Z Kardiol 93:407–412 (2004)
DOI 10.1007/s00392-004-0073-5

CASE REPORT

W. Meyners
S. Peters
M. Trümmel
B. Koehler

Successful recanalization of an occluded coronary artery by percutaneous coronary intervention, systemic administration of tirofiban, a glycoprotein IIb/IIIa inhibitor, and intracoronary thrombolysis with alteplase

Erfolgreiche Rekanalisation einer verschlossenen Koronararterie durch perkutane Koronarintervention, systemische Gabe von Tirofiban, einem Glykoprotein-IIb/IIIa-Inhibitor und intrakoronare Thrombolyse mit Alteplase

Zusammenfassung Ein 51-jähriger Patient wurde wegen eines subakuten Hinterwandmyokardinfarkts in unserer Institution aufgenommen. Die Koronarangiographie zeigte einen thrombotischen Verschluss der rechten Koronararterie. Die perkutane Koronarintervention einschließlich Implantation von 3 Stents war nicht effektiv (TIMI 0 Fluss). Ergänzend zur bereits initiierten systemischen Gabe von Tirofiban, einem Glykoprotein-IIb/IIIa-Inhibitor, erhielt der Patient eine intracoronare Thrombolysetherapie (ICT) mit Alteplase (recombinant tissue-type plasminogen activator, rt-PA). Die Kontrollangiographie am darauffolgenden Tag zeigte eine vollständige Reperfusion (TIMI Grad 3); nach 7 Monaten konnte weiterhin ein TIMI 3 Fluss dokumentiert werden. Nach unserer Kenntnis handelt es sich hier um den ersten Bericht zur Kombination der systemischen Gabe von Tirofiban mit einer ICT.

Schlüsselwörter
Myokardinfarkt – perkutane Koronarintervention – Glykoprotein-IIb/IIIa-Inhibitor – Tirofiban – intrakoronare Thrombolyse – Alteplase

Received: 3 July 2003
Accepted: 17 December 2003

Dr. med. W. Meyners (✉)
St.-Marien-Krankenhaus Siegen
Medizinische Klinik II – Kardiologie
Kampenstr. 51
57072 Siegen, Germany
E-Mail:
w.meyners@marienkrankenhaus.com

Priv.-Doz. Dr. med. Stefan Peters
Dr. med. Martina Trümmel
Brigitte Koehler
Klinikum Dorothea Christiane Erxleben Quedlinburg
Klinik für Innere Medizin – Kardiologie
Ditfurter Weg 24
06484 Quedlinburg, Germany

Summary A 51 year-old male was admitted to our institution with subacute inferior myocardial infarction. Coronary angiography showed thrombotic occlusion of the right coronary artery. Percutaneous coronary intervention including the delivery of 3 stents was unsuccessful (TIMI grade 0 flow). In addition to an ongoing systemic administration of tirofiban, a glycoprotein IIb/IIIa inhibitor, the patient received intracoronary thrombolysis (ICT) with alteplase (recombinant tissue type plasminogen activator, rt-PA). There was complete reperfusion on control angiography the following day (TIMI grade 3 flow); 7 months later, there was still TIMI grade 3 flow. To our knowledge, this is the first report on systemic administration of tirofiban combined with ICT.

Key words Myocardial infarction – percutaneous coronary intervention – glycoprotein IIb/IIIa inhibitor – tirofiban – intracoronary thrombolysis – alteplase

Introduction

Intracoronary thrombolysis (ICT) was a frequently performed procedure for acute myocardial infarction or complicated percutaneous coronary intervention in the 1980s and the first half of the 1990s. Subsequently, systemic thrombolysis was found to be a superior treatment for acute myocardial infarction that was readily available in most institutions. Furthermore, the introduction of coronary stenting and gly-

coprotein IIb/IIIa blockade into interventional cardiology decreased the rate of bail out situations significantly; meanwhile, these advancements were also found to improve outcome in acute myocardial infarction in experienced centers. Consequently, nowadays ICT is used rarely in clinical practice. However, our report indicates that ICT might deserve reconsideration in the setting of massive intracoronary thrombosis as an adjunct to percutaneous coronary intervention and glycoprotein IIb/IIIa blockade.

Case report

A 51 year-old male was admitted to the cardiology department because of a 5 day history of chest pain with suspected myocardial infarction.

