Stenting versus non-stenting treatment of intermediate stenosis culprit lesion in acute ST-segment elevation myocardial infarction: a multicenter randomized clinical trial

Jing DAI[1], Shu-Zheng LYU[1], Yun-Dai CHEN[2], Xian-Tao SONG[1], Min ZHANG[1], Wei-Min LI[3],
Yang ZHENG[4], Shang-Yu WEN[5], Shao-Ping NIE[1], Yu-Jie ZENG[1], Hai GAO[1], Yi-Tong MA[6],
Shu-Yang ZHANG[7], Li-Jun GUO[8], Zheng ZHANG[9]

[1]Department of Cardiology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing, China
[2]Department of Cardiology, Chinese PLA General Hospital, Beijing, China
[3]Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China
[4]Department of Cardiology, the First Bethune Hospital of Jilin University, Changchun, Jilin, China
[5]Department of Cardiology, Daqing Oilfield General Hospital, Daqing, Heilongjiang, China
[6]Department of Cardiology, the First Affiliated Hospital of Xinjiang Medical University, Urumchi, Xinjiang Uygur Autonomous Region, China
[7]Department of Cardiology, Peking Union Medical College Hospital, Beijing, China
[8]Department of Cardiology, Peking University Third Hospital, Beijing, China
[9]Department of Cardiology, the First Hospital of Lanzhou University, Lanzhou, Gansu, China

Abstract

Background   The benefit/risk ratio of stenting in acute ST-segment elevation myocardial infarction (STEMI) patients with single vessel intermediate stenosis culprit lesions merits further study, therefore the subject of the present study. **Methods and results**   It was a prospective, multicenter, randomized controlled trial. Between April 2012 and July 2015, 399 acute STEMI patients with single vessel disease and intermediate (40%–70%) stenosis of the culprit lesion before or after aspiration thrombectomy and/or intracoronary tirofiban (15 μg/kg) were enrolled and were randomly assigned (1: 1) to stenting group (n = 201) and non-stenting group (n = 198). In stenting group, patients received pharmacologic therapy plus standard percutaneous coronary intervention (PCI) with stent implantation. In non-stenting group, patients received pharmacologic therapy and PCI (thrombectomy), but without dilatation or stenting. Primary endpoint was 12-month rate of major adverse cardiac and cerebrovascular events (MACCE), a composite of cardiac death, non-fatal myocardial infarction (MI), repeat revascularization and stroke. Secondary endpoints were 12-month rates of all cause death, ischemia driven admission and bleeding complication. Median follow-up time was 12.4 ± 3.1 months. At 12 months, MACCE occurred in 8.0% of the patients in stenting group, as compared with 15.2% in the non-stenting group (adjusted HR: 0.42, 95% CI: 0.19–0.89, P = 0.02). The stenting group had lower non-fatal MI rate than non-stenting group, (1.5% $vs.$ 5.5%, P = 0.03). The two groups shared similar cardiac death, repeat revascularization, stroke, all cause death, ischemia driven readmission and bleeding rates at 12 months. **Conclusions**   Stent implantation had better efficacy and safety in reducing MACCE risks among acute STEMI patients with single vessel intermediate stenosis culprit lesions.

1   Introduction

The basic principle of treating acute ST-segment eleva-

tion myocardial infarction (STEMI) is to achieve effective myocardial reperfusion.[1] Primary percutaneous coronary intervention (PCI) with stent implantation has been the standard therapy in acute STEMI patients. Compared with medical treatment alone, stent implanting can achieve larger lumen gain and helps to reduce the re-occlusion risk of the infarct-related artery (IRA). However, the risks of no re-flow phenomenon, stent thrombosis, stent restenosis, among other complications, might impair patients' progno-

sis. What is the benefit/risk ratio of stenting in acute STEMI patients with single vessel intermediate stenosis culprit lesions or whether they could be stabilized without stenting? Data is limited, therefore the subject of the present study?

2   Methods

2.1   Study design

It was a prospective, multicenter, randomized, controlled trial. This study was in compliance with the declaration of Helsinki. The protocol was approved by the institutional review board of each participating medical center. Written informed consent was obtained from each participant before inclusion. The present study has been registered in the World Health Organization International Clinical Trials Registry Platform (ChiCTR-TRC-13003120).

The randomization was utilized by means of voice-response system. The randomization codes were developed with a number generator and were randomly permuted to achieve balanced groups.

Patients were prospectively enrolled between April 2012 and July 2015 from nine large medical centers in China. A registry information system was set up. Independent observers were assigned for quality assessments. The trial administration, as well as the data management and the statistical analyses were performed at the Beijing Anzhen Hospital.

2.2   Patient selection

Inclusion criteria were: 18–80 years old; acute ischemia chest pain of more than 30min, ST-segment elevation of more than 0.1 mV in at least two leads or new left bundle-branch block on the ECG, troponin level elevation; time from symptom onset of less than 12 h; single vessel disease; intermediate stenosis culprit lesions (40%–70% diameter reduction).

Exclusion criteria were: rescue PCI after thrombolysis; clinically unstable status (cardiogenic shock, acute heart failure, sustained ventricular fibrillation); multi-vessel disease; stenosis of more than 70% or less than 40% in diameter; acute stent thrombosis; severe heart valve disease; cardiomyopathy; active bleeding; history of intracranial bleeding; multiple organ failure; malignancies; and concomitant disease with life expectancy less than one year.

2.3   Prehospital pharmacologic treatment

Patients were pretreated with aspirin (300 mg), clopidogrel (600 mg) or ticagrelor (180 mg) and unfractionated heparin (100 IU/kg). For patients who received intravenous tirofiban administration, the dose of unfractionated heparin

was adjusted to be 70 IU/kg. Other treatments include pain relief therapy, abolition of prelethal arrhythmias, etc.

