The COMPLIANCE 360° Trial

The principal investigator of the COMPLIANCE 360° trial discusses its rationale, study design, and potential therapeutic implications.

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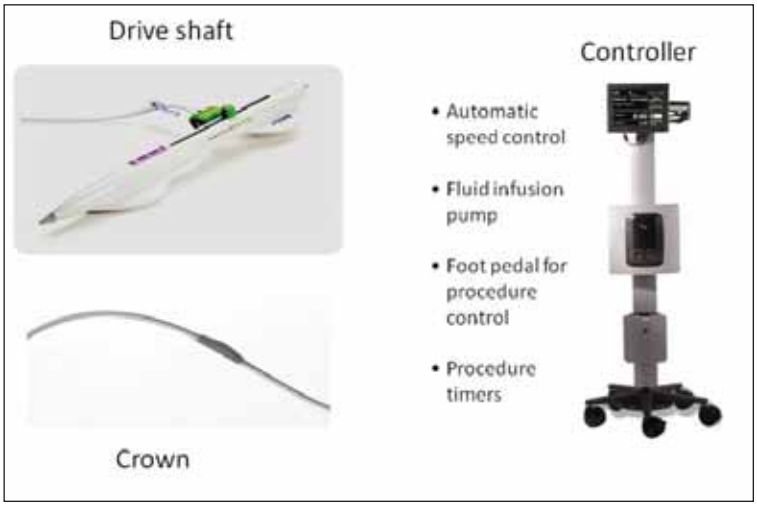

(Courtesy of Cardiovascular Systems, Inc.)

Figure 1. The Diamondback 360° Orbital PAD (peripheral artery disease) system (Cardiovascular Systems, Inc., St. Paul, MN).

Despite a growing number of studies demonstrating the clinical superiority of nitinol stenting over balloon angioplasty for treating femoropopliteal disease, and even some evidence to suggest an advantage of primary stenting to secondary stenting after suboptimal balloon angioplasty, many practitioners continue to employ provisional stenting in this vascular segment. Prominent among the reasons stated for this approach are the lack of effective therapy for in-stent restenosis and the perceived undesirability of placing stents in the distal superficial femoral artery (SFA) and popliteal artery. The adductor canal portion of the SFA and the popliteal artery are subject to a number of well-described forces, including contraction, expansion, compression, flexion, and torsion, all of which tend to provide an inhospitable environment for stents. It has been shown in cadaver limbs that the SFA shortens up to 23% and the popliteal artery up to 14% with 90° knee flexion.[1] After stent placement, the stented segment becomes more rigid than the unstented segment, which must then shorten and flex more to accommodate the necessary vascular conformational changes.

This problem is magnified by longer stented segments and overlapping stents, making stent kinking and fracture more likely. Stent fractures have been shown to be associated with increased rates of restenosis.[2,3] Approaches to minimize stent placement in this relative "no-stent zone" are therefore frequently sought and consequently beckon the use of various atherectomy devices along with balloon angioplasty.

Scholten et al showed that 72% of SFA occlusions involve the adductor canal hiatus, the region where vessel mobility is greatest.[4] This is also the segment where calcium deposition tends to be most frequent. Fitzgerald et al demonstrated through intravascular ultrasound (IVUS) investigation that approximately three-quarters of peripheral and coronary lesions that develop dissections after balloon angioplasty contain calcium, and 87% of these dissections occur adjacent to the calcified segment.[5] Thus, the region in and around the adductor canal hiatus presents the interventionist with several challenges.

It appears that a successful approach to treating lesions in this location would take into account all of the adverse influences previously mentioned. In a provisional stent approach, tools that would minimize the risk of dissection and secondary, or bailout, stenting would be beneficial. Because calcium plays a pivotal role in the genesis of dissection, a device that would remove calcium would logically be advantageous. When we speak of dissection and dissection planes, what we are really impugning is the vari-

ability in lesion compliance from segment to segment around the circumference of the vessel. The juxtaposition of calcified and noncalcified lesion segments represents the prototypical example of an abrupt transition in lesion compliance, which predisposes to the development of vessel dissection. The Diamondback 360º Orbital PAD system, whose chief mechanism of action results in removal of calcium-containing and other noncompliant plaque, would therefore seem to be a rational adjunctive therapy in treating these lesions. The Diamondback 360º system, by virtue of its orbital action, allows treatment of larger vessel diameters with relatively low-profile devices and therefore is well suited for the femoropopliteal vascular territory. The Diamondback 360º system has been previously well-described (Figure 1).[6]

Figure 2. Calcified SFA stenosis (A). The Diamondback 360º 2.25-mm solid crown (B). A 4-atm PTA with 6-mm balloon (C). The final result (D).

