Effects of intracoronary tirofiban administration on diabetes mellitus complicated by acute myocardial infarction in female patients undergoing emergency percutaneous coronary intervention

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Abstract: This study aims to investigate the short-term efficacy and safety of intracoronary tirofiban administration during emergency percutaneous coronary intervention (PCI) for female patients with diabetes mellitus complicated by acute ST-elevation myocardial infarction (STEMI). A total of 113 female diabetic patients with STEMI and who were undergoing emergency PCI were randomized into two groups: control group (A, n=56) and tirofiban group (B, n=57). The female groups were compared with the male group (group C) comprising 196 male diabetic patients with STEMI. These male diabetic patients also received tirofiban during emergency PCI in the same period. Compared with group A, groups B and C showed significantly increased thrombolysis in myocardial infarction (TIMI) 3 flow and TIMI myocardial perfusion grade (TMPG) 3. Moreover, groups B and C exhibited distinctly shortened average length of hospital stay, markedly decreased incidence of post-infarction angina, severe arrhythmia and cardiac function of Killip class III-IV (P<0.05) after PCI. The number of patients with TIMI 3 flow and TMPG 3 in group B was less than that in group C (P<0.05) and higher incidence of moderate bleeding than that in groups A and C (P<0.05). Tirofiban could effectively improve TIMI flow and myocardial perfusion. This drug could also reduce the incidence of post-infarction angina, severe arrhythmia and heart failure in female diabetic patients with STEMI undergoing emergency PCI. However, tirofiban could increase the incidence of moderate bleeding.

Keywords: Female, diabetes mellitus, acute myocardial infarction, emergency percutaneous coronary intervention, tirofiban

Introduction

The epidemiology, prevention, diagnosis, clinical manifestations, treatment and prognosis of coronary heart disease (CHD) differ between males and females. Compared with males, females suffer from CHD at an advanced age; females also manifest atypical angina symptoms. Furthermore, the diameter of their coronary artery is smaller than that in males; thus, the success rate of coronary revascularisation in females is lower than that in males; those who undergo coronary revascularisation exhibit a higher incidence of complications and mortality [1, 2]. Impaired glucose metabolism is one of the main risk factors of arteriosclerosis, and 80% of patients with diabetes mellitus (DM) die from cardiovascular diseases; thus, the risk of DM corresponds to that of CHD [3]. In clinical practice, acute myocardial infarction (AMI) is commonly associated with hyperglycaemia; in the early stage of myocardial infarction (MI), the body may produce an emergency response, stimulating the neuroendocrine system to generate catecholamines, such as cortisol and adrenaline; these hormones can promote glycogen decomposition and lipid catabolism, thereby increasing blood glucose and free fatty acid levels [4, 5]. Inadequate insulin secretion and insulin resistance of patients with diabetes prevent myocardial cells to utilise glucose completely, resulting in an acute increase in blood sugar concentration [6]. Studies have confirmed that a significant positive correlation is observed between hyperglycaemia and occurrences of heart failure, arrhythmias and other complications; moreover, hyperglycaemia significantly increase the mortality of patients with
In female patients undergoing emergency percutaneous coronary intervention (PCI)

Several consequences, including high incidence of no-flow and slow-flow, increased major adverse cardiac events (MACE), complications and high mortality, have been observed in patients with DM complicated by acute MI (AMI) undergoing emergency PCI [9, 10]. To improve the microcirculatory reperfusion of diabetic patients with angina during PCI and reduce MACE rate after PCI, medical practitioners administer tirofiban hydrochloride, an effective platelet glycoprotein (GP) IIb/IIIa receptor antagonist [10]. However, the incidence of no-flow and slow-flow is significantly higher in female diabetic patients with AMI than that in non-diabetic patients with angina during emergency PCI. The occurrences of heart failure, malignant arrhythmia, cardiogenic shock, other complications and mortality are high [11]. We aimed to investigate the efficacy and safety of intracoronary tirofiban administration during emergency PCI in female diabetic patients with acute ST-elevation MI (STEMI).