2.4   Catheterization procedures

During invasive procedure, unfractionated heparin was intravenously administered when needed to maintain therapeutic activated clotting time.

All patients underwent primary coronary angiography (CAG), door to angiography time was less than one hour. CAG was performed with the use of 6 F or 7 F sheath via trans-radial or trans-femoral approach.

Angiographic characteristics, which include the thrombolysis in myocardial infarction (TIMI) coronary blood flow and thrombus burden, were assessed and recorded. In high thrombus burden lesions, thrombus debulking therapy (manual aspiration thrombectomy or intracoronary administration of glycoprotein IIb/IIIa inhibitor) was done when necessary, and was at the discretion of the cardiologist.

In patients who received manual aspiration thrombectomy, adequate thrombectomy was carried out to obtain normal coronary blood flow. The thrombectomy device was a 6-French (crossing profile, 0.068 in) Export Aspiration Catheter (Medtronic Cardio Vascular, Santa Rosa, CA, USA).

As for the use of glycoprotein II b/III an inhibitor, intravenous tirofiban administration was selectively used, with 0.4 μg/kg per min for 30 min. In high thrombus burden lesions or in case of no re-flow phenomenon, tirofiban was intracoronary administered with bolus dose of 15 μg/kg, followed by intravenous administration with maintenance dose of 0.1 μg/kg per min for 24–48 h. Intracoronary nitrates administration was recommended to obtain maximal epicardial vessel vasodilation.

Residual stenosis of culprit lesions was measured after normal ante-grade coronary blood flow was restored. Patients whose CAG confirmed to be with single vessel intermediate (40%–70%) stenosis culprit lesions were randomly assigned in a 1: 1 ratio to receive either standard primary PCI with stent implantation (stenting group) or pharmacologic therapy and PCI (thrombectomy) but without dilatation or stenting. Patients who were allocated to the stenting group received standard primary PCI with stent implantation, with or without balloon dilation. Types of instruments and intervention strategies were left to the operators.

Apart from the selective thrombus debulking therapy received, patients assigned to the non-stenting group received neither stent implantation nor balloon dilation. Because in the non-stenting group, stent implantation is not intended, balloon dilatation alone is avoided for fear of risks of coronary dissection and endothelial injury after balloon dilata-

tion. To assure the stability of the lesion, the lesion was wired, no less than 10 min of observation was recommended before the removal of the sheath. For patient safety consideration, during hospitalization, patients assigned to non-stenting group would be considered for urgent CAG and stent implantation in case of refractory angina, re-infarction, malignant ventricular arrhythmia, worsening heart failure, severe hypotension and cardiac shock. Perioperative events and complications were evaluated and recorded.

2.5　Angiographic variables analysis

Coronary blood flow was graded according to the Thrombolysis in Myocardial Infarction (TIMI) grading system.[2] Normal coronary blood flow was defined as TIMI 3 flow. Thrombus burden was assessed and classified with TIMI thrombus grades, large thrombus burden lesions were defined as thrombus Grade 4–5 and small thrombus burden as thrombus Grade 0–3.[3]

Post invasive procedure, patients' angiographic and intervention procedural records were collected and were further analyzed in the central angiographic laboratory in Beijing Anzhen Hospital. Quantitative coronary angiography (QCA) was used to assess angiographic characteristics. Corrected TIMI frame count (CTFC) was used to further assess the coronary blood flow. CTFC ≤ 23 frames shows normal fast coronary blood flow; CTFC > 23 but ≤ 40 frames is taken as a little slow but still normal blood flow; CTFC > 40 frames represents slow re-flow; if the CTFC > 60 frames, the blood flow is actually quite slow.[4]

In order to assess myocardium reperfusion effects, ST segment resolution in ECG was evaluated. ECGs were recorded on admission and 30 to 60 min post invasive procedure. Resolution degree of ST-segment elevation was classified as complete (> 70%), partial (30%–70%), or none (< 30%).[5] Persistent ST-segment deviation was classified as < 2 mm, 2–10 mm, and > 10 mm. The presence or absence of pathologic Q waves was also recorded.[5]

2.6　Post procedural therapy

Both groups received optimized pharmacologic therapy. Post invasive procedure, patients were continued on a maintenance dose of ticagrelor (180 mg/day) or clopidogrel (75 mg/day) for 12 months and aspirin (100 mg/day) lifelong. Other medications included β blockers, statins, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), nitrates, among others.

2.7　Endpoints

The primary endpoint was 12-month rate of major adverse cardiac and cerebrovascular events (MACCE), a composite of cardiac death, nonfatal myocardial infarction (MI), repeated revascularization and stroke. Secondary endpoints were 12-month rates of all cause death, ischemia driven admission and bleeding complication.

Cardiac death was defined as death from heart disease, including cardiac tamponade, cardiac rupture, heart failure, re-MI, malignant arrhythmia and sudden unexpected death.[6] Nonfatal MI was defined as recurrent severe chest pain lasting for > 30min, with ischemic ECG changes and troponin level elevation to > 99th percentile of normal population at participating site laboratory.[7] Reasons of repeat revascularization were significant stenosis (> 70% in diameter reduction) of vessels accompanied with angina or re-MI. Stoke was defined as new focal neurological deficit lasting > 24 h, and confirmed by computed tomography or magnetic resonance imaging.[8] Bleeding complication was defined according to the TIMI bleeding criteria.[9]

A follow-up database was set up. Patients were followed up during clinical visits or by phone.

