Comparison of *In Vivo* Longitudinal Strength and Conformability Following Stent Implantation in Rabbit Iliac Artery

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**ABSTRACT:** Objectives. The aim of this study was to determine the *in vivo* longitudinal strength and conformability of various stent platforms following stent implantation in rabbit iliac arteries. Background. Recently, longitudinal coronary stent deformation has been highlighted and bench tests have demonstrated differences in longitudinal strength among various stent platforms. However, this has not been investigated in an *in vivo* setting. This is of interest because there may be a trade-off between longitudinal strength and conformability. Methods. We evaluated 4 types of commercially available stents: Multi-Link 8 (Abbott Vascular); Omega (Boston Scientific); Integrity (Medtronic); and Nobori (Terumo Corporation). To investigate the longitudinal strength, constant axial force was applied to the stent edge by a guiding catheter after deployment in a rabbit iliac artery. The amount of longitudinal stent deformation was calculated by measuring stent length. In order to evaluate conformability, stents were deployed crossing over the iliac bifurcation and the bifurcation angles were measured before and after stent implantation. If the change in the angle was small, the stent was considered to be more conformable. Results. The Omega stent demonstrated significantly greater longitudinal compression compared with other stents (Omega, 17.4 ± 9.3%; Multi-Link 8, 2.8 ± 2.3%; Integrity, 2.8 ± 1.4%; Nobori, 3.8 ± 3.2%; *P*<.01), but Omega showed better conformability, as evidenced by the smallest percent change in the bifurcation angle (Omega, 12.7 ± 0.8%; Multi-Link 8, 25.7 ± 2.4%; Integrity, 28.3 ± 1.1%; Nobori, 28.1 ± 6.8%; *P*<.03). Conclusion. In this rabbit model, the Omega stent, which has the platform of the Element stent, showed less longitudinal strength but greater conformability compared with the other stent platforms.

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Steady progress in the second (or later) generation of drug eluting stent (DES) design has led to better clinical outcomes; however, there is no longer much difference among the newer DESs in regard to clinical outcomes since the development of newer-generation DESs has focused on improvements in safety profiles with sustained efficacy. Advances in biocompatible polymers, drug coatings, and thinner stent struts have all contributed to further improvements in long-term restenosis and stent thrombosis rates. Preclinical studies have demonstrated that the second-generation DESs show faster endothelial recovery and less inflammatory reaction in long-term follow-up compared with the first generation DES, mainly due to the aforementioned higher biocompatibility of polymers, optimal drug elution properties, and thinner stent struts. Kolandaivelu et al reported that thicker metal stent struts were associated with a 1.5-fold increase in thrombogenicity using an *ex vivo* flow-loop model. Furthermore, randomized trials showed that stents with thinner struts had reduced rates of late restenosis compared with thicker strut designs in the bare-metal stent era, suggesting that the end-luminal injury and subsequent inflammatory response are much less likely with thinner stent strut implantation. Therefore, the majority of current DESs use thin strut stents. In addition, to improve flexibility, deliverability, and conformability of the stents, the number of intrastrut links has been reduced and “closed-strut design” (as in first-generation DESs) is no longer popular in contemporary DES design.

Recently, longitudinal stent deformation (LSD) as a complication of percutaneous coronary intervention (PCI) has been highlighted and emerged as a concern in selected stent platforms. In case studies, LSD has been produced by post-dilatation balloons or guide catheters that were advanced into the vessel during pullback of the protection guidewire of side branches and became lodged between the stent strut and vessel wall after stent implantation in the main vessel. The patients whose stents underwent LSD were reported to have poor prognosis, with significant morbidity/mortality and adverse outcomes reported in 14% of cases, including stent thrombosis (although the incidence of this phenomenon in the real world is not fully understood). Some bench-top tests have been reported in which the rate of compression and elongation varied among the contemporary stents; these properties represent the longitudinal strength of the stent. In these reports, it seems that the Omega bare-metal stent (BMS), which has the platform of the Element DES, has the least longitudinal strength. However, friction between the stent struts and vessel wall have not been taken into account in these bench tests. Also, no reports have shown the relationship between longitudinal strength and conformability of the stent platform. The aim of this *in vivo* study was to determine the longitudinal strength and conformability of the various stent platforms following stent implantation in non-atherosclerotic rabbit iliac arteries.
Methods