Methods

Subjects

We randomly distributed 113 female diabetic patients with STEMI and subjected to emergency PCI between January 2010 and December 2014 in our hospital into two groups: 1) control group (A, n=56) with a mean age of 59.3±7.2 years (age range of 51 years to 75 years) and 2) tirofiban group (B, n=57) with a mean age of 58.6±9.7 years (age range of 49 years to 76 years). In group C, a total of 196 male diabetic patients with STEMI received tirofiban during emergency PCI during the same period. AMI and DM were diagnosed according to ACC/AHA 2004 Guideline for STEMI [12] and WHO 1999 criteria [13], respectively. The inclusion criteria were listed as follows: 1) STEMI onset ≤12 h; 2) patients diagnosed with DM; and 3) patients who agreed with emergent PCI. The exclusion criteria were listed as follows: 1) STEMI onset ≥12 h; 2) patients with suspected aortic dissection; 3) uncontrolled hypertension ≥180/110 mmHg (1 mmHg=0.133 kPa); 4) rescue PCI after thrombolysis; 5) history of cerebral haemorrhage and ischaemic stroke within one year; 6) severe liver and renal dysfunction; 7) history of haemorrhagic disease; and 8) AMI complicated by cardiac shock and severe left ventricular dysfunction. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Zhengzhou People’s Hospital. Written informed consent was obtained from all participants.

Emergency PCI

After admission, the patients were subjected to 18-lead electrocardiogram (ECG) monitoring, oxygen inhalation therapy and routine examinations, including blood glucose, lipid, and myocardial enzyme and troponin tests immediately. These patients were also treated with 300 mg of aspirin and 600 mg of clopidogrel. Coronary angiography (CAG) was performed using Judkins technique by inserting sheath into the right radial artery (n=292) or into the right femoral artery (n=17). Heparin (3000 U) was injected into this sheath. Heparin (7000 U) was again injected to guide the catheter into the coronary artery orifices after CAG. If CAG showed a thrombus-like shadow, then an aspiration catheter was used to remove this thrombus (three, three and five cases in groups A, B and C, respectively). A wire was then guided and inserted through the occlusive lesion. Intracoronary tirofiban (Xinweining, Wuhan Yuanda Pharmaceutical Group Co., Ltd., China) was then administered at a dose of 10 µg/kg within 3 min. Groups B and C were subjected to continuous intravenous pumping at 0.15 µg/kg·min for 24 h. CAG was repeated to observe coronary blood flow, which could indicate whether percutaneous transluminal coronary angioplasty stenting or direct stenting should be performed using a sirolimus-eluting stent (Beijing Lepu Medical Technology Co., Ltd.). Postoperative myocardial enzyme, troponin, ECG, ultrasonic cardiogram and liver and renal functions were reviewed. The patients continued to receive 100 mg/d of aspirin and 75 mg/d of clopidogrel, statins, and angiotensin converting enzyme inhibitor, β-receptor blocker and anti-diabetic drugs. Only criminal arteries were subjected to emergency PCI, and elective PCI was performed after 7 d to 14 d, if this procedure was necessary.

Observation index

According to CAG, we statistically analysed the lesion characteristics and other indices of the three groups. These characteristics were listed as follows: diameter and length of stent in crim-
In female patients undergoing emergency percutaneous coronary intervention