2.8　Statistical analysis

All statistical analyses were performed with the use of Statistical Package for Social Science software, version 17.0 (SPSS Inc., IBM, Armonk, New York). Continuous variables were checked with normality test (Kolmogorov-Smirnov test). Normal data was presented as mean ± SD. For non-normally distributed parameters, nonparametric test was used as appropriate. The two groups' continuous variables were compared with two-tailed Student's *t* test or Wilcoxon rank sum test (Mann-Whitney *U* test). Categorical variables were presented as percentages and were compared using the Chi-square test or Fisher's exact test. Cox proportional hazard model analysis was conducted to estimate the variables' hazard ratio (HR) and its 95% confidence interval (CI) for clinical endpoints. Multivariate Cox proportional hazard model was used to adjust baseline risk factors and to find predictors of clinical events over long term follow-up. Variables with a *P* value < 0.10 were candidates for multivariate regression model. A 2-tailed *P* value < 0.05 was considered statistically significant.

3　Results

3.1　Patients' enrollment and follow-up

Figure 1 shows the study flow chart. Between April 2012 and July 2015, a total of 2966 acute STEMI patients were initially screened from the nine participating hospitals and received CAG. According to patients' angiographic characters, the following patients were ineligible: 1359 patients were with multi-vessel disease; 1085 patients were with
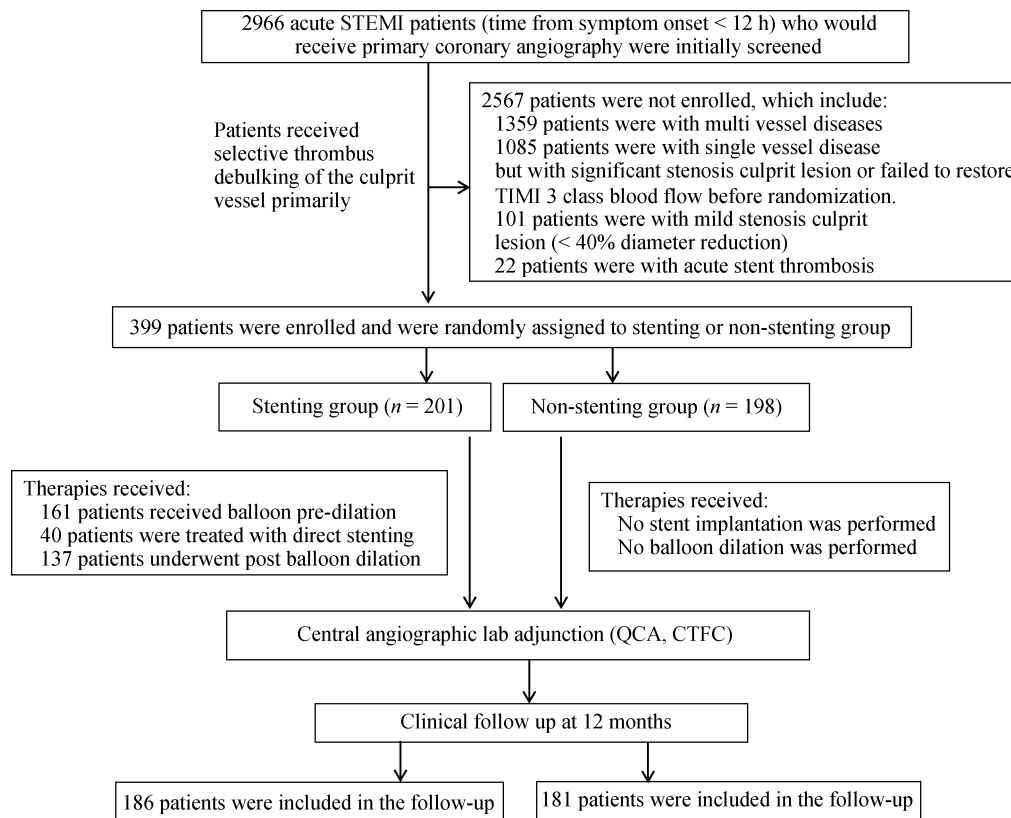
Figure 1.   Study flow chart. CTFC: corrected TIMI frame count; PCI: percutaneous coronary intervention; QCA: quantitative coronary angiography; STMEI: ST-segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction.

single vessel disease but with significant stenosis culprit lesions (> 70% of diameter reduction); 101 patients were with mild stenosis culprit lesions (< 40% of diameter reduction); and 22 patients were with acute stent thrombosis.

Therefore, 399 patients met study criteria and were randomly divided into stenting group (*n* = 201) and non-stenting group (*n* = 198). During follow-up, 32 patients dropped out without definite reasons. Therefore, 367 (92.0%) patients completed 12 months' follow up. Data from all participating patients, including study dropouts, were analyzed. No crossover occurred between the two groups.

3.2   Baseline clinical characteristics

Table 1 summarized the baseline characteristics of the patients and the medical treatment received at inclusion. Baseline clinical characteristics were similarly distributed between two groups, with overall mean age of 54.8 ± 11.9 years old, and predominantly (83.7%) male. There were no significant differences in cardiovascular risk profile, concomitant diseases and laboratory findings between two groups. The two groups shared similar perioperative pharmacotherapies (Table 1) and medication at 12 month follow up (Table 2).

3.3   Angiographic and invasive procedural characteristics

Procedural data of the 399 patients are shown in Tables 3–6. The presented angiographic and intervention procedural data are based on the assessment of QCA.

The mean time from symptom onset was 5.73 ± 2.3 h. The mean door to angiography time was 54.8 ± 9.2 min. 78.9% of these patients underwent CAG via trans-radial access.

