Endovascular Treatment for Venous Diseases:
Where are the Venous Stents?

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ABSTRACT: There is a growing need for dedicated endovascular devices to treat pathologies affecting the venous system. However, because of a lack of research into venous diseases and treatments, the optimal design, material, and mechanical properties of venous stents remain unknown.

Development of the ideal venous stent should be based on a thorough understanding of the underlying venous pathology. There are multiple venous diseases that differ from each other depending on their location (iliocaval, superior vena cava), mechanism (thrombotic versus non-thrombotic lesions), and chronicity. Thus, it is likely that stent material, design, and features should differ according to each underlying disease.

From a mechanical point of view, the success of a venous stent hinges on its ability to resist crushing (which requires high global and local radial rigidity) and to match with the compliant implant environment (which requires high flexibility). Device oversizing, textile coverage, and drug coating are additional features that should be considered in the context of venous diseases rather than directly translated from the arterial world.

This review examines the unique forces affecting venous stents, the problems with using arterial devices to treat venous pathologies, preliminary results of a study comparing crush resistance of commercially available laser-cut stents with a novel braided stent design, and its applicability to venous interventions.

INTRODUCTION

Although veins and arteries are both vessels, they have very different functions, structural constitutions, mechanical properties, flow patterns, and pathologies. Whereas arterial diseases are well studied, venous pathologies command less interest from vascular specialists, whether due to lack of awareness, prior success, or funding; thus, understanding of the history and development of dedicated treatment for venous diseases lags behind that of arterial diseases. There are innumerable devices available to treat arterial pathologies (e.g., angioplasty balloons, stents, stent grafts, drug-eluting devices, atherectomy devices, guidewires, and catheters), yet not a single balloon or stent has been specifically designed or approved by the U.S. Food and Drug Administration (FDA) for use in veins. As a result, surgeons use arterial devices to treat all types of venous pathologies and, in turn, encounter complications regarding material sizes, mechanical properties, and patency.

Studies examining long-term results of venous balloon angioplasty and stenting are inconsistent. A recent systematic review found that global primary and secondary patency rates range from 32% to 98.7% and 66% to 96%, respectively.[1]

Patency rates were lower for thrombotic lesions than for nonthrombotic lesions, although they had high technical success and acceptable complication rates.[2] It is not yet known whether this variability is due to venous wall remodeling after deep venous thrombosis, to the stent's characteristics, or to something else.

Most teams treat veins using stents or stent grafts designed for arterial pathologies despite universal recognition that arteries and veins have different structures and behaviors. Both the size and compositional differences of these vessels affect their mechanical properties, and blood flow pressure and velocity vary as well. The consequences of these differences were highlighted in a pilot study by Gordon et al., who deployed similar stent grafts in the abdominal aorta and inferior vena cava of two pigs and evaluated the results after 1 month using contrast angiography and histology.[3] While the arterial stents showed no stenosis on angiography and minimal in-stent intimal proliferation on histology, the same stents deployed in the venous system showed evidence of significant in-stent stenosis and increased intimal hyperplasia with fibrin deposition. It is unknown whether these differences were due to blood flow, vessel characteristics, or the interaction between a specific device and vessel.

Despite the gaps in research, the European Society for Vascular Surgery guidelines on the management of chronic venous disease recommend that percutaneous transluminal angioplasty and stenting be the first-line treatment in patients with clinically relevant chronic iliocaval or iliofemoral obstruction or those with symptomatic nonthrombotic iliac vein lesions (Class IIa, Level B).[4] A recent randomized study comparing outcomes of medical treatment versus iliac vein stenting in patients with chronic venous diseases found significant reduction in pain and Venous Clinical Severity Score and significant improvement in quality of life with the endovascular treatment.[5]

Although endovascular treatment for venous diseases appears promising and safe,[1] the inconsistency of available studies underscores the need to improve knowledge about optimal venous stent design and materials, track long-term clinical outcomes, and develop dedicated FDA-approved endovascular devices that treat specific venous pathologies. This review examines the multiple features that must be considered to develop the ideal venous stent.

UNDERSTANDING THE UNDERLYING VENOUS PATHOLOGY

For optimal treatment of venous disease, physicians must have a thorough understanding of different venous pathologies and their underlying physiopathology, the natural history and evolution of venous structure, and the vein's mechanical properties and function. As with arterial diseases, venous pathologies are varied and can be divided into thrombotic and nonthrombotic disease, each with different pathophysiological processes and responses. Stent outcomes are different for the two disease types, with slightly lower patency rates for thrombotic lesions.[2] Furthermore, the unique characteristics of a thrombosed vein will cause long-term modifications in blood flow and vessel characteristics. In lower extremity deep venous thrombosis, vein wall response persists for at least 6 months after partial or total thrombus resolution, translating into vein thickening and increased biomarkers.[6]

Whereas a thrombosed artery will remain a well-defined tube even after long-term occlusion, a chronically thrombosed vein will undergo fibrous retraction, almost resulting in vessel disappearance in some cases. This presents challenges for vessel catheterization and balloon angioplasty alone, with the possibility of immediate venous recoil. In addition, acute and chronic thrombotic venous diseases are differentiated by the structure and properties of the thrombus and the venous wall at each stage. During the early/acute phase, the venous thrombus is soft, mainly composed of red cells, platelets, and fibrin with a surrounding thin and inflammatory venous wall. By the chronic phase, the thrombus tends to incorporate into the venous wall,

ultimately forming an undifferentiated fibrotic entity made mostly of collagen. It is likely that stent designs, mechanical properties, and coatings might be different depending on whether the lesion is nonthrombotic, acute thrombotic, or chronic thrombotic.

