

New DES Platforms

Does the metal alloy matter?

BY BARBARA HUIBREGTSE, DVM, AND JUAN F. GRANADA, MD

Advances in materials science have promoted the development of a new generation of cardiac stents.¹ This new generation of devices appears to be more flexible and conformable than previous-generation stents. Despite significant reduction in strut dimensions, these devices have been able to maintain radiopacity and radial strength in comparison to previous-generation stainless steel stents.¹⁻³ Although some reduction in angiographic restenosis has been achieved, the biggest impact realized by the development of these devices is the enhancement of the deliverability of drug-eluting stents (DES).^{2,3} Metal alloys resulting in greater flexibility and, therefore, deliverability offer a significant advantage over stainless steel for use in design of cardiovascular stents, allowing treatment of more complex lesions in a greater number of patients.

HISTORICAL BACKGROUND

Metal alloys with improved capabilities beyond that of stainless steel have been in use over the past decade. Surface coatings, such as gold, were initially investigated to increase radiopacity in the presence of thinner struts. However, this strategy resulted in higher restenosis rates and poorer clinical outcomes.^{4,5} Subsequent development of cobalt chromium (CoCr) alloys (L605 and MP35N) resulted in a reduction in strut thickness (from stainless steel stents).²

The development of thin-strut stent platforms (based on CoCr and stainless steel) showed an important reduction in angiographic restenosis.^{2,3} However, several limitations were rapidly identified in clinical practice. First, thin-strut stents based on stainless steel are difficult to visualize, making the implantation procedure more challenging and less predictable. Second, early generations of CoCr stents experienced higher degrees of stent recoil with moderate gains in radiopacity compared to stainless steel.¹ Further developments in stent design and alloy

composition have resulted in the development of several platforms that are more deliverable and less injurious to the vessel wall while still retaining radiopacity, compression and fracture resistance, and resistance to recoil.

ALLOY COMPOSITION AND STENT DESIGN

Stent design and composition contribute to the final properties of clinical stent performance. In order to improve the performance of stainless steel stents, alloy composition was modified by the creation of CoCr alloys (MP35N and L605) or, more recently, the addition of platinum to stainless steel to create a platinum chromium stent (PtCr). The chromium content of all three alloys is similar; however, the PtCr stent has platinum (33%) with a relative reduction in iron compared to stainless steel, and in nickel compared to MP35N.⁶ The resulting properties, such as density, tensile strength, and

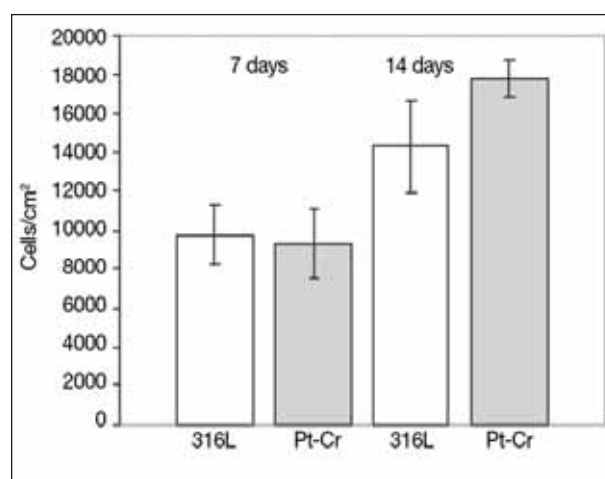


Figure 1. Comparison of endothelial cell coverage of stainless steel and PtCr Element stents. Reprinted with permission of O'Brien BJ, Stinson JS, Larsen SR, et al. A platinum chromium steel for cardiovascular stents. *Biomaterials*. 2010;31:3755-3761.¹

TABLE 1. COMPARISON OF COMPOSITION OF STENT ALLOYS AND RELATED PROPERTIES

	Elemental Composition by Weight (%)			
	316L Stainless Steel	Platinum Chromium Alloy	L605 Cobalt Chromium Alloy	MP35N Cobalt Alloy
Iron	64	37	3 maximum	1 maximum
Platinum	–	33	–	–
Cobalt	–	–	52	34
Chromium	18	18	20	20
Nickel	14	9	10	35
Tungsten	–	–	15	–
Molybdenum	2.6	2.6	–	9.75
Manganese	2 maximum	0.05 maximum	1.5	0.15 maximum
Titanium	–	–	–	1 maximum
Properties of Resulting Alloy Independent of Stent Design				
Density (g/cm ³) radiopacity	8	9.9	9.1	8.4
Tensile Strength (MPa)	595	834	1,000	930
Elastic modulus (GPa)	193	203	243	233

Adapted from Allocco et al.⁷ and O'Brien et al.¹

elastic modulus of these alloys, are compared in Table 1.