Overall, the initial angiographic finding (before thrombectomy) showed that the mean diameter stenosis is 84.6% ± 17.4%. A total of 357 (89.5%) patients presented with high thrombus burden lesions (Grade 4–5) and received thrombectomy. Tirofiban administration was performed in 201 (51.9%) patients. After thrombus debulking therapy, the mean residual stenosis of culprit lesion was 51.1% ± 5.8% (diameter reduction), TIMI 3 class blood flow was achieved in 399 patients.

In stenting group, direct stent implantation was performed in 116 (57.7%) patients. The other 85 (42.3%) patients received balloon pre-dilation before stenting. All implanted stents were drug eluting stents. Post balloon dilation

Table 1.   Baseline clinical characteristics and medical treatment of 399 patients enrolled.

	Stent group (*n* = 201)	Non-stent group (*n* = 198)	*P* value
Age, yrs	54.7 ± 11.5	54.9 ± 13.1	0.87
Male	173 (86.1%)	161 (81.3%)	0.20
Smoking	105 (52.2%)	102 (51.5%)	0.89
Diabetes mellitus	58 (28.9%)	42 (21.2%)	0.08
Hypertension	79 (39.3%)	85 (42.9%)	0.46
Previous stroke	4 (2.0%)	3 (1.5%)	1
Previous MI	8 (4.0%)	5 (2.5%)	0.41
Anterior wall infarction	103 (51.2%)	99 (50%)	0.80
Heart rate, beats/min	77.1 ± 14.3	74.7 ± 12.6	0.08
Blood pressure, mmHg			
Systolic	118.9 ± 16.7	122.0 ± 17.9	0.07
Diastolic	74.5 ± 11.1	75.8 ± 11.5	0.25
Troponin, µg/L	64.2 (102.0–22.7)	50.2 (75.3–32.1)	0.34
CK, U/L	2041 (2956.5–909.6)	1562.5 (2568.8–980)	0.25
CK-MB, U/L	167.5 (270.9–94.4)	158 (237.5–105.3)	0.19
LVEDD, mm	49.5 ± 4.9	48.7 ± 5.5	0.13
LVEF			0.40
< 50%	53 (26.4%)	45 (22.7%)	
≥ 50%	148 (73.6%)	153 (77.3%)	
Perioperative medication			
Aspirin	210 (100%)	198 (100%)	1
P2Y12 receptor inhibitor	201 (100%)	198 (100%)	1
ACEI/ARB	137 (68.2%)	126 (63.6%)	0.34
β-blockers	164 (81.6%)	155 (78.3%)	0.41
Statins	201 (100%)	198 (100%)	1

Data were presented as median (Qu-QL), mean ± SD or *n* (%). Laboratory results were based on the data before coronary angiography. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CK: creatine kinase; CK-MB: creatine kinase myocardial band; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Table 2.   Medication at 12-month follow up (data from patients with completed follow-up record).

	Stent group (*n* = 186)	Non-stent group (*n* = 198)	*P* value
Aspirin	183 (98.4%)	179 (98.9%)	1
P2Y12 receptor inhibitor	184 (98.9%)	173 (95.6%)	0.06
ACEI/ARB	126 (67.7%)	115 (63.5%)	0.40
β-blockers	151 (81.2%)	142 (78.5%)	0.52
Statins	172 (92.5%)	163 (90.1%)	0.41

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

Table 3.   Perioperative angiographic characteristics of 399 patients enrolled.

	Stent group (*n* = 201)	Non-stent group (*n* = 198)	*P* value
Time from symptom onset, h	5.68 ± 2.1	5.82 ± 2.7	0.56
Door-to-balloon time, min	54.2 ± 9.8	55.4 ± 8.6	0.19
Trans-radial angiography	162 (80.6%)	153 (77.3%)	0.42
IRA			0.62
LAD	103 (51.2%)	99 (50%)	
LCX	21 (10.4%)	27 (13.6%)	
RCA	77 (38.3%)	73 (36.9%)	
Reference vessel diameter, mm	3.42 ± 0.43	3.48 ± 0.51	0.20
Extent of stenosis, %	83.9 ± 17.2	85.3 ± 18.8	0.44
*Lesion length, mm	18.7 ± 10.61	19.8 ± 7.94	0.24
TIMI thrombus burden			0.93
1–2 class	6 (3.0%)	5 (2.5%)	
3 class	14 (7.0%)	17 (8.6%)	
4 class	29 (14.4%)	27 (13.6%)	
5 class	152 (75.7%)	149 (75.3%)	
CTFC**			0.88
< 40	4 (2.0%)	3 (1.5%)	
40–60	24 (11.9%)	26 (13.2%)	
> 60#	173 (86.1%)	169 (85.3%)	
Thrombus aspiration	181 (90.0%)	176 (88.9%)	0.75
Tirofiban administration			
By intravenous	156 (77.6%)	149 (75.2%)	0.64
By intracoronary	101 (50.2%)	106 (53.5%)	0.51

Data were presented as mean ± SD or *n* (%). *A total of 301 patients (152 *vs.* 149) with total occlusion of the infarct-related artery were not analyzed; **the frame rate for CTFR measurement was 15 frames/s; #301 patients' lesions (152 *vs.* 149, respectively) were total occlusion due to acute thrombus, these patients' CTFC were counted as > 60 frames. CTFC: corrected TIMI frame count; IRA: infarct related artery; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; TIMI: thrombolysis in myocardial infarction.

Table 4.   Residual nature of lesion after thrombectomy.