Stent platforms. Four different currently available stent platforms were evaluated: Multi-Link 8 BMS (Xience Prime DES platform; Abbott Vascular), Omega BMS (Promus/Taxus Element DES platform; Boston Scientific), Integrity BMS (Resolute Integrity DES platform; Medtronic), and Nobori DES (Terumo Corporation). Table 1 shows the stent characteristics for each design, including stent thickness, material, design, and number of links between hoops.

Animal preparation and procedures. The study protocol was reviewed and approved by the Education and Research Support Center, Department of Animal Care at Tokai University in Kanagawa, Japan.

Longitudinal stent compression study. To investigate the longitudinal strength in an in vivo setting, the following procedures were performed. Rabbits were anesthetized with isoflurane using a facemask. Surgical access site was obtained via the carotid artery using a sterile technique and a 4 Fr vascular sheath was inserted through the left carotid artery. After the angiography of the aorta and bilateral iliac arteries, three PCI guidewires were advanced into the ipsilateral iliac artery. The stent was delivered along with one of the guidewires and then deployed in the iliac artery at a target stent-to-artery ratio of 1.3:1 and the other two guidewires were positioned between the stent strut and the vessel wall. After stent implantation, the stent delivery system was removed, including the guidewire which was used for the stent deployment; the remaining two guidewires stayed anchored in their positions. A 4 Fr straight guide catheter was advanced along with the two anchored guidewires until the guide catheter was located just proximal to the stent edge. Using the automated mechanical arm with digital force gauge, the guide catheter was advanced until the force exceeded 2 newtons (Figures 1 and 2). The stent lengths before and after the procedure were measured and the percent changes after the stent compression were calculated. The same procedure was repeated in the other iliac artery. Four stents from each stent platform (3.0 x 23 mm Multi-Link 8; 3.0 x 24 mm Omega; 3.0 x 22 mm Integrity; and 3.0 x 24 mm Nobori) were tested in a total of 8 rabbits.

Stent conformability study. In order to assess conformability of the stent, further experiments were performed in another series of rabbits. After anesthesia was induced, a 4 Fr vascular sheath was inserted through the right femoral artery. Angiography was performed from the iliac artery to aorta. A PCI guidewire was inserted in the right iliac artery and advanced to the left iliac artery, crossing over the iliac bifurcation; the stent was then deployed at the iliac bifurcation at nominal pressure (Figure 3). After stent implantation, the stent delivery balloon and guidewire were gently removed. We first drew a line along the abdominal aorta and bilateral iliac arteries and then measured the iliac bifurcation angle before and after stent implantation with digital morphometry (Win ROOF image-processing software, version 6; Mitani Corporation). The change in the bifurcation angle was expressed as percent change.
Due to the larger vessel size at this location, a stent diameter of 3.5 mm was selected (3.5 x 23 mm Multi-Link 8; 3.5 x 24 mm Omega; 3.5 x 22 mm Integrity; and 3.5 x 24 mm Nobori) and a total of 8 rabbits were used (n = 2 each). A smaller change in bifurcation angle by stent implantation indicates the stent is more conformable.

Statistical analysis. Values were expressed as mean ± standard deviation. One-way analysis of variance (ANOVA) was used to compare statistical differences in continuous values between the groups in the stent longitudinal strength study. A P-value <.05 was considered statistically significant (JMP software, version 9.2; SAS Institute, Inc).

