EDITORIAL COMMENT

Late Stent Thrombosis

Can it Be Prevented?*

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Stent thrombosis (ST) remains a serious complication of percutaneous coronary intervention (PCI), which carries with it a high rate of morbidity and mortality (1-3). The first step in avoiding this problem is understanding how it develops and what factors might reduce risk. Because ST is, fortunately, now rare in the setting of optimal procedural technique and dual antiplatelet therapy (DAPT), it has been difficult to study. Furthermore, early ST (before 30 days) is more common than later events, and there have been limited data of both the predictors and consequences of ST in the late and especially very late periods after PCI (4-8). In this issue of *JACC: Cardiovascular Interventions*, Waksman et al. (9) present the DESERT (Drug-Eluting Stent Event Regis-

try of Thrombosis) study in which they set out to characterize the clinical predictors and consequences of late (beyond 30 days) and very late stent thrombosis (VLST) (beyond 1 year) after the implantation of drug-eluting stents (DES). The authors identified 492 cases of ST from cardiac catheterization laboratory procedures and matched these cases to controls who received a DES in the same institution and on the same date. This retrospective design provided a large number of cases of what is generally a rare event in most prospective studies (e.g., about 1% to 2% over

5 years of follow-up). Clinical and angiographic review and ascertainment of events even beyond 5 years after PCI provided rich data that complement existing retrospective studies (7), prospective registries (8), and randomized trials (6).

Cases were selected based primarily on angiographic (rather than post-mortem) evidence of ST. The study identified factors present at the time of initial stent placement that predicted thrombosis beyond 30 days, many of which are consistent with prior studies, for example, lesion length, presence of thrombus, and residual stenosis of the stented segment. Although previous studies have reported mortality rates following early or late ST of 20% and higher (1), the current study (9) reports a rate of 3.8%.

The investigators suggest that the lower mortality rate seen in late and VLST compared with historically higher mortality rates in acute and subacute ST is due to "a different pathological mechanism for this [VLST] phenomenon." Another recent registry study reported a mortality rate of 3.6% to 3.8% (7). Although it is true that reports before these have focused primarily on early ST, the more common event, one must exercise caution in interpreting expectations regarding the mortality from retrospective analyses because of limitations in how cases of ST are identified. In prospective studies, all patients provide consent for follow-up, and in most studies to evaluate new devices, near complete follow-up is expected to be performed to ascertain all mortality and causes, and a committee to review clinical, angiographic, and pathological evidence to ascertain ST is mandatory. By contrast, retrospective studies rely on the ascertainment of cases using various methods. In this example, cases were ascertained based on presentation for angiography at the participating study sites. By definition, cases must have survived to present to the study site and undergo angiographic confirmation. Cases of sudden death, which are routinely observed in prospective studies, would not be captured in this

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study (9) or the study by Armstrong et al. (7) because they would not reach angiography, and as a result, mortality rates were likely underestimated.

To have an impact on clinical care, a study to examine risk factors should provide assessment of which factors might be modified to decrease risk. Two key treatment choices in this regard are stent type and antiplatelet regimen. Regarding DES type, the investigators observed no effect between earlier and later designs despite randomized trials supporting lower late ST rates for current DES compared with prior designs (6,10,11). Limitations of the available data might be the cause of this discrepancy from randomized trial data. First, lack of power (<10% of subjects received newer DES), and second, the method used for selecting cases and controls may have undermined the ability to examine effects of stent choice. Because stent type is segregated by calendar time and institution (e.g., which stents were prevalent in an institution on a given day), matching cases and controls on site and day limits the ability to compare the effect of different stent types. Similar limitations might be present for comparing the effects of procedural technique, with operators clustered on the same day. Intracoronary imaging provided some interesting observations in the study, but it was not routinely performed at the time of either the index procedure or ST.

As in prior studies, ST occurred in subjects both on and off of DAPT. It is difficult to compare drug types for the same reasons that limit stent type comparisons in this dataset. Regarding whether continuing therapy beyond a certain time could prevent ST, the study 1104 offers limited data. DAPT duration and adherence were not recorded for controls, and it is not possible, therefore, to compare DAPT duration and its impact on ST risk. The true effect of DAPT given beyond 1 year and ST risk is not well understood currently, but the final follow-up of the DAPT study this year will provide randomized data comparing a strategy of 1 year versus longer periods in preventing VLST (12).

Although prospective studies of late ST and VLST are difficult to conduct because the incidence of late ST and VLST is low, we must be cognizant of both the strengths and limitations of retrospective data. Treatment comparisons benefit from randomization to avoid selection bias, or the residual bias inherent in retrospective analysis. Prospective data and comprehensive follow-up ensure that hazards and the impact of risk factors can be accurately estimated. Late ST and VLST remain serious complications of coronary stenting that, although rare, deserve ongoing consideration for methods of prevention. The current study by Waksman and colleagues (9) provides a level of detail and duration of follow-up as well as a breadth of patients and procedures that have not previously been achieved in prospective studies.

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