Table 1. Comparison of clinical data among three groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (A, n=56)</th>
<th>Tirofiban group (B, n=57)</th>
<th>Male tirofiban group (C, n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.3±7.2</td>
<td>58.6±9.7</td>
<td>57.7±11.2</td>
</tr>
<tr>
<td>Hypertension [cases (%)]</td>
<td>35 (71.43)</td>
<td>37 (77.08)</td>
<td>97 (75.19)</td>
</tr>
<tr>
<td>Smoking history [cases (%)]</td>
<td>3 (5.36)</td>
<td>2 (3.51)</td>
<td>137 (69.90)a,b</td>
</tr>
<tr>
<td>Hyperlipemia [cases (%)]</td>
<td>27 (48.22)</td>
<td>29 (50.88)</td>
<td>89 (45.41)</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>87.3±10.2</td>
<td>88.7±11.7</td>
<td>88.3±13.9</td>
</tr>
<tr>
<td>PCI history [cases (%)]</td>
<td>3 (5.36)</td>
<td>4 (7.02)</td>
<td>16 (8.16)</td>
</tr>
<tr>
<td>Preinfarction angina [cases (%)]</td>
<td>4 (7.14)</td>
<td>3 (5.26)</td>
<td>38 (19.39)a,b</td>
</tr>
<tr>
<td>Family history of CHD [cases (%)]</td>
<td>6 (10.71)</td>
<td>8 (14.04)</td>
<td>30 (15.31)</td>
</tr>
</tbody>
</table>

Note: compared with group A, aP<0.05; compared with group B, bP<0.05.

Table 1. Comparison of clinical data among three groups

The incidence of pre-infarction angina and smoking history were higher in males (group C) than in females (groups A and B). No statistical differences were observed in age, hypertension, hyperlipemia, renal function, previous PCI and family history of CHD among the three groups (P>0.05; Table 1).

Results

Comparison of clinical data

The differences in single-, double- and triple-vessel disease, left main coronary artery lesions and treated target arteries during emergency PCI were not statistically significant among the three groups (P>0.05). Implant
In female patients undergoing emergency percutaneous coronary intervention, stents in females were smaller and longer than those in males ($P<0.05$). The number of patients who exhibited TIMI3 flow and TMPG3 after PCI was higher in groups B and C than in group A ($P<0.05$). By comparison, the number of patients in group B with TIMI3 flow and TMPG3 was less than that in group C ($P<0.05$, Table 2).

**Length of hospital stay, PCI characteristic and incidence of complication**

No statistical differences were observed in the meantime from admission to balloon dilation, the number of patients implanted with more than two stents and underwent elective PCI, the incidence of re-infarction during hospitalisation, acute and subacute stent thrombosis, cardiac shock and 30-d mortality ($P>0.05$). Compared with group A, groups B and C showed significantly shortened average length of hospital stay ($P<0.05$) and decreased incidence of post-infarction angina, severe arrhythmia and cardiac function of Killip class III-IV ($P<0.05$). The incidence of post-infarction angina and severe arrhythmia was significantly higher in group B than that in group C ($P<0.05$). By contrast, the differences in the incidence of severe and mild bleeding were not significant among the three groups ($P>0.05$); group B exhibited a higher incidence of moderate bleeding than groups A and C ($P<0.05$, Table 3).

**Discussion**

CHD is among the major causes of death in women [16, 17]. More than one-third of women suffer from cardiovascular disease, and $>50\%$ of patients who die from cardiovascular disease are females. Furthermore, specific gender

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**Table 2. Comparison of coronary artery lesion characteristics among three groups [cases (%)]**

<table>
<thead>
<tr>
<th>Lesion characteristics</th>
<th>Control group (A, n=56)</th>
<th>Tirofiban group (B, n=57)</th>
<th>Male tirofiban group (C, n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-vessel disease</td>
<td>15 (26.79)</td>
<td>12 (21.05)</td>
<td>45 (22.96)</td>
</tr>
<tr>
<td>Double-vessel disease</td>
<td>22 (39.29)</td>
<td>25 (43.86)</td>
<td>76 (38.78)</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>19 (33.93)</td>
<td>20 (35.09)</td>
<td>75 (38.27)</td>
</tr>
<tr>
<td>Left main coronary artery disease</td>
<td>5 (8.93)</td>
<td>5 (8.77)</td>
<td>12 (6.12)</td>
</tr>
<tr>
<td>Target arteries in emergency PCI</td>
<td>30 (53.57)</td>
<td>29 (50.88)</td>
<td>115 (58.67)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>11 (19.64)</td>
<td>11 (19.30)</td>
<td>42 (21.43)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>15 (26.79)</td>
<td>17 (29.82)</td>
<td>39 (19.90)</td>
</tr>
<tr>
<td>Stent diameter (mm, x±s)</td>
<td>2.82±0.29</td>
<td>2.84±0.31</td>
<td>3.16±0.42$^{a,b}$</td>
</tr>
<tr>
<td>Stent length (mm, x±s)</td>
<td>24.52±3.74</td>
<td>25.03±4.77</td>
<td>21.39±4.29$^{a,b}$</td>
</tr>
</tbody>
</table>