Results

Longitudinal stent compression study. Sixteen stents were successfully implanted in 8 rabbits and tested with an applied force of 2 newtons each. The Omega stent demonstrated significantly greater longitudinal compression compared with other stents (Omega, 17.4 ± 9.3%; Multi-Link 8, 2.8 ± 2.3%; Integrity, 2.8 ± 1.4%; and Nobori, 3.8 ± 3.2%; P<.01) (Table 2, Figures 4 and 5). In contrast to previous results reported for bench testing, the degree of longitudinal compression was relatively small since the compression was only 20% in the Omega stent and the majority of the shortened strut was localized in the proximal segment of the stent.

Stent conformability study. Eight stents were successfully implanted at the bifurcation of the iliac artery in 8 rabbits. All stents spanned the iliac bifurcation, resulting in a positive change in the bifurcation angle due to stent implantation (Omega, 61.6 ± 6.9° to 70.6 ± 8.6°; Multi-Link 8, 55.3 ± 4.5° to 74.4 ± 3.7°; Integrity, 58.4 ± 11.2° to 81.5 ± 17.0°; and Nobori, 59.8 ± 7.5° to 83.1 ± 2.6°). Among these, the Omega stent showed the least percent change of bifurcation angle (ie, the Omega was the most conformable), whereas there were no significant differences between Multi-Link 8, Integrity, and Nobori stents (Omega, 12.7 ± 0.8%; Multi-Link 8, 25.7 ± 2.4%; Integrity, 28.3 ± 1.1%, and Nobori 28.1 ± 6.8%; P<.03) (Table 3, Figures 6 and 7).

Discussion

To the best of our knowledge, this is the first in vivo study to assess longitudinal strength and conformability of various intra-coronary stent designs. We found that the Omega stent (which has the platform of the Element DES), showed the least longitudinal strength compared with other stent platforms, whereas the same stent (Omega) demonstrated the best conformability among the tested stents, thus suggesting that there may be a trade-off between high conformability and high longitudinal strength.

The development of the enhanced technologies of intracoronary stents allows us to treat more complex lesions by PCI in the
DES era. As the lesion severity (i.e., tortuosity and calcification) increases, greater performance in deliverability, conformability, and resistance to stent fracture is required in stent design. The thinner stent strut, low-profile of the stent delivery system, flexible design, and fewer intrastrut links contribute to improved deliverability and conformability. Therefore, newer stent platforms have applied these design optimizations; however, a recent series of case reports and bench tests demonstrated that the Omega stent, one of the newest stent platforms, is prone to show longitudinal deformation by relatively low external force, suggesting these improvements in stent properties may be accomplished at the cost of longitudinal strength. In our study, the Omega stent also demonstrated significantly greater longitudinal compression compared with other stents, which was consistent with previous reports. The differences in stent and link design are shown in Figure 8. Although the Omega platform has acceptable radial strength,24 Omega demonstrates a significantly lower resistance to longitudinal compression because of the off-set peak-to-peak design with double-angled links. It should be noted that Multi-Link 8 has a thin strut with 3 intra-hoop linkers, but this design did not show reduced longitudinal strength. Therefore, the particular stent design appears to play an important role in determining the longitudinal strength.

Nonetheless, unlike previously reported bench studies, the degree of longitudinal compression in the current study was relatively smaller (17.4%) compared with those reported by Ormiston et al (50%) and Prahbu et al (47%),22,23 and the deformed strut was generally localized in the proximal segment of the stent. Thus, the friction between the stent strut and vessel wall does affect the results. Therefore, the assessments of the stent performance should be confirmed in an in vivo setting rather than solely by bench testing. In fact, in a clinical setting, LSD was not identified in the PLATINUM, PERSEUS Workhorse, or PERSEUS Small Vessel trials, which were the randomized trials of the Element DES including 2034 patients.25-27 However, in these trials, highly complex lesions such as those with moderate-to-severe calcification, severe tortuosity, ostial disease, use of rotablation, and left main disease were excluded. Therefore, the operators should still be cautious about the possibility of longitudinal stent deformation with the Element platform in the real-world setting.

