The Systems Biocompatibility of Coronary Stenting

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KEYWORDS

• Stent biocompatibility • Bare metal stent • Drug-eluting stent • Durable polymer
• Bioresorbable polymer • Stent thrombosis • Restenosis

KEY POINTS

- Cardiovascular innovation, and the coronary stent in particular, has played a key role in advancing our understanding of biocompatibility.
- Stent biocompatibility is contextual and must be measured relative to clinical performance; what is biocompatible in some settings need not be in others.
- Along with biomaterial innovation, advances in device design, drug use, and deployment practices have made contemporary stenting a highly optimized practice.
- The trend toward lower profile and/or fully bioresorbable devices has created both challenges and opportunities to further improve clinical performance.

INTRODUCTION

The coronary stent has propelled our understanding of the term "biocompatibility" (Fig. 1A). Stents are expanded at sites of arterial blockage and mechanically reestablish blood flow. This simplicity belies the complex reactions that occur when a stent contacts living substrates, the confluence of which dictate clinical efficacy and safety. Biocompatible materials no longer seek to eliminate biological reactions, but rather to elicit the appropriate response; stents, as with all implanted devices, should perform rather than merely exist. Because ultimate performance is assessed in the patient, stent biocompatibility is the multiscale examination not only of material and cell, but of material, structure, and device in the context of cell, tissue, and organism.[1,2]

After the first placement of coronary stents in 1986,[3] stent thrombosis (ST; Fig. 1B) and in-stent restenosis (ISR; Fig. 1C) were recognized as major adverse responses.[4–7] ISR occurs in the months to years after stent placement and arises from excessive vascular smooth muscle cell (SMC) proliferation and neointimal hyperplasia.[4] Because overgrowth drives need for revascularization, ISR is a key measure of efficacy. ST, driven by local activation/accumulation of platelets and coagulant proteins, is considered the main safety index and carries risk for unheralded occlusion.[8] These processes overlap. Thrombotic mediators and recruitment of blood-borne components such as monocytes and eosinophils drive local inflammation and the SMC response.[9] Also, clotting occurs in this injured/inflamed microenvironment, of which the stent plays an

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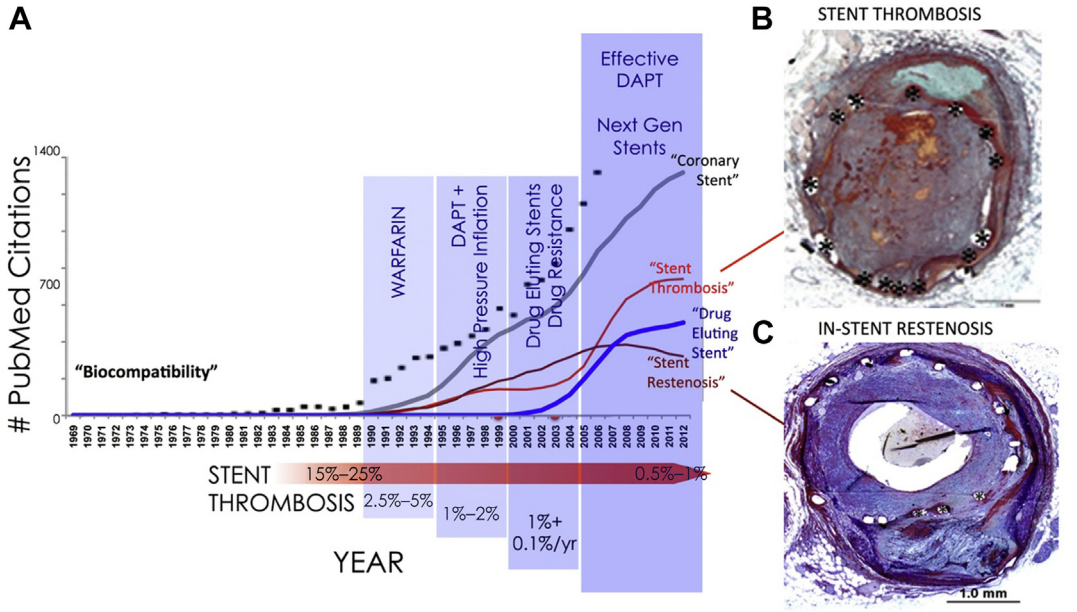

Fig. 1. (*A*) Annual PubMed citations for "biocompatibility" (*dotted-line*), and "Coronary Stent" (*gray*) showing their temporal association, as well as "stent thrombosis" (*red*) and "stent restenosis" (*dark red*), which emerged shortly after. Rates of stent thrombosis have been driven down from greater than 15% to less than 1%, as a result of many factors. Examples of vascular obstruction from (*B*) stent thrombosis and (*C*) in-stent restenosis as key safety and efficacy measures, respectively. DAPT, dual antiplatelet therapy. (*Adapted from* Alfonso F, Byrne RA, Rivero F, et al. Current treatment of in-stent restenosis. J Am Coll Cardiol 2014;63:2659–73; and Nakano M, Yahagi K, Otsuka F, et al. Causes of early stent thrombosis in patients presenting with acute coronary syndrome: an ex vivo human autopsy study. J Am Coll Cardiol 2014;63:2510–20; with permission.)

inciting but partial role.[10,11] Subendothelial components such as tissue factor and matrix ligands impinge directly on clotting pathways.[12] This complex environment varies dynamically as the body reacts, responds, and heals with reestablishment of an intact endothelial layer.

The grail of stent biocompatibility has been to find materials that resist thrombotic and inflammatory reactions while maximizing endothelialization and simultaneously providing radial support, flexibility, and radiopacity. Because many goals run counter to one another (ie, reduction of platelet adhesion at the expense of endothelial adhesion; increased radial support at the expense of higher profile, less flexible devices), biomaterial design is necessarily a process of optimization. This review tracks the major biomaterial advances in coronary stents design, and discuss biocompatibility in the context of multiparameter, optimized clinical performance.

BARE METALS AND PASSIVE MATERIALS

To meet the challenges of percutaneous deployment, metals with high moduli of elasticity and yield strengths have been a staple. Of the metals, surgical grade 316L stainless steel (SS), recognized for its high resistance to corrosion, has served as the historical benchmark. In 2005, Sprague and Palmaz[13] reported a composite stent biocompatibility index and ranked a range of stable materials based on in vitro thromboinflammatory and endothelial cell responses. In this head-to-head comparison, SS ranked most biocompatible. Although such in vitro surrogates have debatable relevance to in vivo contexts, they carry an important implication. Despite being labeled 'biocompatible,' SS alone falls short of meeting clinical demands. Initial ST rates on SS platforms are as high as 15% to 25%.[3,5] Although this early incidence was overcome by accompanying antithrombotic strategies and improvements to stent design and interventional practices (see Fig. 1A),[5,14] ISR with SS devices persisted at rates of 20% to 30%, driving the need for biomaterial advance.[15,16]

Passive Coatings

Coatings applied to metal structures are able to impart them with beneficial surfaces while maintaining bulk properties. Overtime, even resistant metals such as 316L SS corrode and release ions (ie, nickel, chromium, and molybdenum).[17] Despite well-recognized nickel allergies,