	Stent group (*n* = 201)	Non-stent group (*n* = 198)	*P* value
MLD, mm	1.69 ± 0.52	1.78 ± 0.56	0.10
Extent of stenosis, %	51.4 ± 5.6	50.8 ± 6.9	0.34
Lesion length, mm	12.8 ± 4.86	12.4 ± 4.17	0.32
CTFC			0.92
< 23	75 (37.3%)	78 (39.4%)	
23–40	103 (51.2%)	101 (51.0%)	
40–60	20 (10.0%)	17 (8.6%)	
> 60	3 (1.5%)	2 (1.0%)	

Data were presented as mean ± SD or *n* (%). CTFC: corrected TIMI frame count; MLD: minimal luminal diameter.

Table 5. Angioplasty procedure.

	Stent group (*n* = 201)	Non-stent group (*n* = 198)	*P* value
Balloon dilation without stent	0	0	1
Stent implantation	201 (100%)	0	< 0.01
Balloon pre-dilation	85 (42.3%)	-	
Direct stent implantation	116 (57.7%)	-	
Post-dilation	124 (61.7%)	-	
Total length of stent, mm	16.9 ± 4.32	-	
Mean size of stent, mm	3.39 ± 0.56	-	
Mean stent number	1.48 ± 0.56	-	

Data were presented as mean ± SD or *n* (%).

Table 6. Angiographic results post procedure and intra-procedure complications.

	Stent group (*n* = 201)	Non-stent group (*n* = 198)	*P* value
MLD, mm	3.33 ± 0.49	1.89 ± 0.92	< 0.01
Residual stenosis, %	2.74 ± 0.92	46.7 ± 8.9	< 0.01
CTFC			< 0.01
< 23	97 (48.3%)	78 (39.4%)	
23–40	70 (34.8%)	101 (51.0%)	
40–60	25 (12.4%)	17 (8.6%)	
> 60	9 (4.5%)	2 (1.0%)	
Intra-procedure complications			
Acute occlusion	2 (1.0%)*	0 (0)	0.50
Flow limiting dissection	1 (0.5%)	0 (0)	1
Non-protocol repeat catheterization	0 (0)	0 (0)	1

Data were presented as mean ± SD or *n* (%). *Acute side branch occlusion after stent implantation. CTFC: corrected TIMI frame count; MLD: minimal luminal diameter; TIMI: thrombolysis in myocardial infarction.

was performed in 124 (61.7%) patients. In non-stenting group, neither balloon dilatation nor stent implantation was performed.

It is noticeable that 22 (11.1%) patients who were allocated in the non-stenting group were with small thrombus burden lesions (TIMI thrombus Grade ≤ 3 class). This might be associated with early spontaneous myocardial reperfusion after anti-thrombus pharmaceutical therapy. These 22 (11.1%) patients just received CAG, with no aspiration thrombectomy nor other invention therapies performed.

3.4 Immediate invasive effects and intra-procedure complications

Post invasive procedure, the residual minimal luminal diameter (MLD) was 3.33 ± 0.49 mm in the stenting group versus 1.89 ± 0.92 mm in the non-stenting group, $P < 0.01$. Normal fast blood flow (CTFC < 23) was achieved in 48.3% of the patients in stenting group versus 39.4% in the

non-stenting group. Meanwhile, slow blood flow was more common in the stenting group (16.9%), compared with the non-stenting group (10.6%), $P = 0.01$ (Figure 2).

As for the myocardial reperfusion assessed by ECG, the two groups had similar PCI to post-procedural ECG time, which was 41 min (interquartile range, 24–63) in the stenting group, and 39 min (interquartile range, 21–58) in the non-stenting group, $P = 0.39$. In the stenting group, 55.7% of the patients were found with complete ST-segment resolution on ECG, compared with 39.4% of the patients in the non-stenting group, $P < 0.01$. In the stenting group, 56.4% of the patients had no persistent ST-segment deviation, as compared with 42.1% in the non-stenting group, $P = 0.03$ (Figure 3). While, 22.7% of the patients in the stenting
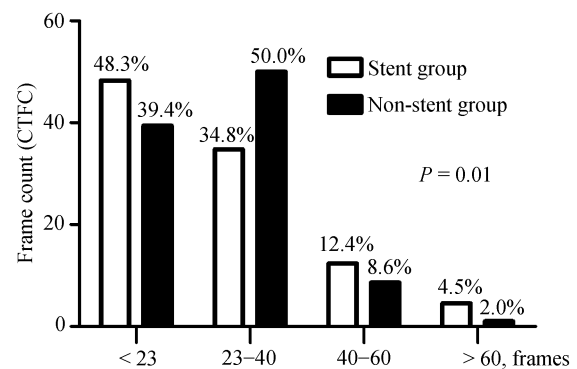

Figure 2. Post procedural coronary blood flow (corrected TIMI frame count). CTFC: corrected TIMI frame count; TIMI: thrombolysis in myocardial infarction.
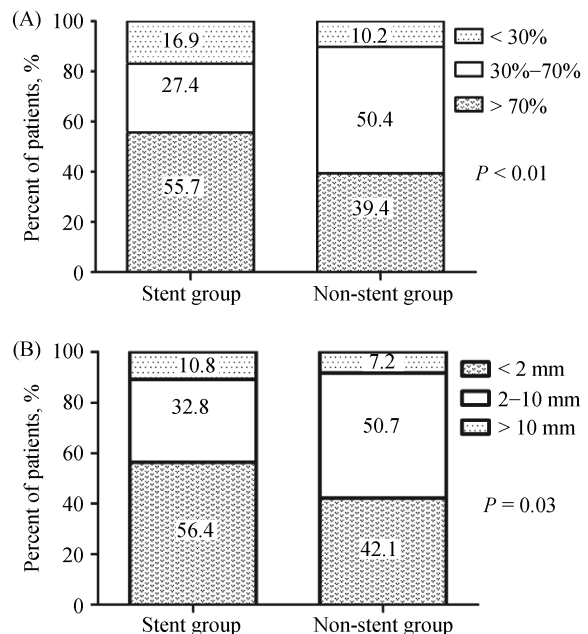

Figure 3. Myocardium reperfusion effects evaluation post procedure. (A): Resolution of ST-segment elevation; (B): persistent ST-segment deviation.

group versus 20.9% in the non-stenting group had no pathologic Q waves on ECG, *P* = 0.73.

