Very late drug-eluting stent thrombosis after nonsteroidal anti-inflammatory drug treatment despite dual antiplatelet therapy

Bela Merkely MD PhD DSc¹, Emese Toth-Zsomboki MD PhD², David Becker MD¹, Bernat Janos Beres MD², György Szabó MD¹, Katarina Vargova MD², Gabor Fülöp MD¹, Gabor Kerecsen MD², Istvan Preda MD PhD DSc², Christian Spaulding MD³, Robert G Kiss MD PhD²

B Merkely, E Toth-Zsomboki, D Becker, et al. Very late drug-eluting stent thrombosis after nonsteroidal anti-inflammatory drug treatment despite dual antiplatelet therapy. *Can J Cardiol* 2009; 25(4):229-232.

BACKGROUND: Drug-eluting coronary stent implantation emerged as a safe and effective therapeutic approach by preventing coronary restenosis and reducing the need for further revascularization. However, in contrast to bare metal stents, recent data suggest a unique underlying pathology, namely late coronary stent thrombosis and delayed endothelial healing.

OBJECTIVE: To report a case of very late coronary stent thrombosis (834 days after implantation) requiring repeat urgent target-vessel revascularization. Importantly, six days before the acute coronary event, combined nonsteroidal anti-inflammatory drug therapy was initiated.

RESULTS: Although a dual antiplatelet regimen was continuously maintained, aggregation measurements indicated only partial antiplatelet effect, which returned to the expected range when nonsteroidal anti-inflammatory drugs were omitted.

CONCLUSIONS: The observation indicates that, even 834 days after drug-eluting stent implantation, effective combined antiplatelet therapy might be crucial in certain individuals and the possible impact of drug interactions should not be underestimated. Further efforts should focus on the challenging task of identifying patients or medical situations with prolonged, increased risk of stent thrombosis.

Key Words: Myocardial infarction; Nonsteroidal anti-inflammatory drugs; Platelet aggregation inhibitors; Stents; Thrombosis

Coronary stent thrombosis is a rare (1) but life-threatening complication of coronary angioplasty that usually occurs within 30 days of stent implantation (acute or subacute stent thrombosis). Within the first 30 days, the frequency of stent thrombosis is similar after either bare metal stent or drug-eluting stent (DES) implantation, when dual antiplatelet therapy is maintained (1). Recently, concerns have emerged about the high risk of late stent thrombosis (more than 30 days) after DES implantation due to delayed coronary endothelialization, late stent malapposition or aneurysm formation (2). Based on a meta-analysis of multicentre, randomized studies, the predicting factors of late stent thrombosis include stent length and the discontinuation or ineffectiveness of thienopyridine-based antiplatelet therapy (1).

There are few reports on very late stent thrombosis (VLST) (occurring more than one year after implantation), likely because of the lack of late follow-up in randomized studies on coronary stents. We

Une thrombose très tardive de l'endoprothèse à élution de médicament après un traitement aux anti-inflammatoires non stéroïdiens, malgré une bithérapie antiplaquettaire

HISTORIQUE : L'implantation d'endoprothèses coronaires à élution de médicament a émergé comme une démarche thérapeutique sécuritaire et efficace, car elle prévient une resténose coronaire et réduit la nécessité de revascularisation. Cependant, contrairement aux endoprothèses à métal nu, de récentes données laissent supposer la présence d'une pathologie sous-jacente unique, la thrombose tardive de l'endoprothèse coronaire et le délai de guérison endothéliale.

OBJECTIF : Déclarer un cas de thrombose très tardive de l'endoprothèse coronaire (834 jours après l'implantation) exigeant une reprise ciblée et urgente de la revascularisation d'un vaisseau. Fait important, six jours avant l'événement coronaire aigu, le patient avait commencé à prendre une association d'anti-inflammatoires non stéroïdiens.

RÉSULTATS : Malgré le maintien continu d'une bithérapie antiplaquettaire, les mesures d'agrégation ont indiqué un effet antiplaquettaire partiel seulement, qui ont retrouvé la plage normale après l'arrêt des anti-inflammatoires non stéroïdiens.

CONCLUSION : D'après l'observation, même 834 jours après l'implantation de l'endoprothèse à élution de médicament, une thérapie antiplaquettaire combinée efficace pourrait être essentielle chez certaines personnes, et il ne faudrait pas sous-estimer les répercussions possibles des interactions médicamenteuses. Il faudrait se pencher davantage sur la tâche difficile de dépister les patients ou les situations médicales associés à un risque prolongé et accru de thrombose de l'endoprothèse.

report a case of VLST that occurred more than two years after primary angioplasty with sirolimus-eluting stent implantation in a patient on concomitant nonsteroidal anti-inflammatory drug (NSAID) therapy.