Preoperative TIMI grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control group (A, n=56)</th>
<th>Tirofiban group (B, n=57)</th>
<th>Male tirofiban group (C, n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0~1</td>
<td>52 (92.86)</td>
<td>54 (94.74)</td>
<td>183 (93.37)</td>
</tr>
<tr>
<td>2</td>
<td>4 (7.14)</td>
<td>3 (5.26)</td>
<td>13 (6.63)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Postoperative TIMI grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control group (A, n=56)</th>
<th>Tirofiban group (B, n=57)</th>
<th>Male tirofiban group (C, n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0~1</td>
<td>5 (8.93)$^a$</td>
<td>2 (3.51)$^c$</td>
<td>1 (0.51)$^{a,c}$</td>
</tr>
<tr>
<td>2</td>
<td>11 (19.64)</td>
<td>4 (7.02)</td>
<td>5 (2.55)$^a$</td>
</tr>
<tr>
<td>3</td>
<td>40 (71.43)$^c$</td>
<td>51 (89.47)$^{a,c}$</td>
<td>190 (96.94)$^{a,b,c}$</td>
</tr>
</tbody>
</table>

Preoperative TMPG

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control group (A, n=56)</th>
<th>Tirofiban group (B, n=57)</th>
<th>Male tirofiban group (C, n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0~1</td>
<td>54 (96.43)</td>
<td>55 (96.49)</td>
<td>191 (97.45)</td>
</tr>
<tr>
<td>2</td>
<td>2 (3.57)</td>
<td>2 (3.51)</td>
<td>5 (2.55)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Postoperative TMPG

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control group (A, n=56)</th>
<th>Tirofiban group (B, n=57)</th>
<th>Male tirofiban group (C, n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0~1</td>
<td>9 (16.07)$^d$</td>
<td>3 (5.26)$^d$</td>
<td>1 (0.51)$^{a,d}$</td>
</tr>
<tr>
<td>2</td>
<td>12 (21.43)$^d$</td>
<td>2 (3.51)$^a$</td>
<td>3 (1.53)$^a$</td>
</tr>
<tr>
<td>3</td>
<td>35 (62.50)$^d$</td>
<td>52 (91.23)$^{a,d}$</td>
<td>192 (97.96)$^{a,b,d}$</td>
</tr>
</tbody>
</table>

Note: compared with group A, $^aP<0.05$; compared with group B, $^bP<0.05$; compared with preoperative TIMI grade: $^cP<0.05$, compared with preoperative TMPG: $^dP<0.05$. 

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In female patients undergoing emergency percutaneous coronary intervention differences in pathophysiology, clinical manifestations and short- or long-term efficacy have been observed [17]. Early, continuous and sufficient recanalisation of infarct-related artery is one of the most important treatments for AMI [18]. Emergency PCI can also effectively reduce MACE in male and female patients with AMI [19, 20]. However, atypical symptoms of myocardial ischaemia are observed in women [16, 17]. In our research, female subjects exhibited significantly lower incidence of pre-infarction angina than male subjects. Acute myocardial ischaemia in females is characterised by non-specific symptoms, including retrosternal pain, nausea, vomiting, shortness of breath and fatigue. Moreover, ECG and exercise ECG exhibit low sensitivity and specificity in the diagnosis of CHD in women. AMI is diagnosed in late stages under ischaemic conditions because of unspecific symptoms, atypical ECG and lack of early drug and lifestyle intervention. Thus, several treatments, such as thrombolysis, coronary revascularisation and angioplasty, are delayed, resulting in the high incidence of complications and mortality in female patients with AMI.