The patient was completely well until 5 days prior to this admission when he had acute chest pain with radiation to the neck, and diaphoresis. He received an unknown therapy by his general practitioner that included some type of injection but symptoms persisted. There was a history of hypertension, and treatment consisted of captopril 12.5 mg twice daily. The patient had quit smoking 12 months earlier. His father had suffered a myocardial infarction.

On admission, blood pressure was 170/110 mmHg, heart rate was 72/min. Body height was 173 cm, and he weighed 85 kg (body mass index 28.4 kg/m^2). Physical examination was otherwise unremarkable, there were no signs of heart failure.

The ECG was consistent with subacute inferior myocardial infarction: It showed sinus rhythm with a rate of 90/min, there were significant Q-waves in leads II, III and aVF as well as descending ST-segment depression in leads I, aVL, and V2 (Fig. 1). On echocardiography, the left ventricle was found to be of normal size with symmetric hypertrophy (interventricular septum 13 mm, left ventricular posterior wall 13 mm). There was hypokinesia of the basal segments of the septum, the inferior wall, the posterior wall and the lateral wall. The left ventricular ejection fraction was 50%. Laboratory tests indicated subacute myocardial infarction (Fig. 2).

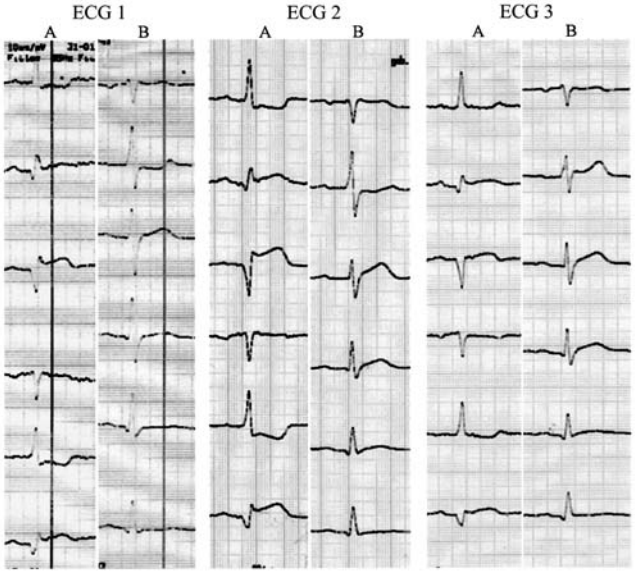

Fig. 1 A 12 lead ECG on admission (panel 1), after PCI (panel 2), and after intracoronary thrombolysis (panel 3). "A" indicates leads I, II, III, aVR, aVL, and aVF, "B" indicates leads V1 to V6 (from top to bottom)

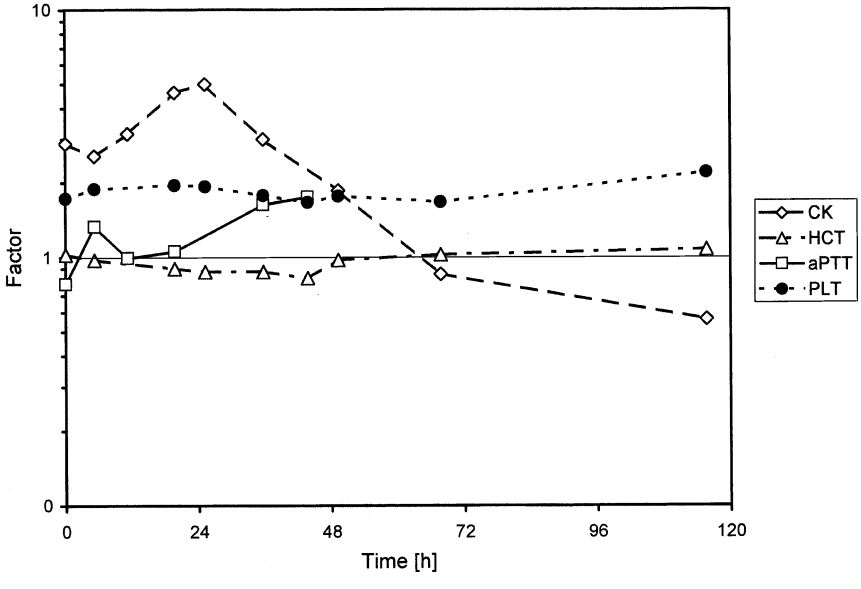

Fig. 2 Laboratory values are depicted on a logarithmic scale as a factor in relation to the upper limit of normal (CK: 3.15 µmol/l*s, aPTT: 40 s) or lower limit of normal (HCT: 40%, PLT: 150,000/µl). *CK* creatine kinase, *aPTT* activated partial thromboplastin time, *HCT* hematocrit, *PLT* platelets

