3 (2.5%)	0.8622
Atrial fibrillation	1 (0.5%)	0	1 (0.8%)	NA
AMI	1 (0.5%)	0	1 (0.8%)	NA
Cerebral infarction	1 (0.5%)	0	1 (0.8%)	NA
Readmission	23 (12%)	5 (7.2%)	18 (14.9%)	0.1210

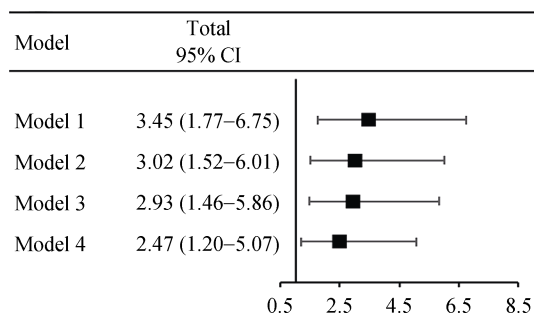Data are presented as *n* (%). AMI: acute myocardial infarction.

Table 4. Multivariate analysis for influential factors of invasive strategy.

| Variable	*β*	Standard error	Wald	*P*-value	OR	95% CI
Age	0.61	0.43	2.05	0.15	1.85	(0.80–4.26)
Creatinine	0.01	0.01	3.91	0.05	1.01	(0.10–1.03)
Diastolic pressure	−0.01	0.02	0.67	0.41	0.99	(0.95–1.02)
Heart rate	0.015	0.01	1.21	0.27	1.02	(0.99–1.04)
GRACE score	−0.01	0.02	0.40	0.53	0.99	(0.95–1.03)
LVEF	0.51	0.52	0.96	0.33	1.66	(0.60–4.56)
Killip class						
II	0.55	0.45	1.53	0.22	1.74	(0.73–4.15)
III	0.18	0.75	0.06	0.81	1.20	(0.27–5.28)
IV	−0.17	1.11	0.02	0.88	0.84	(0.10–7.39)
Previous myocardial infarction	0.52	0.47	1.24	0.27	1.68	(0.67–4.22)
Previous CABG	1.18	0.75	2.48	0.12	3.24	(0.75–14.06)
III degree atrioventricular block	5.11	1.23	0.002	0.97	2.45	(0.79–3.23)
Renal insufficiency	−0.001	0.60	0.002	0.97	0.99	(0.31–3.25)
Anaemia	0.43	0.57	0.56	0.45	1.53	(0.50–4.65)
Aspirin	2.72	0.66	0.009	0.98	3.41	(0.44–4.89)
Statins	−4.46	0.69	0.001	0.97	1.20	(0.45–1.89)
Diuretic	1.30	0.43	8.94	0.003	3.65	(1.56–8.53)

Variables with *P* < 0.1 in univariate analysis were included. CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction.

3.5 Mortality

Multivariate Cox regression models were established with death and survival time (death time-treatment time) as dependent variables, and treatment strategy as independent variables in this study, yielding an unadjusted HR of 3.45 (95% CI: 1.77–6.75, *P* = 0.0003), an adjusted HR of 3.02 (95% CI: 1.52–6.01, *P* = 0.0017), an adjusted HR of 2.93 (95% CI: 1.46–5.86, *P* = 0.0024) and an adjusted HR of 2.47 (95% CI: 1.20–5.07, *P* = 0.0137) for the conservative group versus the invasive group (Figure 1).

Model	Total 95% CI
Model 1	3.45 (1.77–6.75)
Model 2	3.02 (1.52–6.01)
Model 3	2.93 (1.46–5.86)
Model 4	2.47 (1.20–5.07)

Figure 1. Multivariate Cox regression models for accessing the association between the invasive and conservative strategies and mortality. Model 1: unadjusted model; Model 2: adjusted for age, gender; Model 3: adjusted for age, gender, hypertension, diabetes, hyperlipemia, anemia; and Model 4: adjusted for age, gender, hypertension, diabetes, hyperlipemia, anemia, previous myocardial infarction, previous CABG, III degree atrioventricular block and renal insufficiency. The conservative strategy compared with the invasive strategy, *P* < 0.05. CABG: coronary artery bypass graft.
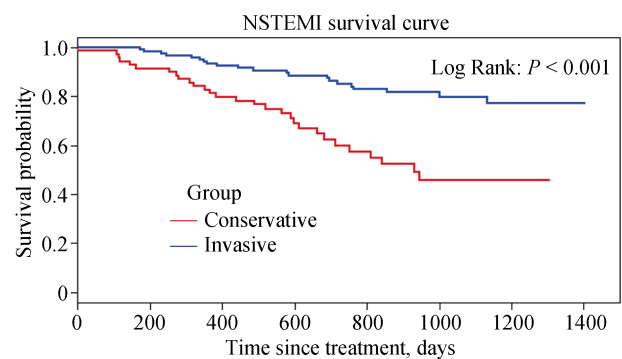
Figure 2. Survival probability of the invasive strategy versus the conservative strategy. The invasive strategy compared with conservative strategy, *P* < 0.001. NSTEMI: non-ST-segment elevation myocardial infarction.

As shown in Figure 2, there was a significant difference in survival probability between conservative group and invasive group. The survival probability of conservative group was remarkably reduced with time since treatment than that of invasive group (*P* < 0.001).