FORCES APPLIED ON THE STENT

The venous wall is prone to deformation due to multiple conditions, such as respiratory and heart cycle, outside and inside pressure, and organ function. Blood flow exerts different types of stress on the venous wall, including radial, circumferential, and axial stresses (where the circumferential and axial components are dominant)[7-9] and wall shear stress, depending on the velocity gradient and blood viscosity. Once a stent is deployed in the venous system, the venous wall will react to the deformation caused by the device.

The stent itself will be subjected to external forces from the surrounding tissues and internal stress from blood pressure and inertia of the blood. The imbalance of these forces can lead to device malposition or migration. Moreover, external forces may be heterogeneous along the vein (i.e., from localized high external compression or fibrous retraction), resulting in irregular mechanical interaction between the vein and stent along the length of the stent. This is especially the case in nutcracker or May-Thurner syndromes.[10] Such localized high external forces will further increase the risk of device migration. One solution is to increase the stent length; however, this would result in stent protrusion into the vena cava, which might increase the risks of contralateral iliac vein thrombosis.[11]

Even by limiting the analysis to a short and rectilinear segment, several elements must still be taken into account to contend with the forces generated by the stent. For example, the stent is passively anchored in place by the radial force it applies to the venous wall, and blood pressure adds internal constraints. Wall adhesion is also affected by the device's compliance and the presence of an active fixation system, such as hooks. The type of pathology and patient-specific anatomy (angulations) further modify the stresses applied on the stent. These multiple forces create a relatively complex system for study.

THE IDEAL VENOUS STENT

The perfect venous stent will restore physiological blood flow without modifying the vein's mechanical properties and function, thus allowing blood return from the periphery to the heart and balancing blood volume and pressure between organs. The following features will impact stent performance and treatment outcomes and should be considered when treating venous diseases:

- Stent structure: material composition (stainless steel, alloys such as Elgiloy®, nickel titanium/nitinol), stent size/design, strut thickness, cell design (laser cut vs braided structures, closed vs open cell)
- Mechanical properties: radial strength, radial stiffness, acute recoil, foreshortening, global and local crush resistance
- Deployment method: self-expandable versus balloon expandable
- Visibility under fluoroscopy and artifacts during computed tomography and magnetic resonance imaging
- Bare-metal versus covered stents
- Presence of a drug

The main stress affecting the stent-vessel system is circumferential parietal stress generated by blood pressure; this compounds the effect of the device's radial pressure and facilitates anchoring of the stent. Compared to the arterial system, blood pressure is much lower in veins and results in lower circumferential parietal stress. Optimal stent anchoring in the venous system might thus require devices with higher radial pressure than those used for arteries.

Whereas arterial diameters are more likely stable over time, venous distention raises questions about optimal stent size and oversizing rate. The ability of veins to contract and dilate according to systemic conditions is crucial for balancing blood volume. The respiratory cycle alone can lead to doubling of the vena cava or axillary vein diameter.[12] Compliance and flexibility of venous stents should thus be much higher than in arterial stents.

Most device companies suggest using an oversizing rate between 5% and 20% when choosing an arterial stent; therefore, the device diameter is larger than the vessel diameter.[13,14] This oversizing compresses the device after deployment, generating an increased radial force exerted by the stent against the vessel wall. The goal is to ensure apposition of the stent and wall and reduce device migration.[15] Since external

forces may be heterogeneous along the vein (e.g., localized fibrous retraction or neighbored pulsatile artery), both global and local crush resistance must be considered to avoid local stent compression and migration.

Most teams suggest using uncovered stents when treating venous disease to avoid occluding collaterals. With respect to restenosis and secondary interventions, however, a few studies have shown the feasibility (and even suggested improved outcomes) of using expanded polytetrafluoroethylene (ePTFE)-covered nitinol stents versus uncovered bare metal stents for treating central venous thrombosis and occlusions.[16,17] It is unclear what value ePTFE has in improved patency, but one could postulate that flow dynamics may play a role.

There is a growing interest in using drug-eluting balloons and stents to treat arterial disease, especially to counteract intimal hyperplasia and restenosis.[18] There is no doubt that such therapies will be used in the venous system, too. Paclitaxel and tacrolimus are commonly added to arterial stents to inhibit inflammatory and growth factors. Intrastent restenosis can also be caused by circumferential thrombus formation; thus, heparin-coated stents may warrant exploration. Further studies are required to better understand the mechanism of intrastent restenosis and rethrombosis in the venous system before these drug-coated devices are used on patients.