The patient received acetylsalicylic acid 500 mg i.v. and clopidogrel 300 mg p.o. as well as unfractionated heparin (bolus 8000 IU, infusion 1000 IU/h) and tirofiban, a glycoprotein IIb/IIIa inhibitor (bolus 10 µg/kg, infusion 0.15 µg/kg/min) within 30 minutes after admission.

Coronary angiography was started 134 minutes after admission. It showed proximal thrombotic occlusion of the right coronary artery (Fig. 3 a). In addition, there were stenoses of the first diagonal branch of 80% and the proximal circumflex artery of 90% at the bifurcation of the first obtuse marginal branch, respectively. An attempt to reopen the RCA was unsuccessful: We used a 7F femoral right 4.0 guiding catheter with sideholes. A guide wire was placed in the distal vessel (Biotronik Galeo J-Tip

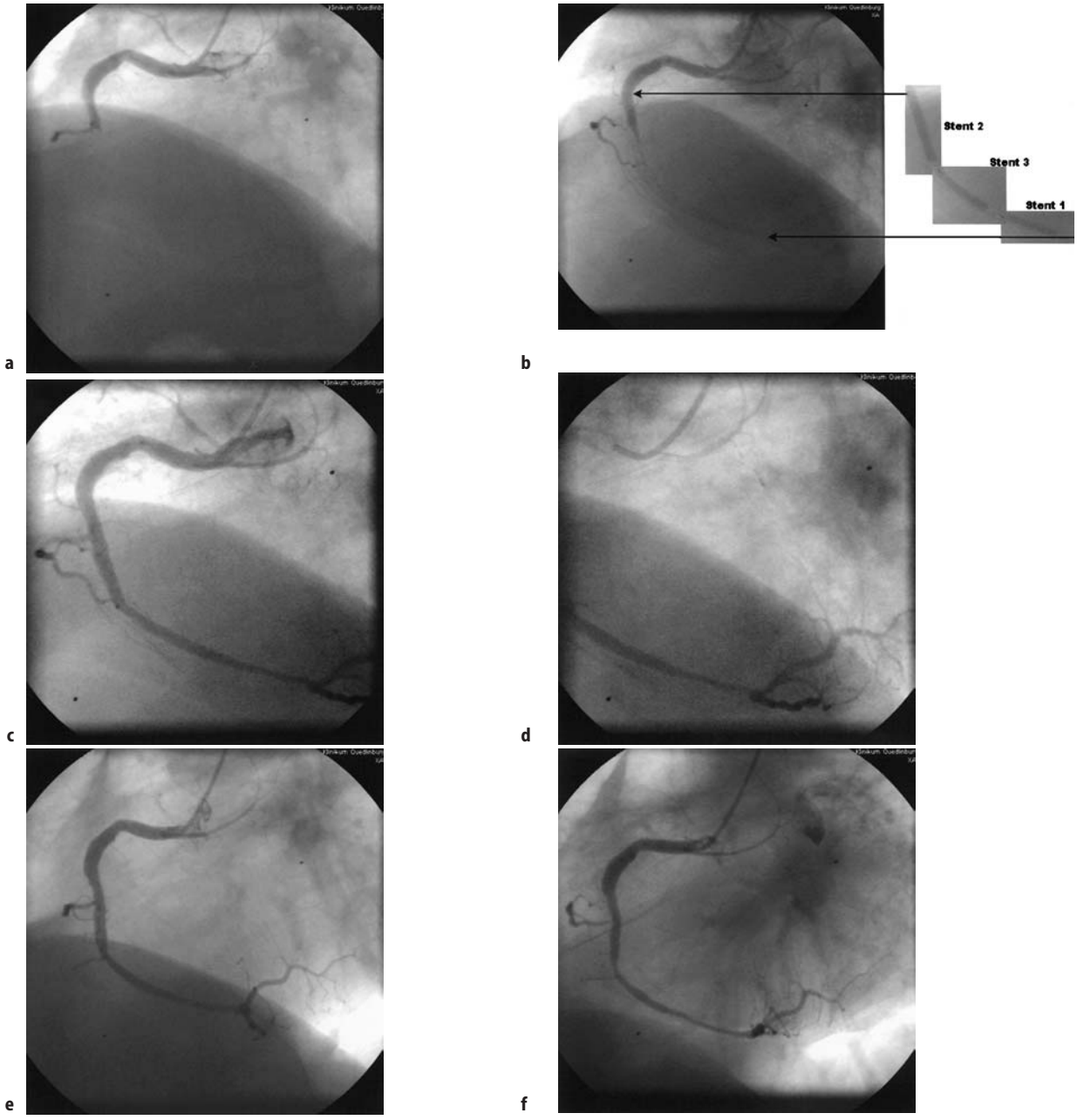

Fig. 3 a–f Angiography of the RCA (LAO 60°). **a** After admission. **b** After percutaneous intervention. 3 stents were implanted, the sites of implantation are indicated on the right side. Arabic numerals refer to the sequence of implantation. Stent 1: Sorin Sirius CarboStent 3.0/25 mm, inflation pressure 10 bar. Stent 2: Sorin Sirius CarboStent 4.0/25 mm, inflation pressure 10 bar. Stent 3: Sorin Sirius CarboStent 3.5/25 mm, inflation pressure 10 bar. **c** Proximal vessel after intracoronary thrombolysis. **d** Distal vessel after intracoronary thrombolysis. **e** After 30 days. **f** After 7 months

0.014″). Several dilatations were performed without reinstituting significant flow (VIVA adanté 3.0/20 mm, inflation pressure 4–6 bar). Subsequently, 3 stents were implanted (Fig. 3b). Finally, there was still complete thrombotic occlusion (TIMI grade 0). The procedure was characterized by the following data: duration 72 minutes, fluoroscopy time 21.9 minutes, amount of contrast media 220 ml, area dosage product 17322 $cGy * cm^2$.

The guiding catheter was exchanged by a 5F diagnostic Judkins right catheter, and intracoronary thrombolysis with alteplase was started: 15 mg were infused within 30 min, subsequently 35 mg were infused within 17.5 hours (2 mg/h).

The next morning, we confirmed an unchanged position of the Judkins right catheter within the ostium of the right coronary artery. Repeat angiography showed complete recanalization of the right coronary artery (TIMI grade 3). There were still mural thrombi visible, especially within the segment of the most distal stent, but there was no limitation of flow or significant localized narrowing (Fig. 3c, d).