Although atherectomy devices have been traditionally thought of as debulking devices, the Diamondback 360º system's chief function in treating femoropopliteal disease is not maximal debulking as much as it is compliance change. By removing the hard, calcified plaque, the device acts to produce a more uniform, circumferential lesion compliance and therefore eliminates the abrupt compliance transitions that act to promote vessel dissection upon balloon dilatation. Furthermore, allowing all 360º of the vessel circumference—rather than just the noncalcified segments—to participate in the vessel stretch that accompanies balloon dilatation should require less force and be accompanied by less acute vessel recoil. Thus, the true benefit of this device in treating femoropopliteal disease may not be in how much but rather which tissue it removes. This therapeutic mechanism is supported by anecdotal reports and abstract presentations as manifested by decreased rates of bailout stenting and provides the rationale for the COMPLIANCE 360º (Comparison of Orbital Atherectomy and Balloon Angioplasty for Calcified Femoropopliteal Disease) trial.[7,8]

COMPLIANCE 360º TRIAL

The COMPLIANCE 360º trial is a multicenter, prospective, randomized study comparing balloon angioplasty to the Diamondback 360º system in treating calcium-containing, de novo femoropopliteal lesions. Low-pressure adjunctive balloon angioplasty (≤ 4 atm) may be used in the Diamondback 360º arm (when required) to achieve a final residual stenosis < 30%. The pressure at which the balloon achieves its full profile will be recorded in both arms as a proxy for compliance estimation. A representative case from this author's unpublished series of patients treated with this approach is shown in Figure 2. Bailout stenting may be used in either arm where a residual stenosis of < 30% cannot otherwise be achieved using the intended therapy and will count as a target lesion revascularization (TLR) event for both arms. The primary endpoint is TLR or restenosis at 6 months with a secondary endpoint at 12 months. Restenosis is defined by a peak systolic velocity ratio of > 2.5 using duplex ultrasound. Both the angiograms and duplex ultrasound studies will be core lab adjudicated to maximize the legitimacy of the results. There will be no lesion length constraints, which is often the case in the randomized stent trials. Also, the entire length of the popliteal artery will be fair game, except for the most distal 2 cm above the anterior tibial takeoff to allow an opportunity for optimal surgical revascularization should it be needed. Additional secondary endpoints will include TLR, target vessel revascularization, and restenosis (as independent endpoints) at 6 and 12 months. Clinical variables such as Rutherford class will be obtained at baseline, 1, 6, and 12 months along with ankle-brachial index measurement and duplex ultrasound examination. COMPLIANCE 360º is a 50-patient pilot study that is currently enrolling.

A calcium scoring system, which is believed to better reflect the calcium distribution in this vascular territory, has been devised for this study (Table 1). This system takes into account both the arc of calcium (< or > 180º) and percent of lesion length (< or > 50%) as judged by fluoroscopy. Such a scoring system specific to these vessels is currently lacking, and it would improve our ability to interpret results among different studies in this vascular territory if such a standard

TABLE 1. CALCIUM SCORING SYSTEM

Score	Qualitative	Circumference	Length
0	None	None	None
1	Mild	< 180° (one side of vessel only)[a]	< half of total lesion length
2	Moderate	< 180° (one side of vessel only)	≥ half of total lesion length
3	Moderately severe	≥ 180° (both sides of vessel at same location)	< half of total lesion length
4	Severe	≥ 180° (both sides of vessel at same location)	≥ half of total lesion length

[a]*Calcium may be on either side at any point along the lesion.*

were adopted, particularly given the apparent influence of calcium on therapeutic outcomes. By using this semiquantitative system, it is hoped that an even better understanding regarding the role of calcium in dissection and restenosis can be learned.

A subgroup of patients will undergo prospective IVUS examination after completion of each therapy to better understand their effect on the lesion and on vessel architecture. IVUS images obtained after using the Diamondback 360° system appear to show little vessel wall injury with intact media and no change in external elastic membrane area when used as stand-alone therapy, which is most often the case when used in tibial vessels.[6] Histologic data from porcine and cadaver arteries subjected to the Diamondback 360° demonstrate relatively minor injury to the internal elastic lamina (Cardiovascular Systems, Inc., unpublished data; animal studies, February 2004 and November 2004; cadaver study, November 2006). Although any atherectomy device that removes relatively hard plaque has the effect of improving lesion compliance, the Diamondback 360° system is the only peripheral device with a mechanism of differential sanding that allows it to discriminate among various tissue types based on their compliance. The theoretical advantage of this mechanism is decreased vessel wall injury as a result of the ability of the relatively elastic vessel wall to flex away from the device. The residual, relatively soft plaque elements after Diamondback therapy might then be more effectively treated with balloon angioplasty. Whether this approach translates into lower restenosis rates remains to be proven, and it is hoped that the COMPLIANCE 360° trial will shed some light on this.

CONCLUSION

Going forward, if the study shows a lower rate of bailout stenting but unclear benefit with respect to restenosis, a logical next area of inquiry would be combining the Diamondback 360° system with drug-eluting balloons (DEB) for treatment of noncompliant lesions. Studies using DEBs for infrainguinal disease show great promise but some disparate results. Some of these results may be postulated to be a consequence of differences in drug application (paclitaxel) to the balloon surface among different manufacturers. The mostly favorable results may be adversely affected by the need for adjunctive, or bailout, stenting in a significant proportion of these patients. While antirestenotic drugs have proven effective in suppressing the proliferative response to injury, when applied via balloons, the vessel wall still remains vulnerable to dissection as with any balloon angioplasty intervention. Furthermore, the addition of a bare-metal stent appears to negate the benefit of the DEB, at least in the coronary arteries.[9] An approach that would minimize the need for this mechanical support device should then allow the DEB to have the greatest effect on the chief remaining culprit for restenosis—hyperplasia. ■

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