

EDITORIAL COMMENT

Drug-Eluting Stent Fracture

Promise and Performance*

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All promise outruns performance.

—Ralph Waldo Emerson (1)

The saga of drug-eluting stents (DES) continues from their hyperbolic introduction into clinical practice in 2003 through a period of scrupulous clinical safety introspection, emerging as the principal device therapy for percutaneous coronary intervention with renewed enthusiasm in today's era of prolonged oral dual antiplatelet therapy. Clinicians, researchers, industry, and regulatory agencies have gained wisdom from the many lessons taught in the global introduction of DES into clinical practice. As clinicians and scientists, we benefit from an organized cognitive approach to solve clinical problems or test new hypothesis. To the risk of oversimplification, one can systematically summarize our experience with DES in clinical practice as a series of lessons: 1) the early signals of potential unanticipated safety issues of hypersensitivity reactions and late thrombosis from

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clinical case reports and post-market surveillance registries (2,3); 2) post-market observational studies from independent researchers elicited concern regarding the long-term safety and efficacy of DES in comparison with bare-metal stents (BMS) (4); 3) clinical and pathologic studies identify delayed healing as the likely mechanism for late and very late DES thrombosis (5); and 4) observational studies indicate a lower probability of late stent thrombosis with optimal stenting techniques, careful case selection, and prolonged dual oral antiplatelet therapy with aspirin and clopidogrel (6,7). Thus, the early signals after introduction of DES into clinical practice generated safety concerns supported by long-term observational data that defined the problem of late thrombosis, which necessitated refinements in clinical practice to improve patient outcomes.

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In this issue of the *Journal*, Nakazawa et al. (8) provide unique pathologic insights into the frequency, anatomic, morphologic, and clinical histologic events associated with stent strut fracture, yet another lesson learned with DES. The assumption that commercially available BMS were suitability designed to serve as a vehicle for drug delivery is dubious, given recent clinical reports of adverse cardiac events associated with DES strut fracture and the pathologic data first reported in the *Journal*.

The aim of the study by Nakazawa et al. (8) was to assess the incidence of stent fracture at autopsy using high-contrast film-based radiography and to investigate the impact of stent fracture on the pathologic findings and histologic clinical outcomes. This pathological study included 170 consecutive lesions derived from a single-center post-mortem DES registry suitable for high-contrast film-based stent radiography and light microscopy to define the incidence of thrombosis and restenosis for stents with and without strut fracture. The authors developed a radiographic classification for strut fracture based on the number of fractured struts and associated material defects of the stent. Strut fracture was classified as grade I (single-strut fracture), grade II (≥ 2 fractured struts), grade III (≥ 2 fractured struts with deformation), grade IV (strut fractures with transection without gap), and grade V (strut fractures with gap within the stent body).

In this pathologic study, the authors reported a higher frequency of DES strut fracture than previously described by clinical observational studies that utilized angiographic methods to detect strut fracture. Case studies and single-center clinical observational studies report an approximate 1% to 5% incidence of DES strut fracture (9). In the pathologic study by Nakazawa et al. (8), DES strut fracture was detected in 51 of 177 (29%) lesions examined in this post-mortem cohort. The differences in the observed frequency of DES strut fracture in the clinical and pathologic studies likely reflects the inferior resolution of imaging techniques applied in clinical research compared with the methods for pathologic analysis of stents, although the possibility of selection bias indeed may contribute to the higher frequency of DES strut fracture reported in the present pathologic study. The systematic pathologic analysis applied in the report by Nakazawa et al. (8), however, yields critical novel insight into the mechanisms and potential clinical events associated with stent strut fracture dependent on the mode of mechanical failure of the prosthesis.