CASE PRESENTATION

On February 15, 2004, a 39-year-old man with a 2.5 h inferior ST segment elevation myocardial infarction (STEMI) and a medical history of diabetes mellitus and hypertension was referred for primary percutaneous coronary intervention (PCI). Coronary angiography demonstrated total occlusion of the proximal right coronary artery (RCA) (Figure 1A) and 70% stenosis of both the middle portion of the left anterior descending artery and the left circumflex artery. Two overlapping Cypher stents (3.0 mm × 23 mm and 3.0 mm × 13 mm; Johnson & Johnson, Canada) were implanted in the RCA with excellent angiographic results (Figure 1B). Creatine kinase (CK)

¹Heart Center; ²Department of Cardiology, State Health Center and Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; ³Cardiology Department, Cochin Hospital, Paris 5 School of Medicine, Rene Descartes University, Paris, France

Correspondence: Dr Robert G Kiss, Department of Cardiology, State Health Center, Robert K Boulevard 44, Budapest 1134, Hungary.

Telephone 11-36-1-465-1966, fax 11-36-1-465-1857, e-mail robertgaborkiss@gmail.com

Received for publication December 27, 2006. Accepted June 23, 2007

Figure 1 Angiography. **A** The patient's initial atherothrombotic acute right coronary artery (RCA) occlusion. **B** Successful recanalization of the coronary artery via drug-eluting stent (DES) implantation. **C** Eight months later, no restenosis developed in the previously stented RCA. **D** Very late DES thrombosis occurred 834 days after the first coronary intervention, and resulted in complete occlusion of the RCA. **E** Using balloon dilation, the occluded vessel was repetitively recanalized (**F**)

peaked at 1315 U/L (normal range is less than 195 U/L) and CK-MB peaked at 110 U/L (normal range is less than 25 U/L). The patient had an uneventful recovery.

The patient was readmitted eight months later with Canadian Cardiovascular Society class II stable angina pectoris for coronary angiography. There was no instant restenosis in the RCA (Figure 1C). Angioplasty of the unchanged, left-sided coronary lesions was considered to be high-risk (type C lesions) and was not performed. The patient had no further chest pain after modification of the medical regimen.

TABLE 1
Platelet aggregation numerical results

	Peak aggregation (%)		Disaggregation* (%)	
	On NSAID	Without NSAID	On NSAID	Without NSAID
ADP, 5 µM	60	38	29	0
Collagen, 1 µg/mL	54	54	43	17
Adrenaline, 2 µg/mL	37	16	37	10

*Determined as platelet aggregation (%) 6 min after adding platelet agonists.
NSAID Nonsteroidal anti-inflammatory drug

On May 30, 2006, 834 days after the first coronary intervention, the patient was readmitted to the emergency department with acute chest pain. He had taken dual antiplatelet drugs (acetylsalicylic acid [ASA] 100 mg and clopidogrel 75 mg) continuously. However, he had been treated with diclofenac (75 mg twice per day) and meloxicam (15 mg twice per day) six days before the acute coronary event, which was prescribed for herniated lumbar intervertebral discs. An electrocardiogram indicated inferior STEMI; angiography revealed total thrombotic occlusion in the proximal portion of the RCA stents (Figure 1D). During PCI, the occlusion was successfully opened using a 2.0 mm × 20 mm Maverick (Boston Scientific, USA) and a 3.25 mm × 20 mm Mercury balloon catheter (Abbott GmbH and Co KG, Germany) (Figures 1E and 1F). CK and CK-MB peaked at 651 U/L and 56 U/L, respectively.

Platelet aggregometry was first performed 48 h after the PCI (24 h after the cessation of eptifibatide therapy) with sustained 75 mg clopidogrel, 100 mg ASA, NSAIDs and cyclooxygenase (COX)-2 inhibitor medication. Peak aggregation and platelet disaggregation were determined in platelet-rich plasma at 37°C with stirring at 1000 rpm in a CARAT-TX4 aggregometer (Carat Diagnostics, Hungary). By using standard activators (ADP 5 µM, collagen 1 µg/mL, adrenaline 2 µg/mL), platelet hyperreactivity was observed (Table 1 and Figure 2). NSAID/COX-2 inhibitor therapy was withdrawn and the antiplatelet regimen was continued as described above. Seven days later, repeat platelet aggregometry indicated effective platelet inhibition, particularly pronounced platelet disaggregation (Table 1 and Figure 2). Arachidonic acid-induced aggregations were completely inhibited, as expected. For safety reasons, the patient was discharged on high-dose dual antiplatelet therapy (ASA 300 mg and clopidogrel 150 mg per day); at the nine-month follow-up examination, he was asymptomatic with no bleeding complications.

