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EDITORIAL COMMENT

New Insights on Stent Thrombosis

In Praise of Large Nationwide Registries for Rare Cardiovascular Events*

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Stents represent the default strategy in interventional cardiology (1). In the last decade, drug-eluting stents (DES) have been widely embraced because of their unprecedented ability to drastically inhibit neointimal proliferation. Accordingly, the clinical need for repeat revascularization has been significantly reduced despite the widespread use of coronary interventions in ever increasingly complex clinical and anatomic scenarios. However, the risk of stent thrombosis (ST) remains an issue of serious concern (2). DES have been unable to reduce the incidence of this complication but have changed its temporal pattern of presentation, widening the vulnerable period. Actually, this problem has prevented an even wider penetration of DES (1,2).

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ST remains a very rare phenomenon, but it may be associated with devastating clinical consequences (2). Early series suggested that ST was associated with very high mortality (3). Subsequent studies—from less selected patient populations—suggested that the consequences of ST were not so dismal, although clinical outcomes were still poorer than those seen in de novo patients with acute myocardial infarction (4,5). The explanation for this particularly adverse prognosis remains obscure, but the uniquely large thrombus burden seen in patients with ST might play a role (2). Likewise, the underlying mechanisms leading to ST remain poorly elucidated but appear multifaceted. Mechanical factors, delayed endothelialization, and hypersensitivity reactions have all been considered as "local factors" able to generate a "*vulnerable stent*." Furthermore, from a "systemic" perspective, any potent stimulus triggering platelet activation might shift the delicate coagulation balance toward a prothrombotic milieu precipitating the acute event. However, despite intense research efforts, the incidence, predictive factors, underlying pathological substrate, clinical implications, and management of ST still remain incompletely elucidated. All previous studies on ST suffer from a common main limitation: relatively small sample sizes. Therefore, larger studies, with enough power to address the unmet need of information still required on this dreadful complication, are eagerly awaited.

In this issue of *JACC: Cardiovascular Interventions*, Armstrong et al. (6) present the results of an impressively large cohort of patients with ST (7,315 episodes of ST) included in the CathPCI Registry. This study provides unique insights that complement our current knowledge on ST.

Present Study

In the current study, 7,079 patients with ST (1,391 early [19.6%], 1,370 late [19.4%], and 4,318 very late [61%]), of 401,662 patients (1.8%) with acute coronary syndromes prospectively included in the CathPCI Registry, were analyzed (6). Two-thirds of patients received DES and experienced very late ST. Overall in-hospital mortality was only 4.5% and was similar for bare-metal stents (BMS) and DES ST. Patients with early ST showed a higher prevalence of black race, diabetes, and prior heart failure. They also presented more frequently a Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 and left anterior descending coronary artery lesions. Interestingly, in-hospital mortality was 2-fold higher (7.9%) in patients with early compared with late or very late ST. Notably, the poorer clinical outcome of patients with early ST persisted despite adjustment for potential confounders using a previously validated mortality model. Of additional interest, more than one-half of the interventions performed to treat episodes of ST eventually involved a new stent implantation. However, the use of thrombus aspiration devices and glycoprotein IIb/IIIa platelet inhibitors (GPI) (one-third and two-thirds of procedures, respectively) was relatively limited. Early ST was more frequently managed with GPI but also had a higher incidence of major bleedings. To fully appreciate the importance of the novel information unraveled by this study, its results should be examined from the perspective gained during the discussion of some relevant methodological issues.

In addition to its uniquely large sample size, this study has many major strengths. Assessing data quality and potential selection biases are always of paramount importance for the interpretation of large registries. The CathPCI Registry is an initiative of the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, with quality standards validated by the National Cardiovascular Data Registry. Briefly, data elements were prospectively collected during hospitalization in *consecutive* patients using explicit definitions (6). In addition,

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several quality checks—including external audits—were implemented to ensure data reliability. All patients had angiographically confirmed (i.e., definitive) ST. Moreover, to better adhere to the Academic Research Consortium definition and further refine the study cohort, avoiding potential misclassifications, strict additional requirements were mandated. These included careful crosschecking of the dataset to guarantee consistency of pertinent clinical and angiographic variables. For instance, additional description of angiographic thrombus was required for patients with TIMI flow grade 3 (6). On the other hand, nearly 1,000 U.S. centers participated in this study, dissipating any potential concern on external validity. Finally, the selected cross-sectional design offered a very recent (years 2009 to 2010) and tight (16-month time window) snapshot on current clinical practices implemented in patients with ST (6).