4 Discussion

The proportion of elderly patients presenting with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) is increasing and remains the leading cause of death worldwide.[7] Age was identified to be associated with the reduction in survival benefit in elderly patients with STEMI

or NSTEMI.[8] Although the number of deaths from coronary heart disease has gradually decreased over the last decades in western countries, about one-third of all deaths in patients aged older than 35 years remained. Epidemiology of coronary heart disease and ACS along with the fact unveiled a continual increasing mortality in developing countries. Thus effective primary prevention methods need to be implemented around the world and risk groups and areas should be identified for possible improvement.[9]

Management of elderly patients with ACS has many challenges due to the atypical presentation of symptoms compared with younger patients.[10] The elderly patients are considered as a heterogeneous subgroup with various frailties, impairment of cognition and function states. In addition, they are under-represented in large clinical trials. Considering the above rationale, the elderly patients, especially those aged 80 years or older, are less likely to receive invasive treatment than younger patients according to the present guidelines. Therefore, it is imminent to implement effective approaches for managing very elderly patients with NSTEMI, and identify risk groups and areas for possible improvement.

In this study, our results suggested that the invasive strategy including early coronary angiography and subsequent treatment with PCI, CABG, or optimum medical treatment was associated with the lower mortality compared with the only optimum medical treatment in patients aged 80 years or older with NSTEMI received conservative strategy. The primary outcome was death from any cause. The secondary outcome was the composite events, such as readmission and complications. No differences of readmission and complications were observed between the two strategy groups while death reached statistical significance. The level of creatinine and the use of diuretic were proved to be independent influential factors for invasive strategy. Multivariate Cox regression analysis confirmed that the mortality in the conservative group was more than two times higher than that in the invasive group.

Elevated level of serum creatinine is associated with increased cardiovascular disease (CVD) and all-cause mortality. A 10-year prospective cohort study in Japan demonstrated that higher level of serum creatinine, proteinuria, and decreased glomerular filtration rate were significant predictors for mortality from CVD and all causes in the Japanese population.[11] Ndrepepa G, *et al*.[12] and his colleagues unveiled an increment of serum creatinine ≥ 12 μmol/L could independently predict long-term mortality in patients with NSTEMI treated with PCI. Our result was consistent with these findings. In the present study, creatinine level in the invasive group (86.0 mg/dL) was significant higher than that in the conservative group (97.2 mg/dL). Further results showed that creatinine was an independent influential factor for invasive strategy, and a higher mortality occurred in the conservative group, indicating that elevated serum creatinine is associated with increased mortality in the conservative group.

Diuretics are frequently used for removal of retained fluid and symptoms improvement in patients with HF. Previous clinical trial suggested loop diuretics treatment was associated with significant increased long-term mortality at discharge among patients with worsening HF.[13] In a Swedish nationwide trial of 26,218 patients with HF, use of diuretic at discharge was associated with increased long-term all-cause mortality.[14] In this study, 41 patients (59.4%) in the conservative group received diuretics treatment at hospital discharge whereas 33 patients (27.3%) in the invasive group. Multivariate analysis also confirmed that use of diuretic was an independent influential factor for invasive strategy. The result implied that the very elderly patients with NSTEMI treated with diuretic in the conservative group were associated with higher mortality versus those in the invasive group.

Previous trials have suggested the elderly patients might derive great benefit from an invasive strategy after NSTEMI.[15,16] The RIDDLE-NSTEMI study investigated the clinical impact of immediate versus delayed invasive intervention in patients presenting with NSTEMI, and the median age was ≤ 65 years old.[17] A routine invasive or selective invasive strategy in patients with NSTE-ACS was performed in the ICTUS trail[18] or RITA-3 trail,[19] of which the patients were younger than 80 years old. However, the elderly patients (aged 80 years or older) were under-represented in previous trials. Though the Italian elderly ACS study enrolled a total of 313 NSTE-ACS patients aged ≥ 75 years (mean 82 years), this study was underpowered for definitive conclusions about the benefit of an early invasive strategy.[20]

The After Eighty study enrolled consecutive clinically stable patients aged 80 years or older with NSTEMI or unstable angina in the South-East Health Region of Norway,[6] and it was the first randomized controlled trial to be specifically designed for the very elderly population. However, a dilution of the efficacy occurred with increasing age, and whether patients ≥ 90 years old could benefit from the invasive strategy remained poorly elucidated. Unfortunately, the After Eighty study failed to address the effect of invasive management on readmission to hospital and prognosis. In the present study, a total of 190 very elderly patients (aged 80 years or older) presenting with NSTEMI in Fuwai Hos-

pital, Beijing, China were included, and our findings proved that the very elderly NSTEMI patients could benefit from the invasive strategy versus the conservative strategy. And there was no difference in adverse events including readmission and complications between the two strategy groups.

For death from any cause, no difference was seen between the two strategy groups in the After Eighty study.[6] On the contrary, our data illustrated that patients in the conservative group had significant higher death versus patients in the invasive group. Patients with or without unstable angina, and age of patients (whether older than 90 years) might be responsible for this difference. Moreover, the area (China or Norway) might also contribute to this.

4.1 Limitations

This study had some limitations. Firstly, the present study comprised a relatively small sample size which may exist selection bias. Secondly, this single-center study lacks external validation. Therefore, further multi-center, longer term follow-up and large-sample clinical studies are needed.

4.2 Conclusions

In conclusion, we have demonstrated that the invasive strategy including PCI or CABG together with optimum medical treatment is superior to the optimum medical treatment alone in reducing mortality in patients aged 80 years or older with NSTEMI. Our findings provide an evidence for the invasive clinical application of the very elderly patients with NSTEMI in China.

Acknowledgments

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