The high-resolution post-mortem radiography utilized in this pathologic study enables more precise identification and localization of strut fracture, as well as the ability to assess overall mechanical integrity of the prosthesis. The majority of DES strut fractures were minor and not associated with mechanical failure as manifested by an acquired intrastent gap or deformation of the structure (grades I, II, and IV). Strut fractures with an acquired gap or stent fracture were reported in approximately 5% of the cases (9 of 171 lesions),

consistent with the clinical angiographic data reported by others (9). The presence of stent fracture, grade V or severe, was associated with a histologic event, such as thrombosis or restenosis, in 71% of cases. The pathologic data by Nakazawa et al. (8) substantiate clinical reports of a higher frequency of adverse events with stent fracture or mechanical failure of DES stent platform. Importantly, the frequency and mode of failure may differ for the first-generation Food and Drug Administration-approved DES and the nature of the implant technique.

The axial location of stent strut fracture varied by stent type; the majority of the fractures in the Cypher (Cordis, Miami Lakes, Florida) stents were located in flexible N-shaped, undulating longitudinal intersinusoidal-ring connectors, whereas in Taxus Express (Boston Scientific, Natick, Massachusetts) stents, fractures were observed in the straight longitudinal intercrown linker or the modular ring portion. Furthermore, in single stented lesions, the majority of stent fractures were localized in the mid portion of the stent body, except for stents >25-mm length, where the fracture sites were slightly shifted toward the proximal margin. In cases with overlapped stents, most fractures were observed within 5-mm of the overlap zone, with similar frequency in proximal and distal stents. Lesions with strut fracture had a 4-fold longer duration of stent implant (fracture: mean 172 days vs. nonfracture: mean 40 days), more often observed with Cypher stents, had 50% longer stent length, greater number of stents per lesion, and more commonly observed with overlapped stents in comparison to DES without strut fracture. DES strut fractures tended to be more commonly observed in the right coronary artery and in aortocoronary saphenous vein bypass grafts. Longer stent length, use of Cypher stent, and longer duration of implant were identified as independent risk factors of stent fractures by a logistic regression analysis. Interestingly, the degree of vessel calcification did not impact on the frequency of stent strut fracture.

In the pre-DES era, strut fracture or stent deformation was considered as rare, uncommon events usually observed in the application of stents in anatomic locations associated with unique implant techniques (i.e., bifurcation) or when exposed to traumatic extravascular forces (i.e., carotid or popliteal artery). The emergence of stent strut fracture in the era of DES warrants further investigation to determine why apparently mechanically robust balloon expandable stents have a notably higher rate of material fatigue/failure when utilized as a vehicle for drug delivery in comparison to when serving only as a scaffold in the coronary artery. Pre-clinical studies suggest that selected DES may be more prone to fracture than a BMS in a porcine coronary overlap model (10).

Metallic materials may fail due to the extension of processing defects such as pores, inclusions, or cracks. Under constant or cyclic loading, the defects may extend slowly until a critical size is reached, when unstable extension occurs. The subcritical extension of the defects under

constant loading is called *static fatigue*, subcritical extension under cyclic loading is called *cyclic fatigue*. It seems unlikely that the observed differences in mechanical stent failure in the BMS versus the DES era relates to changes in material specifications of uniform tubes, laser manufacturing, or cleaning of residual debris to produce the BMS. These devices were tested prior to regulatory approval with exposure to similar in vitro loading conditions and repeated cyclic stress with presumably similar modes and frequency of failure. The methods utilized to prepare the stent surface for coating, polymer coating materials, and drug may affect the durability of the prosthesis through various in vivo pathways such as corrosion that may provide plausible but an unlikely mechanism for DES strut fracture given the in vivo exposure ranging from 0.1 to nearly 2 years reported in the present study. Interestingly, platinum and cobalt chromium, the alloys used in later generation DES, are less susceptible to corrosion than 316L stainless steel (11).

It is important to note that computational methods such as finite element analysis utilized in the design of stents simplify conditions to static or dynamic loads without accounting for variance in biologic events such as neointimal incorporation of the stent into the vessel wall. The localized stress imparted on nonapposed struts or areas of incomplete or absent neointimal coverage likely differs from stent struts apposed to the vessel wall embedded in 100 to 200 μm of neointima.