Some potential study limitations should be also considered. First, angiographic studies were not centrally reviewed in a core laboratory (6). However, due to the strict screening criteria, the risk of misclassification of angiographically confirmed ST appears negligible. Second, adverse events were not adjudicated by an independent committee. Nevertheless, consecutive patients were enrolled, and authors selected total death as the primary endpoint, which, again, is highly reassuring. However, only patients with ST undergoing coronary interventions were included, and this may lead to survival bias. Other adverse events, in particular recurrent episodes of ST, are relatively frequent in these patients, yet neither data on these episodes nor the requirement of target vessel revascularization were collected. Likewise, many earlier reports suggested that these patients have an adverse prognosis after discharge. However, long-term clinical information was not obtained. Furthermore, compliance to antiplatelet medication was not recorded. Finally, the cross-sectional study design allows assessing the burden posed by this problem on routine real-world catheterization laboratory "activity" but provides no incidence estimates (6).

Treatment of Stent Thrombosis

Despite the widespread concern generated in the cardiovascular scientific community by the problem of ST, it is surprising to realize the scarce information currently available on the value of specific therapies for the management of these patients (2–5). The rarity of this complication, which always conveys a medical emergency, has likely impeded the design of adequate studies aimed to gain the required evidence on the relative efficacy of different interventional modalities. Most investigators, including our own group, suggest a holistic approach to address this challenging scenario (2–9). First, an aggressive management of the intracoronary thrombus (thrombus aspiration, intracoronary GPI) appears warranted. Second, any effort should be made to remove all residual, potentially predisposing mechanical factors (stent fracture, underexpansion, malapposition, edge dissections, inflow–outflow disease) for ST (2,7–9). The use of intracoronary diagnostic techniques (intravascular ultrasound or optical coherence tomography) appears of major value to guide and optimize results of these interventions (7–9). Third, a truly "effective" preventive antiplatelet regimen should be initiated immediately and then maintained for a long time, ideally, indefinitely. The value of systematic use of point-of-care functional tests to assess on-treatment platelet reactivity, or genetic screening tests to disclose adverse polymorphisms, currently remains unproven. However, they certainly constitute attractive options in the individual patient to ensure that the prescribed antiplatelet therapy is being effective. A more pragmatic approach would be the use of the newer, more potent and predictable antiplatelet agents in all patients with ST. In any case, the thrombogenic milieu should be urgently and aggressively reverted, because survivors of ST may not survive recurrences (2–5).

From a mechanical standpoint, careful thrombus aspiration appears essential (7–11). Recent studies suggest that in these patients, thrombus aspiration is associated, not only with better epicardial and microvascular reperfusion (10), but also with favorable clinical outcomes (11). Following thrombus removal, one would anticipate that an aggressive dilation of the underlying stent would be adequate to optimize final results in most patients. In this regard, the high number of patients eventually requiring a new stent implantation in this series is surprising (6). Interestingly, the rate of new stent placement was lowest and the use of GPI highest among patients with early ST (6). The reasons for these distinct treatment patterns remain unknown. However, prior studies (5) and a recent registry from California (12) also suggested that most patients treated for ST received a second stent. Although the value of recurrent stent implantation (stent-in-stent technique) is well established in patients with in-stent restenosis (ISR), its role in the setting of ST remains highly controversial. Unfortunately, this registry was unable to ascertain why some of these patients eventually required a repeat stenting. Therefore, we can only speculate as to why this strategy was selected in most patients. Re-stenting is able to readily provide satisfactory angiographic results, even in patients with persisting suboptimal results after balloon inflation because of resistant in-stent thrombus. Although covering the thrombus with another stent might not be perceived as an elegant strategy, this may constitute the last resort option in some cases. Another possibility is that the new stent was just used to tackle edge dissections or significant obstructive disease adjacent to the original stent. Actually, residual edge dissections and inflow–outflow disease, together with de novo plaque rupture adjacent to the stent, are well-known causes of ST that can be easily "fixed" with overlapping

stents (7–9). Finally, edge dissections may be also generated during the procedure by the use of relatively oversized balloons in the attempt to optimize final angiographic results.

New Evidence Bridging the Gap Between Restenosis and Thrombosis

In some patients, it might be difficult to differentiate severe ISR from true ST due to overlapping clinical and angiographic features. Moreover, the possibility of underlying ISR associated with superimposed thrombosis in some patients with non-early ST, as discussed by Armstrong et al. (6) in their report, is intriguing indeed. Interestingly, complete vessel occlusion was less frequent in patients with non-early ST. This might be the result of a smaller thrombus burden, which in turn may explain the lower use of GPI and the higher use of repeat stenting in this patient subset. Again, we could only speculate on whether this might have contributed to the lower mortality of patients with non-early ST. The demonstration of neoatherosclerosis in some patients with ISR represents a major paradigm shift in the field that may help to bridge the gap between the 2 worlds. Recent studies with coronary angioscopy, intravascular ultrasound, and optical coherence tomography have demonstrated the presence of thin-cap fibroatheroma, lipid-laden neointima, necrotic core, plaque rupture, neovascularization, and more importantly, superimposed red or white thrombi in some patients presenting with unstable symptoms and late/very late ISR/ST (13–16) (Fig. 1). Pathological observations (17) confirmed these phenomena, further suggesting that late in-stent neoatherosclerosis, not only occurs more frequently, but also occurs earlier after DES than after BMS. Currently, this specific substrate may be identified with intracoronary imaging techniques and represents yet another etiology of "*vulnerable stents*" (13–17). Interestingly, many of these