As for the peri-operative complication, overall, no death occurred during invasive procedure, no patient experienced non-protocol pre-discharge catheterization. In the stenting group, one patient happened flow limiting dissection after balloon pre-dilation and two patients happened acute side branch occlusion after stent implantation. All the three patients' problems were resolved during primary PCI. In the non-stenting group, no acute vessel occlusion occurred.

3.5   Clinical outcomes during follow up

3.5.1   Primary endpoints

Median follow-up time was 12.4 ± 3.1 months. Overall, the composite primary endpoint of MACCE occurred in 46 (11.5%) patients. Among which, 7 (1.8%) patients died from cardiovascular disease, 14 (3.5%) patients suffered nonfatal MI, 22 (5.5%) patients received repeat revascularization and 3 (0.75%) patients happened stroke at 12 months.

Kaplan-Meier curve revealed higher MACCE free survival rate in the stenting group (92%) than the non-stenting group (84.8%) at 12 months (HR, 0.42, 95% CI, 0.19–0.89, *P* = 0.02) (Figure 4).
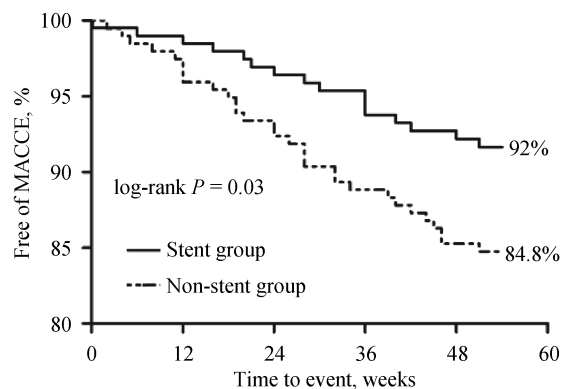

Figure 4.   Kaplan-Meier survival curves of MACCE at 12 months. MACCE: major adverse cardiac and cerebrovascular events.

In multivariate Cox hazards regression analysis, older age, low left ventricular ejection fraction (LVEF) < 50%, slow blood flow (CTFC > 40 frames) were associated with higher MACCE rates. Stenting, aspirin and β blockers use helped to reduce the MACCE risk in these patients (Table 7).

As for the four components of MACCE, the stenting group had lower non-fatal MI rate than non-stenting group.

Table 7.   Cox proportion hazards analysis for predictors of MACCE during 12 months follow-up.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.03	0.99–1.07	0.06	1.05	1.02–1.08	0.048
Male	4.84	0.66–35.64	0.12			
Smoking	1.61	0.61–4.25	0.34			
Diabetes mellitus	1.51	0.68–3.35	0.32			
Hypertension	1.59	0.75–3.38	0.23			
Previous stroke	2.59	0.61–10.94	0.19			
Time from symptom onset (> 6 h)	1.36	0.71–2.60	0.36			
Killip classification	1.40	0.87–2.25	0.17			
LVEF (< 50%)	1.79	0.93–3.47	0.08	3.18	1.46–6.92	0.004
Area of infarction (anterior)	1.29	0.68–2.46	0.43			
Thrombus burden	1.18	0.80–1.74	0.39			
Thrombus aspiration	0.55	0.25–1.18	0.13			
Stent implantation	0.49	0.24–0.98	0.04	0.42	0.19–0.89	0.02
*Slow blood flow	4.31	1.97–9.41	< 0.001	3.54	1.65–7.62	0.001
Aspirin	0.12	0.03–0.50	0.004	0.20	0.04–0.95	0.04
P2Y12 receptor inhibitor	0.26	0.12–0.59	0.001	0.47	0.21–1.05	0.07
ACEI/ARB	0.87	0.39–1.89	0.72			
β blockers	0.40	0.18–0.88	0.02	0.41	0.20–0.82	0.01
Statins	0.36	0.11–1.19	0.09			
Tirofiban	0.55	0.26–1.18	0.13			

*Slow blood flow referred to the residual blood flow to be CTFC > 40 frames post invasive procedure. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CTFC: corrected TIMI frame count; LVEF: left ventricular ejection fraction; MACCE: major adverse cardiac and cerebral events; MLD: minimal luminal diameter; TIMI: thrombolysis in myocardial infarction.

Non-fatal MI occurred in 1.5% of the patients in the stenting group and 5.5% of the patients in the non-stenting group, *P* = 0.03. There were no significant differences in the rates of cardiac death (1.5% *vs.* 2.0%, *P* = 0.72), repeat revascularization (4.5% *vs.* 6.6%, *P* = 0.36), and stroke (0.49% *vs.* 1.0%, *P* = 0.49) between the stenting group and the non-stenting group (Figure 5).