All of these new alloy materials have shown an improvement over conventional stainless steel, with some variation in the mechanical properties overall. The PtCr alloy has the highest density, translating to highest radiopacity; tensile strength is greatest for L605 and less for MP35N and PtCr. Elastic modulus (rigidity) is higher for both CoCr materials, with PtCr falling between stainless steel and the other two alloys.¹ The final stent design builds on the alloy composition to derive the optimum performance from the device. There are a variety of stent designs and alloys available with different properties, as determined by the design and material (Table 2).

Stent elastic recoil is the ability of the stent to maintain initial expansion diameter. Low recoil suggests a lower risk of the stent migrating away from the vascular wall and may translate to lower malapposition rates. Bench testing data have shown that the PtCr Omega (Boston Scientific Corporation, Natick, MA) and stainless steel VeriFlex (Liberté, Boston Scientific Corporation) have lower recoil values (2.1% and 2.8% reduction in diameter)

compared to Coroflex Blue (5.8%; B. Braun Medical Inc., Melsungen, Germany) and the Pro-Kinetic stent (4.5%; Biotronik SE & Co, Berlin, Germany), both made of L605. The Multi-Link 8 (Abbott Vascular, Santa Clara, CA) stent is also made of L605 but has recoil of 3.4%, demonstrating that the combination of design and material determines stent performance properties (Table 2). These data is further supported by other studies.⁸

The physical presence of the stents themselves can cause vascular injury and provide a stimulus for neointimal proliferation.⁹ Therefore, a stent with lower values for conformability requires a lower amount of force to bend the stent; hence, it adapts or conforms more readily to arterial tortuosity. Bench data have shown that the PtCr Omega stent had the highest degree of conformability in comparison to the other tested control stents (Table 2).

BIOLOGICAL RESPONSE

Biocompatibility and vascular response are essential for the evaluation of stents prior to use in humans. Characterization of stent properties, including strut

TABLE 2. COMPARISON OF STENT PLATFORM SPECIFICATIONS FOR BMS

	Specification	Omega Stent	VeriFlex (Liberté) Stent	CoroFlex Blue Stent	Multi-Link 8 Stent	Pro-Kinetic Stent	Integrity Stent
Design element	Material	PtCr	316L stainless steel	L605 CoCr	L605 CoCr	L605 CoCr	MP35N CoCr
	Strut thickness (μm)	81	97	65	81	60–120	91
	Recoil (%) 3.5-mm stents ^a	2.1	2.8	5.8	3.4	4.5	4.1
Bench testing	Conformability (N/mm) 3.5-mm stents ^a	0.11	0.3	0.23	0.34	0.51	0.28
	Conformability (N/mm) 3.5-mm stents ^a	0.11	0.3	0.23	0.34	0.51	0.28

^aTests conducted by Boston Scientific Corporation. Recoil: VeriFlex, n = 33; Omega, n = 15; other, n = 3. Conformability: VeriFlex, n = 15; Omega, n = 5; other, n = 3. Bench test results may not necessarily be indicative of clinical performance.

thickness, resistance to recoil, flexibility, surface characteristics that affect the vascular response, and biocompatibility of the stent can be used to predict the vascular response of new stent designs and materials. Physical properties, such as strut thickness, have been shown to affect vascular healing.^{10–12} In a study comparing strut thickness and endothelial cell coverage for Express, Liberté (VeriFlex), and Element (Omega) stents with strut thicknesses of 132, 97, and 81 μm, the strut coverage was 77%, 88%, and 95%, respectively, at 14 days in a rabbit arterial model.¹¹

The creation of newer alloys, first CoCr and then PtCr, has allowed the reduction in strut thickness and width while maintaining some level of radial strength and resistance to recoil. Table 2 shows the comparative strut dimensions for the latest stent platforms, with CoroFlex Blue (65 μm) having the smallest strut thickness, followed by Omega and Multi-Link 8, each at 81 μm, and Integrity (91 μm; Medtronic Inc., Minneapolis, MN).

In general, the in vivo vascular response to bare-metal stents (BMS) is relatively quiescent, and it can be challenging to discern differences, particularly as designs and alloys more closely approximate one another. While significant differences in strut coverage were described in the rabbit model between Element (Omega) and Express, there is a large (39%) difference in strut thickness between the two stents.¹⁰

The use of cellular assays can help detect differences or establish equivalence of new materials to well-character-

ized materials on a smaller, more specific scale, as demonstrated in a comparison of stainless steel and PtCr stents for endothelialization. Human coronary artery endothelial cells were grown on collagen gels and either PtCr or stainless steel stents of the same design were embedded in the gel (n = 24 stents per stent type at 7 and 14 days). Results showed no significant differences between the two alloys for endothelial cell coverage at either time point, showing equivalent response to the two different alloys of the same strut thickness (Figure 1).¹