DISCUSSION

VLST occurring beyond one year of implantation is an extremely rare clinical entity with few published case reports; based on recent, pooled four-year follow-up data, the incidence of VLST after DES implantation is 0.6% to 0.7% (3,4). Importantly, only two patients were taking dual antiplatelet drugs (noncompliance or withdrawal of thienopyridines). Unfortunately, the optimal duration of antiplatelet therapy beyond one year is not known (1). Previous guidelines suggest dual antiplatelet therapy for three months after sirolimus-eluting and six months after paclitaxel-eluting stent implantation; they recommend that dual antiplatelet therapy should be extended to 12 months at low risk of bleeding (5). Recently, professional societies endorsed continuing a dual antiplatelet regimen uniformly for 12 months after DES implantation (6). Further thienopyridine therapy should be considered individually, mainly in patients with potentially fatal consequences of VLST (6). In our patient, VLST at 834 days was triggered six days after NSAID and COX-2 inhibitor medication, despite the ongoing antiplatelet therapy.

There are three possible implications regarding mechanisms of the present late stent thrombosis case. First, ASA resistance, causing repetitive atherothrombotic episodes and thus, failure of antiplatelet therapy, can be caused by drug interactions (7). Concurrent

Figure 2 Platelet aggregation curves and numerical results (refer to Table 1) indicate platelet hyperreactivity on nonsteroidal anti-inflammatory drug (NSAID) medication (left panel) and effective platelet inhibition after skipping NSAIDs (right panel)

NSAID intake might prevent access of ASA to its COX-1 binding site, resulting in incomplete or reduced acetylation of Ser529 and the inability of ASA to inhibit platelet aggregation or thromboxane A₂ (TXA₂) production (8). Based on this interaction, current guidelines do not recommend the use of ibuprofen for pain relief in STEMI or in secondary prevention. As demonstrated by platelet aggregation induced by collagen, ADP and adrenaline, our patient's platelets were highly reactive when the patient was on NSAIDs and ASA. Following discontinuation of the NSAIDs, the platelets became less reactive to inducers, while inhibition of the secondary phase of platelet activation – represented by platelet disaggregation – was more pronounced (Table 1). However, we cannot rule out the possibility that platelet hyperreactivity was induced by the atherothrombotic event (stent thrombosis) itself. Similarly, pronounced platelet disaggregation might simply represent recovery of normal platelet inhibition after the acute phase. Current guidelines do not recommend platelet aggregation studies following stent implantation,

except for high-risk cases of stent thrombosis. The lack of baseline platelet activity data in the present case limits the interpretation of our results.

The second possible implication is that our patient received a selective COX-2 inhibitor. Regardless of clinical debates on COX-2 selective drugs, it is still not clear through which mechanism they unfavourably affect the cardiovascular system. Most probably, selective COX-2 inhibition tips the prostacyclin/TXA₂ balance toward TXA₂ production (8), causing exaggerated endothelial response to prothrombotic stimuli. In a human setting, it could theoretically increase thrombotic events in individuals at higher risk because of multiple risk factors. It is tempting to speculate that in our case, combined NSAID/COX-2 inhibitor therapy may have concomitantly triggered platelet hyperreactivity and imbalance of thromboxane/prostacyclin, resulting in a prothrombotic endothelial phenotype.

Finally, our patient received NSAIDs to treat his acute lumbar disc disease. Systemic inflammation (indicated by a 9.14 mg/L C-reactive

protein level measured on admission at the time of VLST) promotes atherothrombosis and platelet hyperreactivity, and may induce antiplatelet drug resistance.

The present case report suggests that even 834 days after DES implantation, effective combined antiplatelet therapy may be crucial in certain individuals. In patients with multiple risk factors and DES implantation, potential drug interactions (NSAIDs) or the role of inefficient antiplatelet therapy should not be underestimated; randomized, multicentre studies are needed to provide clinicians with clear evidence. Because ASA alone is unable to prevent stent thrombosis, the timing of clopidogrel discontinuation is one of the most important clinical decisions after stent implantation. Because

clopidogrel therapy cannot be maintained on a lifetime basis in all patients, efforts should focus on the challenging task of identifying patients or medical situations with a prolonged, increased risk of stent thrombosis.

FINANCIAL SUPPORT: The present study was supported by research grants from the Hungarian Science Foundation (OTKA T042605, F046711 and K49488) and from the Hungarian Ministry of Health (ETT 086/2003, ETT 583/2003, ETT 148/2006 and ETT 149/2006). ETZ is a recipient of the 'Bolyai' Scholarship Grant of the Hungarian Academy of Sciences.

REFERENCES

1. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159-68.
2. Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: Biological mechanisms and clinical implications. *Circulation* 2007;115:1051-8.
3. Henderson D, Gunalingam B. Very late stent thrombosis of a sirolimus-eluting stent. *Catheter Cardiovasc Interv* 2006;68:406-8.
4. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998-1008.
5. ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, eds. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2006;113:e166-286.
6. Love MP, Schampaert E, Cohen EA, et al; Canadian Association of Interventional Cardiology; Canadian Cardiovascular Society. The Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society joint statement on drug-eluting stents. *Can J Cardiol* 2007;23:121-3.
7. Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet* 2006;367:606-17.
8. Mitchell JA, Warner TD. COX isoforms in the cardiovascular system: Understanding the activities of non-steroidal anti-inflammatory drugs. *Nat Rev Drug Discov* 2006;5:75-86.