Initially, the patient had complete relief of symptoms. On the third hospital day, he reexperienced chest pain that was found to be due to post infarction pericarditis (pericarditis epistenocardica) with a loud pericardial friction rub. He received treatment with a non-steroidal anti-inflammatory drug (diclofenac 50 mg three times daily p.o.). Subsequently, the patient recovered completely and was discharged 6 days after admission.

After 30 days, elective PTCA and stenting of the circumflex artery were performed without complications (not shown). Angiography of the RCA showed a TIMI grade 3 flow, and there was no localized stenosis (Fig. 3e). After another 6 months, the patient was well, and control coronary angiography was performed (Fig. 3f). Loss of lumen within all three stents was clearly visible, but there was no localized narrowing, and flow was graded TIMI 3. Echocardiography showed hypokinesia of the basal and medial inferior wall as well as the medial anterior wall; overall left ventricular function was unimpaired. Symmetric hypertrophy of the left ventricle was confirmed.

Discussion

Nowadays, optimum therapy of acute myocardial infarction consists of a sophisticated combination of mechanical and pharmacological therapy. Mechanical recanalization is achieved by balloon dilatation and the delivery of intravascular stents. Pharmacological therapy can be divided into multilevel thrombocyte inhibition (acetylsalicylc acid; clopidogrel; glycoprotein IIb/IIIa inhibition), anticoagulation with unfractionated or fractionated heparin as well as the administration of beta blockers, ACE inhibitors and CSE inhibitors.

In the 1980s, when PTCA was increasingly used as a therapy of chronic coronary artery disease, there was a major interest in the local application of thrombolytic agents for the treatment of complicated coronary interventions and acute myocardial infarction [8, 10]. This interest is reflected by the number of publications on this topic which peaked in 1984 (Fig. 4). The subsequent decreasing number of publications appears to correlate inversely with further advancements in clinical practice, i.e., widespread usage of systemic thrombolysis, intracoronary stenting and glycoprotein IIb/IIIa inhibition, respectively.