3.5.2 Secondary endpoints

A total of 9 (2.3%) patients died during one year follow-up, of which, 7 (1.7%) patients died of cardiovascular disease. Other causes of death included stroke (*n* = 1) and cancer (*n* = 1). The all cause death rates were similar between the stenting group (1.5%) and the non-stenting group (3.0%), *P* = 0.34. There was no significant difference in the rate of ischemia driven admission between the stenting group (8.0%) and the non-stenting group (6.1%), *P* = 0.46. A total of 3 (0.75%) patients experienced bleeding complications. The rates of bleeding complication did not differ significantly between the two groups: 1.0% *vs.* 0.5%, respectively, *P* = 1 (Figure 6).
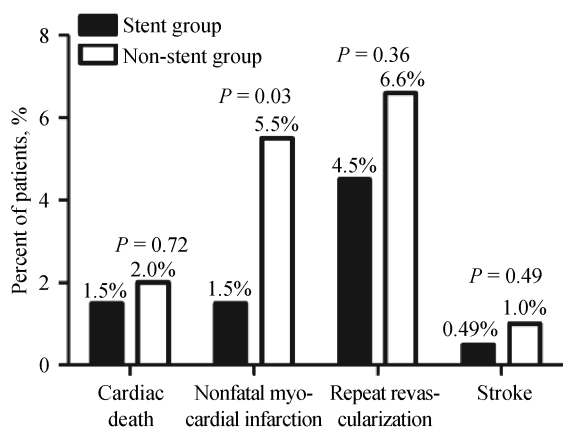

Figure 5.   Components of MACCE at 12 months. MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction.
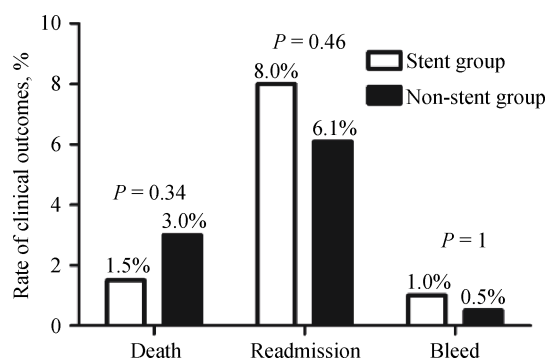

Figure 6.   Secondary outcomes at 12 months.

4   Discussion

The present study might provide a second look at the no stent strategy in the modern era. The main finding of this study is that, for acute STEMI patients with single vessel disease and intermediate (40%–70%) stenosis of the culprit lesion before or after aspiration thrombectomy and/or intracoronary tirofiban (15 μg/kg) were enrolled, stent implanting has better efficacy and safety in reducing MACCE rates during 12 months follow up. Stenting and non-stenting treatments are associated with similar all cause death, ischemia driven admission and bleeding rates at 12 months.

Prior pathology studies have demonstrated that about 35% of the culprit lesions have diameter stenosis of less than 70%.[10,11] The net acute lumen gain in intermediate stenosis lesion is less than those with significant stenosis lesions. In addition, stenting might increase the risks of no-reflow phenomenon, PCI related small MI, side branch occlusion, stent thrombosis and stent restenosis.

No/slow re-flow phenomenon occurs in 12%–32% of the AMI patients during primary PCI.[12] The "no-reflow" phenomenon refers to suboptimal myocardial reperfusion despite epicardial flow restoration in the IRA. The main mechanisms include vasospasm, myocyte reperfusion injury, inflammation, edema and atheroembolization.[13] Apart from MI reperfusion no reflow (myocardial ischemia-reperfusion injury and endothelial damage, among others), stenting might cause additional interventional no reflow risks (distal embolization of atherosclerotic gruel, among others).[14,15] No/slow re-flow phenomenon can cause continuous myocardial ischemia and malignant ventricular remodeling, is associated with higher risks of in-hospital mortality and MACCE.[12] Effective anti-thrombotic therapy, which includes aspiration thrombectomy as well as intracoronary tirofiban[16], is of importance in treating high thrombus burden lesions. Non-stenting approach also helps to reduce the risks of stent restenosis and stent thrombosis. While, the non-stenting approach might have higher IRA re-occlusion risk than the deferred stenting.

Therefore, for acute STEMI patients with single vessel disease and intermediate (40%–70%) stenosis of the culprit lesion, intensive antithrombotic treatment without stenting might be a potential solution.

EROSION study demonstrates that for ACS patients caused by plaque erosion (residual diameter stenosis < 70%), anti-thrombotic therapy without stenting is safe, with similar re-MI rate compared with those who received stent implantation.[17] In the present study, the stenting group had less non-fatal MI rate compared with the non-stenting approach. This difference might be explained by the following reasons.

First, in the present study, acute STEMI which were caused by plaque erosion and plaque rupture were studied as a whole. Compared with ruptured plaque, the eroded plaque has smaller necrotic core and more smooth muscle cells and proteoglycan-rich matrix.[18] The patients enrolled in EROSION trial were more stable than our study. Second, the present study had longer follow-up time (12 months) than the EROSION trial (one month). Third, in the present study, only acute STEMI patients with single vessel intermediate stenosis (40%–70% diameter reduction) culprit lesions were enrolled, stenting was found to have less MACCE rate during long term follow-up.

The DANAMI 3-DEFER trial compared the different strategies between conventional and deferred stenting in STEMI patients. Patients who were allocated to the deferred PCI group received repeat CAG 48 h later. Stent implantation was intended, unless the residual stenosis was < 30%. The conclusion is that routine deferred stenting failed to reduce adverse events compared with the conventional stenting strategy.[19] In the present study, unless non-protocol catheterization caused by ischemia was needed, patients in the non-stenting group did not receive routine deferred stenting.