Future design of DES stent platforms and preclinical fatigue testing should be adapted to account for the biological conditions endured during the life of the implanted prosthesis. The frequency of stent strut fracture for later generation DES with thin-strut cobalt chromium alloys is unknown but will likely differ from the thick-strut stainless steel first-generation DES. Clinical trials should incorporate specific end points to ascertain the frequency and pattern of stent strut fracture for novel DES. The application of 64-slice cardiac computed tomography angiography appears to be a promising technique that could be utilized to further evaluate the structural integrity of stents in patients with observed clinical events or suspected strut fracture (12).

Despite the limitations of previous clinical reports and the present pathologic study, the frequency of DES strut fracture is higher than anticipated, given our experience with BMS. DES strut fracture is more often an incidental clinical finding isolated to a single strut. In more complex coronary disease, DES strut fracture can be severe, resulting in transection of the stent and creating a gap or segment of mechanical failure associated with a high rate of adverse clinical events such as late thrombosis or restenosis. The optimal clinical management of patients with isolated or incidental DES strut fracture is unknown. Clinical observation and extension of dual antiplatelet therapy beyond 1 year should be considered in each case. In patients with stent fracture, extended dual antiplatelet therapy should then be strongly considered together with percutaneous or surgical revascularization dependent on clinical symptoms,

extent of myocardial ischemia on functional testing, and associated anatomic severity of coronary obstruction. The procedural success rates and long-term clinical outcomes for percutaneous coronary intervention (POBA [“plain old balloon angioplasty”], BMS, or DES) in patients with DES fracture have not been established.

The latest lesson learned with DES is the false assumption or “promise” that all bare-metal, balloon-expandable stent designs are suitable for drug delivery. Others have taught the importance of strut uniformity and apposition to the vessel wall to achieve homogeneous drug delivery (13). The development of stent designs to optimize drug delivery while maintaining structural integrity is critical in order to advance the application of DES in patients with more complex coronary artery disease.

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REFERENCES

1. The Works of Ralph Waldo Emerson. New York, NY: Hearst's International Library Company, 1914;1:360.
2. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004;109:701-5.
3. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47:175-81.
4. Lagerqvist B, James SK, Stenestrand U, et al., for the SCAAR Study Group. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;356:1009-19.
5. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;48:193-202.
6. 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.
7. Farb A, Bohm A. Stent thrombosis REDUX—the FDA perspective. *N Engl J Med* 2007;356:984-7.
8. Nakazawa G, Finn AV, Vorpahl M, et al. Incidence and predictors of drug-eluting stent fracture in human coronary artery: a pathologic analysis. *J Am Coll Cardiol* 2009;54:1924-31.
9. Popma JJ, Tiroch K, Almonacid A, Cohen S, Kandzari DE, Leon MB. A qualitative and quantitative angiographic analysis of stent fracture late following sirolimus-eluting stent implantation. *Am J Cardiol* 2009;103:923-9.
10. Wilson GJ, Polovick JE, Huibregtse BA, Poff BC. Overlapping paclitaxel-eluting stents: long-term effects in a porcine coronary artery model. *Cardiovasc Res* 2007;76:361-72.
11. Gotman I. Characteristics of metals used in implants. *J Endourol* 1997;11:383-9.
12. Pang JH, Kim D, Beohar N, Meyers SN, Lloyd-Jones D, Yaghmai V. Detection of stent fractures: a comparison of 64-slice CT, conventional cine-angiography, and intravascular ultrasonography. *Acad Radiol* 2009;16:412-7.
13. Balakrishnan B, Tzafiriri AR, Seifert P, Groothuis A, Rogers C, Edelman ER. Strut position, blood flow, and drug deposition: implications for single and overlapping drug-eluting stents. *Circulation* 2005;111:2958-65.

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