Although discrete differences in vascular response can be difficult to detect using an in vivo model, it is valuable to determine any potential safety risks of a new stent design and/or material before use in humans. One of the best-characterized models, particularly in terms of detecting any potential for a new material to incite inflammation, is the porcine noninjured coronary artery model due to similarities in vessel size and well-characterized response.¹³

In a series of studies, domestic swine received BMS and DES in an overlapping configuration at 30, 90, and 180 days, using the same operator for all implantations. Figure 2 shows representative 180-day responses of previous- and current-generation stents, including stainless steel, the MP35N and L605 CoCr alloys, and PtCr. All groups demonstrated complete tissue coverage of struts with equivalent maximum scores for endothelial cell coverage, an absence of luminal thrombi, and % area stenosis < 40% for all BMS at all time points. Inflammatory

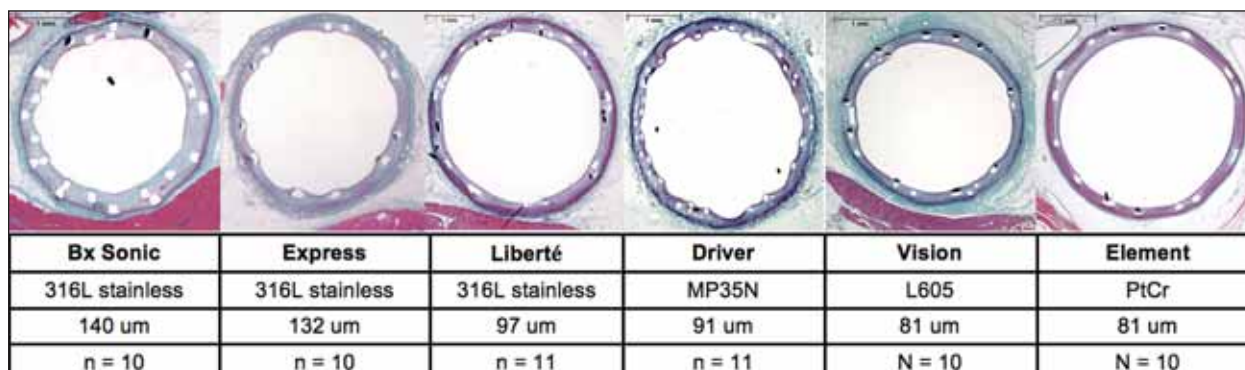


Figure 2. Comparison of histology of coronary arteries at 180 days implanted with BMS in an overlapping configuration. Note the reduction in neointimal formation and vascular response as strut thickness decreases.

response was rare and generally mild. The effect of strut thickness on neointimal formation is evident in first-generation stent designs, such as Bx Sonic (Cordis Corporation, Bridgewater, NJ) and Express.¹⁴

Later-generation stents, such as the Omega, showed a more quiescent response, likely due to improvements in conformability, reduction in strut thickness, as well as improvements in stent manufacturing. In general, the vascular response to all of these alloys and stent designs is minimal.^{14,15}

CLINICAL DATA

Although significant improvements have been achieved in stent materials, design, and delivery systems, overall binary restenosis rates of BMS platforms are still

higher with increased complexity of patients and lesions (Figure 3). Whereas DES restenosis rates have remained stable and low overall, DES binary restenosis rates are also higher in complex patients and lesions. However, the new platforms have enhanced the simplicity, precision, and deliverability success of DES platforms.

Recent clinical trials with DES using new alloys do not typically include the new BMS as comparators and are either: (1) single-arm studies, such as PLATINUM QCA (Promus Element PtCr stent)¹⁶ and SPIRIT PRIME (Xience Prime and Xience Prime long lesion everolimus-eluting coronary stent system [Abbott Vascular]);¹⁷ (2) a comparison of two DES platforms, such as PLATINUM (Promus Element versus Promus/Xience V stents)¹⁸ and EVOLVE (comparing two doses of everolimus on the