A few studies have evaluated the different strategies between PCI and conservative pharmacotherapy in treating ACS patients. Legutko J, *et al*.[20] have studied the borderline coronary lesions in ACS patients, and concluded that PCI and medical therapy yield similar clinical outcomes. Prati and colleges demonstrated that STEMI with plaque erosion could be managed with effective anti-thrombotic therapy without stenting.[21]

Several factors might influence the clinical prognosis of these patients. First, the acute lumen gain was larger in the stenting group than the non-stenting group. Second, in patients who were free from no/slow reflow complications, stenting helped to achieve better myocardium reperfusion effect than non-stenting. As for the reperfusion therapy of STEMI, both the epicardial blood flow restoration and myocardium reperfusion are important.[22] Third, besides reperfusion strategies, other factors of age, cardiac function, among others, also might influence patients' clinical outcomes. In the multivariate analysis, older age, compromised left ventricular function (LVEF < 50%) and no/slow reflow phenomenon were associated with higher MACCE rates. Pharmacologic therapy plays an important role too. The benefits of aspirin and β blocker were independent of the reperfusion strategy.

4.1 Limitations

This study has several limitations. First, for fear of increasing total ischemic time during primary PCI, intravas-

cular ultrasound and optical coherence tomography were not used for objective evaluation of lesions. Second, the present finding could not be generalized to acute STEMI patients with multi-vessel diseases. Also, the conclusion could not be extended for the strategy of stable angina or non-ST segment elevation ACS. Third, deferred stenting was not studied. Fourth, larger studied with longer-term follow-up are warranted.

4.2 Conclusion

In the management of single vessel intermediate stenosis culprit lesions in acute STEMI, stent implantation has better efficacy and safety in reducing MACCE during clinical follow up. Further study and long-term data are warranted.

Acknowledgement

References

1   Arntz HR. Reperfusion strategies in ST-elevation myocardial infarction—current status and perspectives for early and pre-hospital treatment. *Resuscitation* 2008; 77: 296–305.

2   Ganz W. The thrombolysis in myocardial infarction (TIMI) trial. *N Engl J Med* 1985; 313: 1018.

3   Napodano M, Dariol G, Al Mamary AH, *et al*. Thrombus burden and myocardial damage during primary percutaneous coronary intervention. *Am J Cardiol* 2014; 113: 1449–1456.

4   Gibson CM, Cannon CP, Daley WL, *et al*. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996; 93: 879–888.

5   van 't Hof AW, Liem A, de Boer MJ, *et al*. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Zwolle myocardial infarction study group. *Lancet* 1997; 350: 615–619.

6   Stone GW, Adams DH, Abraham WT, *et al*. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol* 2015; 66: 308–321.

7   Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *Eur Heart J.* 2012; 33: 2551–2567.

8   Barber M, Stott DJ, Langhorne P. An internationally agreed definition of progressing stroke. *Cerebrovasc Dis* 2004; 18: 255–257.

9   Mehran R, Rao SV, Bhatt DL, *et al*. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulatio* 2011; 123: 2736–2747.

10 Pijls NH. Acute myocardial infarction and underlying stenosis severity. *Am J Cardiol* 2009; 103: 1204–1205.

11 Frobert O, van't Veer M, Aarnoudse W, *et al*. Acute myocardial infarction and underlying stenosis severity. *Catheter Cardiovasc Interv* 2007; 70: 958–965.

12 Harrison RW, Aggarwal A, Ou FS, *et al*. Incidence and outcomes of no-reflow phenomenon during percutaneous coronary intervention among patients with acute myocardial infarction. *Am J Cardiol* 2013; 111: 178–184.

13 Niccoli G, Burzotta F, Galiuto L, *et al*. Myocardial no-reflow in humans. *J Am Coll Cardiol* 2009; 54: 281–292.

14 Frohlich GM, Meier P, White SK, *et al*. Myocardial reperfusion injury: looking beyond primary PCI. *Eur Heart J* 2013; 34: 1714–1722.

15 Jaffe R, Charron T, Puley G, *et al*. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. *Circulation* 2008; 117: 3152–3156.

16 Tang X, Li R, Jing Q, *et al*. Efficacy and safety of intracoronary versus intravenous administration of tirofiban during percutaneous coronary intervention for acute coronary syndrome: a meta-analysis of randomized controlled trials. *PloS one* 2015; 10: e0129718.

17 Jia H, Dai J, Hou J, *et al*. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). *Eur Heart J*. Published Online First: Aug 30 2016. DOI: https://doi.org/10.1093/eurheartj/ehw381.

18 Alsheikh-Ali AA, Kitsios GD, Balk EM, *et al*. The vulnerable atherosclerotic plaque: scope of the literature. *Ann Intern Med* 2010; 153: 387–395.

19 Kelbaek H, Hofsten DE, Kober L, *et al*. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (danami 3-defer): An open-label, randomised controlled trial. *Lancet* 2016; 387: 2199–2206.

20 Legutko J, Dudek D, Chyrchel M, *et al*. Safety and effectiveness of pharmacologic versus mechanical stabilization of borderline coronary lesions in patients with acute coronary syndromes. *Przegl Lek* 2005; 62: 1–7.

21 Prati F, Uemura S, Souteyrand G, *et al*. OCT-based diagnosis and management of STEMI associated with intact fibrous cap. *JACC Cardiovasc Imaging* 2013; 6: 283–287.

22 Watanabe J, Nakamura S, Sugiura T, *et al*. Early identification of impaired myocardial reperfusion with serial assessment of ST segments after percutaneous transluminal coronary angioplasty during acute myocardial infarction. *Am J Cardiol* 2001; 88: 956–959.