A recent search was performed of the United States Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database to capture case reports detailing events of LSD up to October 2012 for major coronary stents approved by the FDA. A total of 513 unique case reports were identified for all the stent platforms combined. In this analysis, it has been demonstrated that 98% of reported cases with LSD were associated with the Omega (Element) stent platform. The most common treatment was further intervention (80%) including the use of postdilatation (29%) and placement of additional stent (31%). Although the enhanced radiopacity due to its platinum chromium alloy might have caused the increased reporting of LSD in the Omega (Element) stent, there is obviously a higher incidence of LSD in a real-world setting.
In contrast, the Omega platform presented better conformability, as evidenced by the least degree of vessel stretching when deployed in an acutely angled location. Stent conformability is also very important in keeping the natural vessel geometry because acute change in the geometry of coronary arteries after implanting rigid metallic stent could influence clinical outcomes. Alteration of the flow dynamics and increased risk of stent fracture may cause late adverse events. The conformability of these stents was previously assessed in bench tests; however, this is the first report to assess stent conformability in an in vivo model. Compared with the bench test, in vivo models have biological elasticity and pulsation of the vessel, which may be more optimal biologically to predict the results in humans.

The results from the current study emphasize that the stent design is a balance of various parameters, and that the performance of the Element platform obtained from our study represents a trade-off between better conformability and high longitudinal strength. The conformability of the stent platform is associated with the ability of shortening and elongation of the stent. When a stent is deployed in a curved or bent segment of the vessel, the outer side of the stent needs to be elongated and the inner side should be shortened at the same time. The in-phase cross-linking pattern of stent hoop utilized in the Multi-Link 8 and offset peak-to-peak pattern utilized in the Omega are considered to be more conformable than the out-of phase pattern, since each hoop can get closer, especially if a flexible intrastrut link is applied. In order to increase the flexibility, various types of intrastrut link have been developed, such as the ones with a “c” shape (Multi-Link 8) or offset peak-to-peak link (Omega). In offset peak-to-peak design, since the links are not vertically connected, each stent hoop can flexibly change the distance in tortuous vessel by changing the angle of the links, leading to high performance in conformability (Figure 8). Also, as the number of intrastrut links decreases, the conformability should increase. However, it is sometimes difficult to find the optimal balance and acquiring one desirable characteristic may lead to losing other performance, such as the longitudinal strength in this case.

By understanding the characteristics of each stent platform, cardiologists may be able to select the most appropriate stent for the patient depending on the geometry and specific features of the lesions. According to the current study, special caution is needed with the Omega stent in ostial lesions or tapered lesions needing postdilatation, whereas this platform is more appropriate for the heavily tortuous lesion.

Study limitations. First, normal rabbit iliac arteries used in this in vivo test may not be best suited to predict stent behavior in human coronary arteries because vessels with atherosclerosis, such as those with severe calcification and tortuosity, could behave differently and produce different results. However, in vivo tests can evaluate stent platforms in a relatively uniform setting with high reproducibility. Second, the number of the samples was limited (n = 4 for compression and n = 2 for conformability) in the current study. However, because of the high reproducibility (as mentioned above), we believe that the number used in this study was adequate. Third, the
polymer and drug coating of the Nobori platform might have affected the results, whereas the other 3 stents used in this study were BMS designs. Fourth, the change in the illiac bifurcation angle after stent implantation may be partly related to the property of the initial angle, vessel size, dilated stent diameter, and vascular elasticity of each rabbit; however, the properties before the stent implantation were not significantly different because the rabbits were used almost identical in size.

Conclusion
Stent design influences the stent performance, including conformability, flexibility, and longitudinal strength. Reducing the number of intrastent links and optimization of those patterns improves the stent deliverability and conformability. However, there may be a trade-off in the longitudinal strength.

References

Figure 8. Stent hoop patterns in each stent. The Omega and Multi-Link 8 stents have in-phase stent hoop patterns, while Integrity and Nobori have out-of-phase stent hoop patterns. The intrastent linkers of Omega and Multi-Link 8 are designed to facilitate easy compression when the stent is deployed in curved or bent segments of the vessel.