Late Stent Thrombosis After Drug-Eluting Stent Implantation for Acute Myocardial Infarction
A New Red Flag Is Raised

Matthias E. Pfisterer, MD

Late stent thrombosis (ST) made headlines when investigators realized that clinical events related to late ST, although rare, carried a mortality rate of up to 45% and a nonfatal infarction rate of another 30% to 40%. These rates clearly were more than those seen after bare metal stent (BMS) implantation, as first shown prospectively in the randomized Basel Stent Kosten Effektivitäts Trial–Late Thrombotic Events (BASKET-LATE). This led to a “firestorm,” which cooled off in view of the facts that these rare events are counterbalanced to some extent by fewer restenosis-related events in patients treated with drug-eluting stents (DES) versus BMS and that results of meta-analyses of earlier randomized trials and findings of large registries showed no overall excess mortality after DES versus BMS. Still, after DES implantation, late ST does occur, later than after BMS, at a relatively constant rate over time up to at least 4 years after stenting and, unlike after BMS, appears as primary thrombosis with a sudden unexpected clinical event not related to repeat interventions. Autopsy studies showed that delayed healing, ie, the lack of incomplete endothelial coverage of stent struts associated with persistence of fibrin deposits, is the primary pathoanatomic substrate of late ST after DES implantation. This was not found in patients with BMS. Delayed healing is the mechanism for late ST, ie, ST after 30 days of stent implantation, which was confirmed by intravascular ultrasound and angiographic studies, and is quite different from early ST. Here, procedural factors such as incomplete lesion coverage, plaque protrusion, and persistent dissection represent the most important reasons for thrombosis. For late ST, additional risk factors such as incomplete stent apposition, very long stented segments, and bifurcation stenting have been recognized. Still, questions remained regarding the large number of “off-label” DES indications, particularly stent treatment of acute myocardial infarction (AMI).

New Pathological Findings in Patients Treated With DES for AMI

The important study by Nakazawa et al in this issue of Circulation provides new insights into the vascular pathological responses to DES implantation in patients treated for AMI compared with patients receiving DES for stable angina. Briefly, 25 autopsy specimens of patients treated for AMI with an underlying necrotic core and a ruptured fibrous cap were compared with 26 specimens of stable angina patients with thick-cap fibroatheroma serving as controls. Histomorphometric analyses were performed in those 17 and 18 patients, respectively, who died >30 days after stent implantation. Late ST was significantly more frequent in AMI compared with stable patients (41% versus 11%; P=0.04). The histopathological correlates for this finding were a significantly lower neointimal thickness in AMI patients with a higher prevalence of stent struts not covered by endothelial cells (49% versus 9% in stable patients; P=0.01), more fibrin deposits, and more inflammatory cells. Similar differences also were noted between the culprit site compared with nonculprit sites within the same stents of AMI patients, stressing the importance of the necrotic core and its relevance for inhomogeneous healing. The authors concluded that “[v]essel healing at the culprit site in AMI patients treated with DES is substantially delayed compared with the culprit site in patients receiving DES for stable angina, emphasizing the importance of underlying plaque morphology in the arterial response to DES. Our data suggest an increased risk of thrombotic complications in patients treated with DES for AMI.” Obviously, these findings are based on a very selected group of patients, ie, those who died.

What Might Be the Relevance of These Findings in the Clinical Setting?