The criminal coronary artery of females is relatively small and long; as such, smaller and longer stent implants are required for the target arteries [16, 17, 21]. No differences are observed in the incidence of cardiac shock, MI, target lesion and vessel revascularisation, stent thrombosis, lumen loss and in-stent restenosis during the two-year follow-up after a drug-eluting stent is implanted in females and males with angina [21]. However, females with STEMI exhibit a distinctly higher incidence of angina, in-stent restenosis and mortality after these patients are subjected to PCI than males [22-24]. In our study, the implanted stents were smaller and longer in female diabetic patients with STEMI than those implanted in male patients. During emergency PCI, balloon dilation and stent implantation repeatedly stimulate and cause damage to vascular endothelial cells, thereby causing no-flow or slow-flow in criminal arteries. Long stents partly occlude the vessels that directly supply nutrients to the myocardium. This incidence is one of the reasons for the increased number of complications, such as short-term heart failure, arrhythmia and cardiac shock; this incidence is also the pathological basis of long-term lumen loss, restenosis, and target lesion and vessel revascularisation. Furthermore, this incidence is the main cause of high complication and mortality rates in female diabetic patients with STEMI.

DM is the main risk factor of arteriosclerosis; multiple vessels are involved in coronary artery

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (A, n=56)</th>
<th>Tirofiban group (B, n=57)</th>
<th>Male tirofiban group (C, n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (d)</td>
<td>11.2±3.7</td>
<td>8.6±2.1a</td>
<td>8.3±2.9a</td>
</tr>
<tr>
<td>Mean time from admission to balloon dilation (min)</td>
<td>83.3±29.7</td>
<td>85.1±31.8</td>
<td>84.7±39.6</td>
</tr>
<tr>
<td>Patients implanted with over two stents [cases (%)]</td>
<td>10 (17.86)</td>
<td>15 (26.32)</td>
<td>48 (24.49)</td>
</tr>
<tr>
<td>Patients underwent elective PCI [cases (%)]</td>
<td>15 (26.79)</td>
<td>13 (22.80)</td>
<td>47 (23.98)</td>
</tr>
<tr>
<td>Postinfarction angina [cases (%)]</td>
<td>18 (32.14)</td>
<td>9 (15.79)a</td>
<td>12 (6.12)a,b</td>
</tr>
<tr>
<td>Reinfarction [cases (%)]</td>
<td>5 (8.93)</td>
<td>4 (7.02)</td>
<td>4 (2.04)</td>
</tr>
<tr>
<td>Stent thrombosis [cases (%)]</td>
<td>1 (1.79)</td>
<td>0</td>
<td>2 (1.02)</td>
</tr>
<tr>
<td>Severe arrhythmia [cases (%)]</td>
<td>17 (30.37)</td>
<td>7 (12.28)a</td>
<td>8 (4.26)a,b</td>
</tr>
<tr>
<td>Cardiac failure of Killip class III-IV [cases (%)]</td>
<td>13 (23.21)</td>
<td>4 (7.02)a</td>
<td>11 (5.61)a</td>
</tr>
<tr>
<td>Cardiac shock [cases (%)]</td>
<td>2 (3.57)</td>
<td>1 (1.75)</td>
<td>2 (1.02)</td>
</tr>
<tr>
<td>30d mortality [cases (%)]</td>
<td>1 (1.79)</td>
<td>0</td>
<td>1 (0.51)</td>
</tr>
<tr>
<td>Bleeding [cases (%)]</td>
<td>0</td>
<td>1 (1.75)</td>
<td>1 (0.51)</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td></td>
<td>1 (1.75)</td>
<td>1 (0.51)</td>
</tr>
<tr>
<td>Moderate bleeding</td>
<td>1 (1.79)</td>
<td>8 (14.04)a</td>
<td>6 (3.06)b</td>
</tr>
<tr>
<td>Mild bleeding</td>
<td>2 (3.57)</td>
<td>3 (5.26)</td>
<td>7 (3.57)</td>
</tr>
</tbody>
</table>