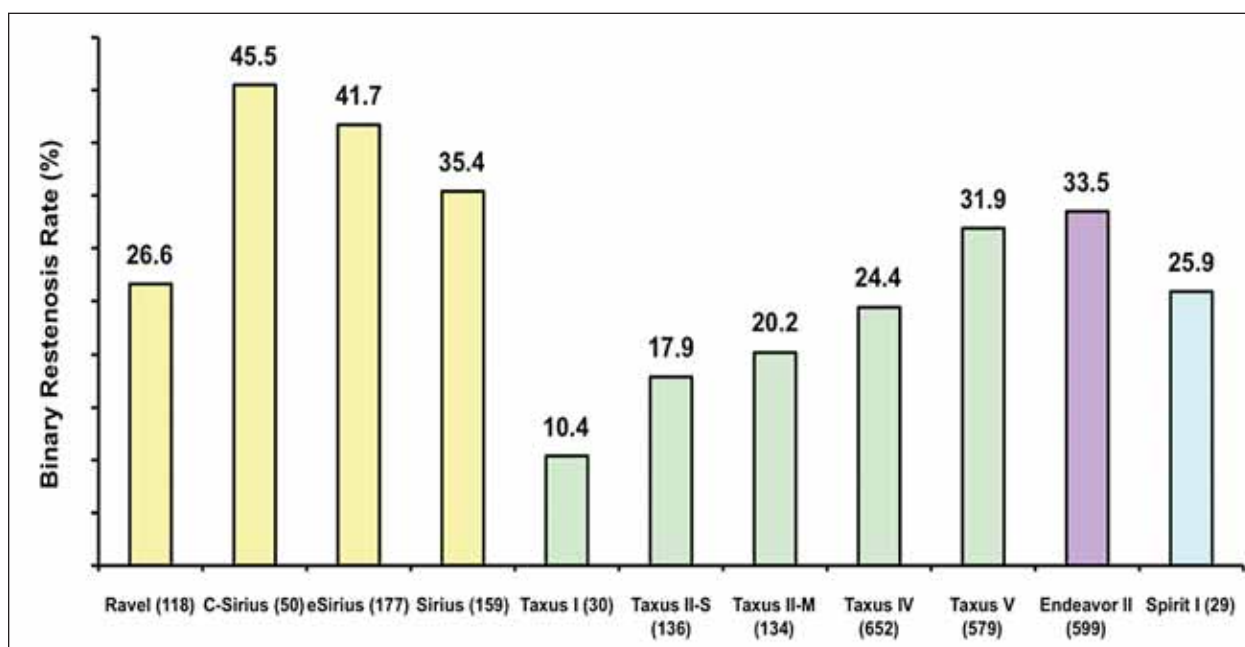


Figure 3. Binary restenosis rate in the BMS arms of randomized trials of DES. Modified from Granada JF. Stent metal alloys. Presented at: 2010 Transcatheter Therapeutics annual meeting; September 21–25, 2010; Washington, DC.

Synergy stent [Boston Scientific Corporation] and the Promus Element stent),¹⁹ or (3) a comparison to historical controls, such as RESOLUTE (comparing the Resolute stent [Medtronic] to the historical Endeavor control)²⁰ and TAXUS PERSEUS Workhorse (comparing Taxus Element to a historical Taxus Express control).²¹

These trial designs limit the ability to make direct comparisons to previous BMS performance in clinical trials (Figure 3).

However, some comparisons of performance criteria related to stent platform can be made between different stent designs with the same drug and polymer formulation. For example, in the PLATINUM Workhorse trial, a higher rate of unplanned stenting was required in patients receiving the Promus (Xience V) stent compared to those receiving the Promus Element stent (9.8% vs 5.9%, respectively; $P = .004$), which was in part driven by a higher number of incomplete lesion coverage seen in the Promus (Xience V) stent group (3.4% vs 1.4%; $P = .01$).¹⁸ These results suggest stent design, as translated to deliverability and radiopacity, may have played a role in superior procedural outcome for the Promus Element stent.

One upcoming clinical trial using a PtCr alloy in a BMS platform is the OMEGA clinical trial. This international prospective, multicenter, single-arm study is currently evaluating the safety and effectiveness of the Omega coronary stent system for the treatment of a single de novo coronary artery lesion in 328 patients. In any case, if the latest-generation BMS platforms continue to demonstrate excellent clinical outcomes, it will become very difficult to show the additional value of emerging material and stent design iterations.

CONCLUSION

Novel alloys have increased the overall strength of stents compared to stainless steel, allowing thinner struts, lower crossing profile, and greater stent conformability. These technological developments have improved the overall deliverability of coronary stents while maintaining their mechanical strength and overall visibility. Although these technical developments have resulted in improved clinical outcomes, the biggest impact has been achieved toward the optimization of DES platforms by increasing access for the interventionist to increasingly complex lesions, and providing a greater array of treatment options for complex patients. ■

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Barbara Huibregtse, DVM, is Director of Preclinical Sciences at Boston Scientific Corporation in Natick, Massachusetts. She has disclosed that she is a full-time employee and shareholder of Boston Scientific. She may be reached at (508) 652-5230; barbara.huibregtse@bsci.com.

Juan F. Granada, MD, is Executive Director and Chief Scientific Officer at Skirball Center for Cardiovascular Research, Cardiovascular Research Foundation, Columbia University Medical Center in New York. He has disclosed that he has received grant/research funding from Boston Scientific Corporation. Dr. Granada may be reached at (845) 580-3114; jgranada@crf.org.

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