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EDITORIAL

Coronary Stent Thrombosis and Mortality: Does the Relationship Stand the Test of Time?

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The advances in coronary stent technology have been tremendous in the past decade, and practicing interventional cardiologists now enjoy the benefits of the current generation devices. Those include excellent deliverability across tortuous vessels, ease of deployment, and significantly reduced rates of in-stent restenosis and stent thrombosis. Combined with perfected interventional techniques for lesion preparation and a background of excellent medical therapy, consisting of antiplatelet agents and statins, we have been able to provide many patients with a durable therapeutic option that is well tolerated. In particular, the incidence of stent thrombosis has been low (≈0.5%) in recent years.[1] In fact, the current guidelines for coronary revascularization allow for a shorter duration of postintervention dual-antiplatelet therapy in patients with increased bleeding risk.[2]

See Article by Ishihara et al.

Stent thrombosis, however, still carries a significant impact on morbidity and mortality. No one can argue against this, and the data are clear. Clinical trials have reported mortality rates as high as 50% in patients with early (within 1 month of the procedure) stent thrombosis.[3] The sudden development of thrombosis, vastly without clear warning signs, is one of the main drivers of bad outcome. This is typically associated with an acute coronary syndrome event that portends a poor prognosis, even when promptly treated.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Ishihara et al[4] report the findings of a multicenter retrospective observational registry study of patients with stent thrombosis. During the years 2008 to 2017, they identified 187 patients with Academic Research Consortium definite stent thrombosis diagnosed at the time of coronary angiography. They report on the long-term outcomes and the clinical predictors of mortality in that cohort of patients. They found that the cumulative mortality was ≈15% at 1 year, with a steady increase up to ≈34% at 10 years. They identified the following independent predictors of mortality: hemodialysis status, culprit lesion in the left main or the left coronary artery, and peak creatine kinase level.

It is important to interpret the results in the context of the population studied. The population was predominantly male (≈85%) patients with a mean age of 65 years who survived the stent thrombosis event long enough to undergo coronary angiography. Therefore, there is an inherent selection bias, and the cohort represents a lower-risk subgroup of all comers with stent thrombosis. Nonetheless, the data provided are important as they pertain to the outcomes of survivors of

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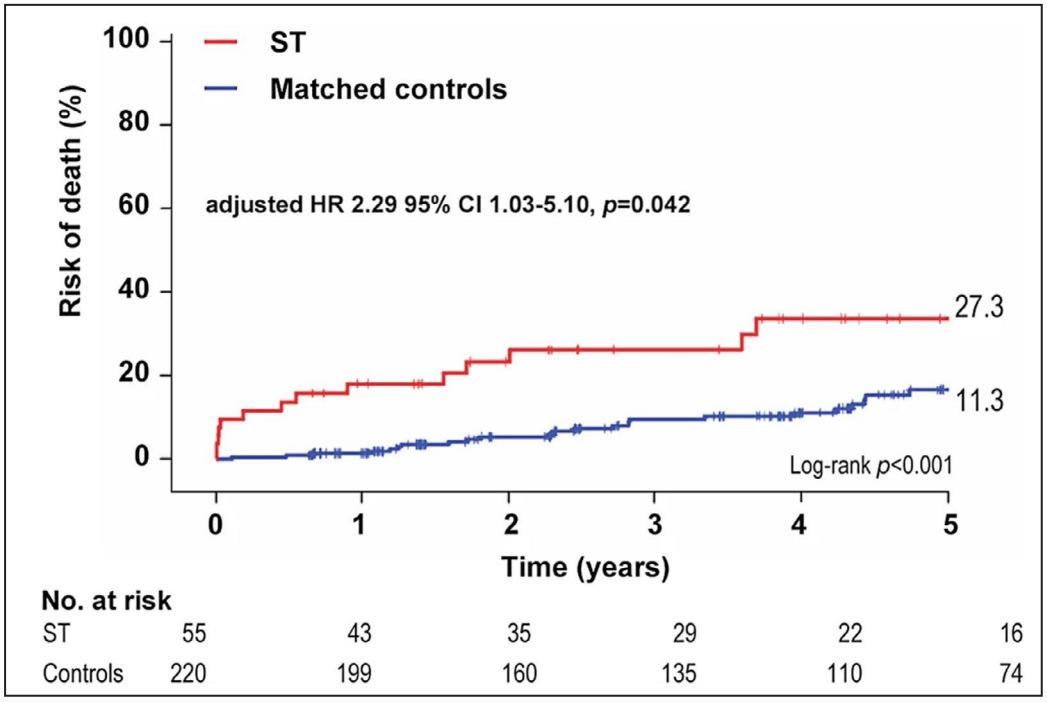

Figure. Kaplan-Meier estimates for the risk of death of angiographically confirmed stent thrombosis (ST) compared with matched controls.
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the initial event. The 1-year mortality rate of near 15% is high and reflects the need to aggressively manage those patients.

But what are the determinants of overall mortality after stent thrombosis? A detailed look at the Kaplan-Meier curves (Ishihara et al[4] Figures 2 and 4B) shows that the cumulative cardiac mortality increases abruptly in the early period following stent thrombosis but appears to increase only slightly beyond 2 years, which indicates that the longer-term mortality is mainly related to other noncardiac causes. In fact, there was no occurrence of cardiac death beyond 5 years. Causes of cardiac mortality early after stent thrombosis include ventricular dysfunction/failure, recurrent fatal infarction (possibly recurrent stent thrombosis), and ventricular arrhythmias. The independent predictors of mortality that Ishihara et al identified are in line with the mentioned causes: left main or left coronary lesions and creatine kinase levels are all surrogate markers of large amount of myocardium affected with the event.