Note: compared with group A, aP<0.05; compared with group B, bP<0.05.
In female patients undergoing emergency percutaneous coronary intervention
disease, which is characterised by diffused lesions in diabetic patients complicated by microangiopathy and diabetic cardiomyopathy [3, 9, 23]. Diabetic patients with AMI are at a high risk of restenosis and require repeat revascularisation. These patients also exhibit an increased risk of repeated MI, stent thrombosis and death. Compared with non-diabetic individuals, female diabetic patients with AMI exhibit a significantly higher incidence of no-flow and slow-flow during emergency PCI [3, 9, 15, 23, 24] female diabetic patients also show a higher incidence of MI, stroke, heart failure and mortality at either acute or chronic phase than non-diabetic individuals [3, 9, 16, 23]. PCI is more effective than thrombolytic therapy in female DM patients complicated by AMI [24]. However, the complication and mortality in females are higher than those in males. Blondal et al. [24] discovered that the hospital mortality of female diabetic patients with AMI accounts for 12%. In our research, fewer patients in the female groups exhibited TIMI3 flow and TMPG3 after PCI than in other groups. The TIMI3 flow in infarct-related artery was initially considered as the gold standard of reperfusion, but a great difference is observed in distal coronary perfusion when TIMI3 flow is restored in epicardial coronary vessels. PCI restores blood flow in epicardial coronary vessels, but the myocardium is not effectively reperfused in 25% to 30% of patients, namely, slow-flow and no-flow [10, 14, 15, 25, 26]. Myocardial perfusion is an effective standard of successful reperfusion. Unlike PCI, TMPG can be performed to evaluate myocardial perfusion more accurately by observing the filling and clearance of contrast in the myocardium. The diffused lesions of epicardial coronary artery in diabetic patients are complicated by microangiopathy and endothelial dysfunction; hyperglycaemia can enhance inflammatory response and platelet-dependent microthrombosis as well as attenuate endothelium-dependent vasodilation, thereby aggravating the disturbances of microcirculatory perfusion [9, 10, 18].

Tirofiban is an effective non-peptide platelet GP IIb/IIIa receptor antagonist that specifically and reversibly binds to platelet surface receptors and inhibits the binding of fibrinogen to GP IIb/IIIa receptor; as a result, the pathway of platelet aggregation is blocked, preventing fibrinogen from binding to the coagulation factor [27]. This mechanism also effectively reduces the incidence of slow-flow and no-flow during PCI [15, 25, 26]. Intracoronary tirofiban improves blood flow (TIMI3) and myocardial perfusion (TMPG3) in diabetic patients with AMI during emergency PCI [15]. However, the effects of intracoronary tirofiban on myocardial perfusion and complications in female diabetic patients with STEMI have not been reported. Our study showed that tirofiban effectively improved TIMI flow and myocardial perfusion, reduced the incidence of slow-flow, no-flow, post-infarction angina, severe arrhythmia and cardiac failure in female diabetic patients with STEMI undergoing emergency PCI. However, the incidence of post-infarction angina and severe arrhythmia was higher in females than that in males. This result may be correlated with small artery diameter, diffused lesions and long implanted stents in females. However, these pathophysiological mechanisms should be further investigated.

Cardiovascular physicians focus on bleeding [28] because of potent anti-platelet effects of tirofiban and application of anti-platelet (aspirin and clopidogrel) and anti-coagulant (heparin) drugs, particularly in diabetic females with AMI. Our research did not statistically differ in the incidence of severe bleeding among the three groups. However, the incidence of moderate bleeding was significantly increased in females and distinctly higher than that in males with STEMI. Nevertheless, further studies should be conducted to determine whether or not gender difference affects the response to drugs.

In conclusion, intracoronary tirofiban effectively improves TIMI flow and myocardial perfusion, reduces the incidence of severe arrhythmia and prevents cardiac failure in female diabetic patients with STEMI.

Acknowledgements

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Disclosure of conflict of interest

None.

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References


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