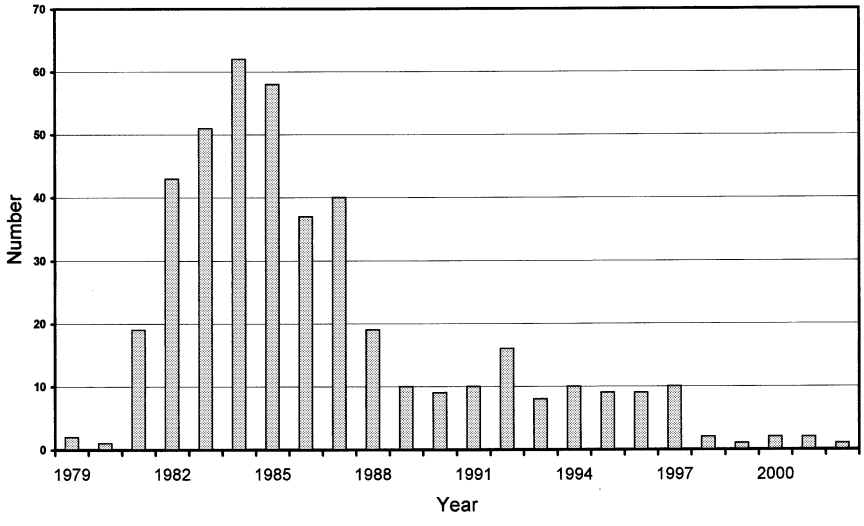

Fig. 4 Number of publications on intracoronary thrombolysis per year were identified by a Medline query with the following syntax in February 2003: "intracoronary thrombolysis" [Title] or "intracoronary streptokinase" [Title] or "intracoronary urokinase" [Title] or "intracoronary tissue plasminogen activator" [Title]

Once subendothelial structures are exposed to the streaming blood, a process of thrombocyte activation, local adhesion and aggregation is initiated. Eventually, activation of plasmatic coagulation leads to the formation of fibrin which stabilizes the platelet thrombus. Both ASS and clopidogrel interfere with platelet activation: ASS is an irreversible inhibitor of cyclooxygenase 1, thereby blocking the thromboxane A2 pathway, and clopidogrel is an irreversible inhibitor of ADP-mediated platelet activation. Blockade of the GP IIb/IIIa receptor suppresses the aggregation of activated thrombocytes by all stimuli, including thrombin. Local application of a fibrinolytic agent reexposes those activated platelets which might in turn propagate thrombus reformation. It has also been suggested that thrombolysis might even cause platelets to become hyperreactive [4]. Therefore, systemic blockade of the GP IIb/IIIa receptor in addition to inhibition of platelet activation, anticoagulation and local fibrinolysis should be beneficial for the treatment of platelet-rich thrombi.

Intracoronary thrombi can be a major obstacle in the attempt to reopen an occluded coronary artery by percutaneous coronary intervention, especially in the setting of subacute infarction. In the present case, standard interventional therapy was unsuccessful because of massive intracoronary thrombosis. At no point in time during the intervention, there was significant flow within the occluded vessel. The angiographic appearance and the procedural course gave no evidence of a massive "no reflow" phenomenon. The patient had already received ASS and clopidogrel perorally as well as heparin and tirofiban intravenously. Intracoronary thrombolysis was added on top of the ongoing therapeutic regimen which finally reinstituted complete perfusion of the target vessel, and there was TIMI grade 3 flow after 30 days and 7 months. Our assumptions would suggest that initiation of GP IIb/IIIa blockade prior to thrombolysis is essential.

The regimen that we used in this patient was derived from our previous experience with combined glycoprotein IIb/IIIa blockade and systemic thrombolysis: Our group has demonstrated that treatment of acute myocardial infarction with a reduced dosage of alteplase (50 mg) in combination with tirofiban in a dosage according to the RESTORE trial [9] with a bolus of 10 μg/kg within 3 min and an infusion rate of 0.15 μg/kg/min results in a patency rate of 87% and a TIMI 3 flow in 79% of cases within 60 minutes. However, using a lower dosage of tirofiban with 0.4 μg/kg/min within 30 min and 0.1 μg/kg/min subsequently according to the PRISM-PLUS trial [1], the patency rate was only 25% at 60 minutes [5]. In this context, it has to be mentioned that the manufacturer of tirofiban endorses the dosage regimen of the PRISM-PLUS trial but not the one that we used according to the RESTORE trial.