In addition, survivors of stent thrombosis are likely to be maintained on longer-term dual-antiplatelet therapy. Therefore, the incidence of bleeding and its associated mortality[5] are increased and hence this may explain the identification of dialysis status in that same study as an independent predictor of mortality, given the baseline high bleeding risk in patients with advanced kidney disease.[6,7] Furthermore, these patients are more likely to receive future cardiac testing (including invasive angiography) to investigate symptoms, therefore subjecting them to additional procedures and their associated risks.

The findings of Ishihara et al that mortality occurs predominantly in the early period following the index stent thrombosis event are similar to those of other studies. Almalla et al[8] reported on 106 patients (mean age, 70 years; 80% men) who presented between 2003 and 2011 with stent thrombosis. They found a 1-year mortality rate of 24% that increased to 36% at long-term follow-up with a median of 5.3 years.

But beyond the early increase in mortality, the outcomes of patients with stent thrombosis appear to be not much different from those who have not experienced such an event. To determine the impact of stent thrombosis on long-term survival, one must conduct a direct comparison of patients with and without stent thrombosis but with similar other clinical characteristics. In a survey of 6545 consecutive patients undergoing percutaneous coronary intervention between 2010 and 2016, Rozemeijer et al identified 55 patients with definite stent thrombosis diagnosed on coronary angiography.[9] They were compared with patients without stent thrombosis in a 1:4 matching according to the indication and date of the intervention. Patients with stent thrombosis had a higher prevalence of diabetes

and history of coronary events and intervention. They were also more likely to have a left ventricular ejection fraction <35% and more complex lesions, thus representing a higher risk group at baseline. At a median follow-up of 4 years, cumulative mortality was significantly higher in patients with stent thrombosis compared with their matched controls (27.3% versus 11.3%; $P<0.001$). On close inspection of the mortality curves (Figure), it is evident that the abrupt increase in the risk of death happens during the first few months after the stent thrombosis event. Following that, the 2 curves follow parallel courses, with no increased mortality specific to patients with history of stent thrombosis over long-term follow-up, despite having more high-risk clinical features at baseline.

How do we summarize the above information and apply it to daily clinical practice? Stent thrombosis is a major event that carries a high immediate mortality rate. This increased risk extends into the early period in survivors who undergo coronary angiography and intervention. Beyond the first few months, there seems to be no increased risk of mortality over up to 10 years of follow-up. These findings have direct implications for the management of those patients. Survivors of stent thrombosis should be followed closely in the first few months after the event and treated with aggressive medical therapy and continued dual-antiplatelet therapy, while balancing their thrombosis and bleeding risks. Beyond the early phase, unless there has been recurrence of events, therapy could potentially be scaled down to a single antiplatelet agent following a shared decision-making process that includes a detailed discussion of risks and benefits and the patients followed up according to the prevailing standard of care, including withholding antiplatelet therapy when needed before noncardiac procedures. As we gather more data on stent thrombosis events with the current generation devices, more solid recommendations can be made about the management of these patients.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Lee S-Y, Hong M-K, Palmerini T, Kim H-S, Valgimigli M, Feres F, Colombo A, Gilard M, Shin D-H, Kim J-S, et al. Short-term versus long-term dual antiplatelet therapy after drug-eluting stent implantation in elderly patients: a meta-analysis of individual participant data from 6 randomized trials. *JACC Cardiovasc Interv*. 2018;11:435–443. doi: 10.1016/j.jcin.2017.10.015
2. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e18–e114. doi: 10.1161/CIR.0000000000001038
3. Secemsky EA, Matteau A, Yeh RW, Steg PG, Camenzind E, Wijns W, McFadden E, Mauri L; PROTECT Trial Investigators. Comparison of short- and long-term cardiac mortality in early versus late stent thrombosis (from Pooled PROTECT Trials). *Am J Cardiol*. 2015;115:1678–1684. doi: 10.1016/j.amjcard.2015.03.010
4. Ishihara T, Okada K, Kida H, Tsujimura T, Iida O, Okuno S, Hata Y, Toyoshima T, Higashino N, Kikuchi A, et al. Long-term outcomes and clinical predictors of mortality following occurrence of stent thrombosis. *J Am Heart Assoc*. 2022;11:e023276. doi: 10.1161/JAHA.121.023276
5. Urban P, Gregson J, Owen R, Mehran R, Windecker S, Valgimigli M, Varenne O, Krucoff M, Saito S, Baber U, et al. Assessing the risks of bleeding vs thrombotic events in patients at high bleeding risk after coronary stent implantation: the ARC-high bleeding risk trade-off model. *JAMA Cardiol*. 2021;6:410–419. doi: 10.1001/jamacardio.2020.6814
6. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100. doi: 10.1378/chest.10-0134
7. van Eck van der Sluijs A, Abrahams AC, Rookmaaker MB, Verhaar MC, Bos WJW, Blankestijn PJ, Dekker FW, van Diepen M, Ocak G. Bleeding risk of haemodialysis and peritoneal dialysis patients. *Nephrol Dial Transplant*. 2021;36:170–175. doi: 10.1093/ndt/gfaa216
8. Almalla M, Schröder J, Hennings V, Marx N, Hoffmann R. Long-term outcome after angiographically proven coronary stent thrombosis. *Am J Cardiol*. 2013;111:1289–1294. doi: 10.1016/j.amjcard.2013.01.268
9. Rozemeijer R, Wing Wong C, Leenders G, Timmers L, Koudstaal S, Rittersma SZ, Kraaijeveld A, Bots M, Doevendans P, Stella P, et al. Incidence, angiographic and clinical predictors, and impact of stent thrombosis: a 6-year survey of 6,545 consecutive patients. *Neth Heart J*. 2019;27:321–329. doi: 10.1007/s12471-019-1253-2