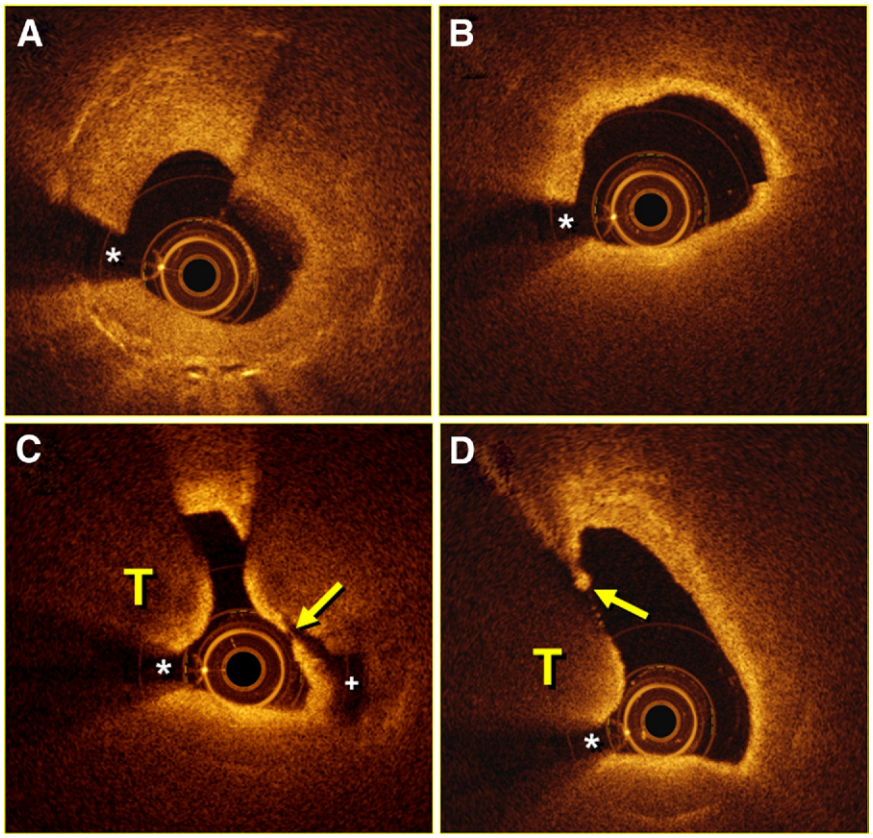

Figure 1. Optical Coherence Tomography Images of a Patient With Very Late In-Stent Restenosis Presenting as ST

In-stent optical coherence tomography images **(A to D)** from a patient presenting with prolonged chest pain 3 years after the implantation of an everolimus-eluting stent in the left anterior descending coronary artery. Angiography only demonstrated a severe, diffuse, in-stent restenosis without images suggestive of thrombi. **(A)** Severe homogeneous neointimal hyperplasia, the stent struts, and some microvessels (6 o'clock) are clearly visualized. **(B)** Bright neointima completely shadowing the stent struts (consistent with lipid-laden or infiltrated neointima). **(C and D)** Images of disrupted intima or ruptured thin cap (thickness 75 μm) **(yellow arrows)** with underlying cavities **(+)**, together with large, protruding red thrombi (T) causing major distal shadowing of the stent. *Wire artifact. All the images were obtained within the stent. This patient, with an initial clinical diagnosis of in-stent restenosis, eventually evolved as a relatively large anterior myocardial infarction (creatine phosphokinase peak 750 IU).

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patients do not suffer from large myocardial infarctions and appear to have less severe thrombotic burden (13–17). Although it is tempting to speculate that the distinct pathological substrate of complicated late in-stent neoatherosclerosis might have a relatively favorable prognosis and require the use of specific coronary interventions, these exciting hypotheses should be confirmed in prospective studies.

Final Remarks

This uniquely large, high-quality registry provides novel important information on clinical characteristics, current therapeutic strategies, and prognosis of patients suffering from ST. Although, in unselected consecutive patients undergoing reinterventions, in-hospital mortality appears to be lower than previously reported, this rare but feared complication still remains associated with significant morbidity and mortality. Management of ST remains highly challenging, and additional evidence is urgently warranted to be able to select from our current therapeutic armamentarium the best possible pharmacomechanical approach, ideally tailored to the characteristics of individual patients. However, here, more than ever, prevention should remain the cornerstone of any therapeutic effort.

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