Reperfusion therapy for acute myocardial infarction is considered to be angiographically successful when TIMI 3 flow is achieved in the infarct-related coronary artery. Recently, myocardial blush grade (MBG) was introduced as an additional angiographic measure of myocardial perfusion that is supposed to reflect microvascular function. There is one prospective single-center study which demonstrated that patients with TIMI 3 flow and an MBG of 0 or 1 had a significantly higher mortality rate than those with TIMI 3 flow and MBG 2 or 3 [3]. We did not assess MBG in this patient but future trials of all types of reperfusion therapy in myocardial infarction should analyze this parameter systematically to determine its true prognostic value.

Another aspect has to be emphasized as well: In the literature the maximum time for intracoronary administration of alteplase is reported to be 60 minutes with a dose range of 10 to 50 mg [10] whereas we used an infusion time of 18 hours. However, we felt that a prolonged infusion time was appropriate in this patient because of the large amount of intravascular thrombi, taking into account that the risk of hemorrhagic complications might be increased. Since control angiography was performed only after 18 hours, we do not know exactly when reperfusion was achieved. In addition, it is obvious that we can not differentiate precisely the relative contribution of each therapeutic agent to the final result.

In the literature, there are only a few case reports and observational studies on ICT with urokinase or alteplase in combination with abciximab [2, 6, 7, 11] which add up to a total of 84 patients. The first case report was published by Eick and co-workers in 1997. None of these studies reported an excess of bleeding complications, and there was evidence of improved procedural results due to GP IIb/IIIa blockade. To our knowledge, this is the first report of ICT combined with the GP IIb/IIIa inhibitor tirofiban. We conclude that sequential systemic GP IIb/IIIa inhibition and intracoronary thrombolysis is a reasonable therapeutic approach in the setting of myocardial infarction and unsuccessful standard interventional therapy due to substantial intracoronary thrombosis. It has to be considered in appropriately selected patients with a low risk of hemorrhagic complications. In our opinion, this therapeutic strategy deserves further systematic evaluation. The selection of the respective agents, the evaluation of their individual therapeutic contribution, their dosage and the timing of application will need further study and refinement.

References

1. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E, for the TACTICS-Thrombolysis in Myocardial Infarction 18 Investigators (2001) Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879–1887
2. Eick B, Haude M, Altmann C, Liu F, Caspari G, Leischik R, Erbel R (1997) Behandlung eines großen intrakoronaren Thrombus mit Urokinase und einem chimären monoklonalen Thrombocytenaggregationshemmer. Dtsch Med Wschr 122:709–715
3. Henriques JP, Zijlstra F, van't Hof AW, de Boer MJ, Dambrink JH, Gosselink M, Hoorntje JC, Suryapranata H (2003) Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation 107:2115–2119
4. Leopold JA, Loscalzo J (1995) Platelet activation by fibrinolytic agents: a potential mechanism for resistance to thrombolysis and reocclusion after successful thrombolysis. Coron Artery Dis 6:923–929
5. Peters S, Trümmel M, Brattström A, Meyners W (2002) Pilot study for the use of dose-reduced alteplase and the glycoprotein IIb/IIIa inhibitor tirofiban in acute myocardial infarction. Z Kardiol 91:233–237
6. Quinn EG, Fergusson DJG (1998) Coronary embolism following aortic and mitral valve replacement: successful management with abciximab and urokinase. Catheter Cardiovasc Interv 43:457–459
7. Rashdan I, Schechter E (2000) Safety and efficacy of abciximab use in conjunction with intracoronary urokinase in patients requiring angioplasty. Catheter Cardiovasc Interv 49: 113–116
8. Rentrop KP, Blanke H, Karsch KR, Wiegand V, Kostering H, Oster H, Leitz K (1979) Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. Clin Cardiol 2:354–363
9. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) Investigators (1997) Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 96:1445–1453
10. Tiefenbrunn AJ (1996) Intracoronary recombinant tissue-type plasminogen activator (rt-PA). Coron Artery Dis 7:637–640
11. Yaryura RA, Zaqqa M, Ferguson JJ (1998) Complications associated with combined use of abciximab and an intracoronary thrombolytic agent (urokinase or tissue-type plasminogen activator). Am J Cardiol 82:518–519