Given the finding that >50% of stent struts are not fully covered by endothelium in autopsy studies months to years after DES implantation, it remains unknown why only a few patients suffer late ST and what determines the point in time that this event occurs. It may be speculated that the same holds true for patients being treated with DES for AMI. In other words, the findings by Nakazawa et al do not mean that all patients with AMI treated with DES will suffer late ST. Other considerations minimize the clinical impact of these pathological findings. In patients with angioplasty and stenting relatively late after acute vessel closure, the amount of rescued viable myocardium may be so small that late reoclusion may not present as a relevant clinical event and therefore may be missed. Sudden cardiac death after AMI may be due to reasons other than reoclusion and ischemic ventricular fibrillation; thus, it may be difficult clinically to identify such cases as being due to late ST, a reason why possible late ST according to the Academic Research Con-
sortium definition is often neglected. The fact that 5 of 8 patients with stent-related death, ie, late ST documented at autopsy, died suddenly in the study by Nakazawa et al shows, however, that not counting late sudden cardiac death as late ST cases biases reported late ST rates in favor of DES. Finally, a difference in hard clinical events related to late ST after DES versus BMS implantation for AMI also may be minimized by the beneficial effect of DES on restenosis and related events as noted in non-AMI patients. However, a recent intravascular ultrasound study in 43 patients with late ST after DES for ST-elevation AMI compared with 76 patients with DES for stable angina also showed an almost 3-fold increased rate of late ST in AMI patients (14% versus 5%). Thus, an increased rate of late ST after DES implantation for AMI compared with stable patients has to be expected, but the true rate in real-world practice still needs to be determined.

Only a few studies on thrombosis after stenting differentiated predictors of early (<30 days) from late (>30 days after stenting) ST. In those that did, acute coronary syndrome as the baseline presentation was the main factor consistently predicting late clinical events related to late ST. This finding parallels the findings by Nakazawa et al. In current real-world settings, acute coronary syndrome is the reason for angioplasty and stenting in ∼60% of patients, about one third of them presenting with ST-elevation AMI. This is a relevant patient population in daily practice that was mostly excluded from the pivotal trials demonstrating the superiority of DES over BMS. In view of the findings of Nakazawa et al, this may be 1 reason why the rate of late ST was very low in those studies even after prolonged follow-up. On the other hand, the rate of late ST of 0.6%/y found in 1 large “all-comer” registry relates only to angiographically proven events. A more realistic magnitude of the late ST problem in clinical practice in patients with acute coronary syndrome has been described in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) stent analysis. In patients on standard dual antiplatelet therapy with clopidogrel, a total ST frequency of 2.75% was noted up to a median of 1 year. This finding is similar to that for total late ST in the BASKET 3-year follow-up data, which included almost 60% of patients with acute coronary syndrome, one third of them with AMI, in which the rate of late ST per year after DES implantation was ∼2.5 times higher than after BMS implantation. A similarly low rate of late ST after BMS was recently confirmed in a large retrospective registry. Unfortunately, true large prospective trials with long-term follow-up evaluating late ST after DES versus BMS in patients with AMI are not available yet. Data presented so far seem conflicting and did not have sufficiently long follow-up.

Implications of These New Pathological Findings

Nakazawa et al conclude that “although the safety of this practice [DES for AMI] is uncertain, our data suggest a significantly increased risk of late thrombotic complications that should be expected in patients treated with DES for AMI.” They also conclude, “Undoubtedly, only prospective studies with much longer follow-up are necessary before we can say definitively whether DES are associated with improved long-term clinical outcome in patients with AMI. Until that time, routine DES implantation for AMI cannot be recommended.” Thus, Nakazawa et al raise a new red flag, a flag of caution for all cardiologists using DES in AMI patients. This is not yet a proven indication. DES should not be used in AMI patients until results of the large randomized trials of DES versus BMS for AMI are available. It is hoped that the investigators will do their best to identify the causes of death in each and every patient who dies during a prolonged follow-up to shed more light on the magnitude of the problem of late ST after AMI in daily practice. An entirely different but also clinically important question is whether these late ST-related events can be prevented by prolonged intense antiplatelet therapy and at what price (bleeding and financial). The limited efficacy of the current regimen is documented by findings by Nakazawa et al, who noted that 25% of late ST events occurred despite dual antiplatelet therapy with aspirin and clopidogrel, very similar to results from the Berne-Rotterdam registry.

Disclosures

None.

References

12. Nakazawa G, Finn AV, Joner M, Ladhik E, Kutrys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and...


Key Words: Editorials ■ angioplasty ■ coronary disease ■ myocardial infarction ■ stents ■ thrombosis
Late Stent Thrombosis After Drug-Eluting Stent Implantation for Acute Myocardial Infarction: A New Red Flag Is Raised
Matthias E. Pfisterer

Circulation. 2008;118:1117-1119
doi: 10.1161/CIRCULATIONAHA.108.803627
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/11/1117

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/