PRELIMINARY PERSONAL EXPERIMENTAL DATA

From a mechanical point of view, the success of a venous stent depends mainly on its ability to resist crushing, so it should be characterized by sufficient radial rigidity. The stent also requires flexibility to align with the compliant implantation environment. If the stent is too rigid, it will induce degradation in the vessel wall, which may lead to unexpected restenosis and/or angulations between the stent and the unstented vein.

	LCS 1	LCS 2	BDS SOFT	BDS RIGID
Diameter	16 mm	14 mm	14 mm	14 mm
Length	63 mm	125 mm	40 mm	40 mm
Stent type	Laser cut	Laser cut	Braided (1 filament)	Braided (multiple filaments)
Structure	Open cells	Open cells	Braid angle 60°	Braid angle 60°/twist

Table 1.
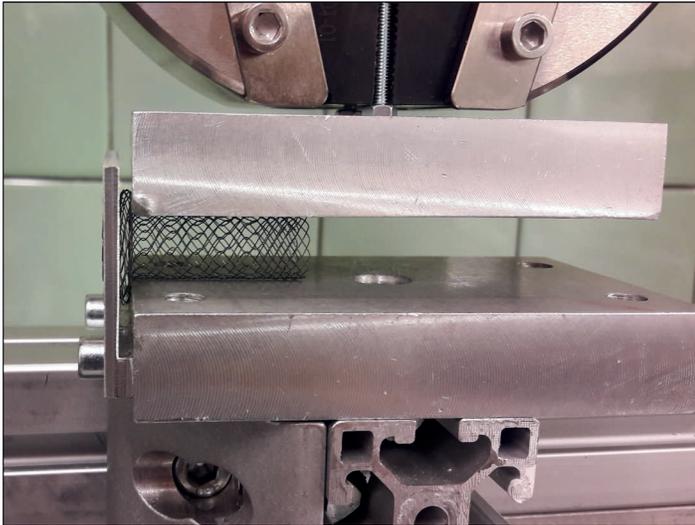Characteristics of stents in the preliminary GEPROVAS study. LCS: laser cut stent; BDS: braided-structure stent

between plaques at a compression rate of 2 in/min (Figure 1). For local resistance, the stents were compressed under the same conditions with a 9-mm diameter rod in the middle and at the end of the stent (Figure 2).

The results yielded several relevant observations. First, compared to LCS, BDS are characterized by larger localized crush resistance (3N on average for BDS vs 1.4N for the strongest LCS commercial stent), with no significant difference between the extremity and center (Figure 3). Even the soft and more flexible BDS outperformed commercially available devices. At the global level, BDS outperformed existing devices by a minimum of 15% (LCS 1) (Figure 4). The second commercial
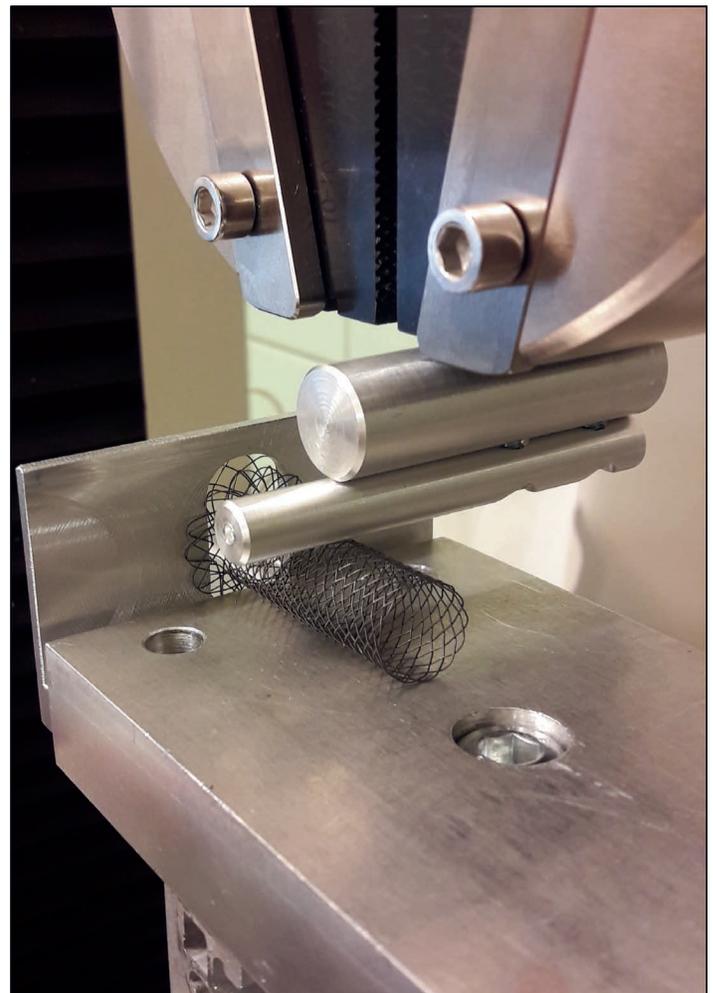

Figure 1.
Testing of global compression. The stents were compressed between plaques up to 50% at a compression rate of 2 in/min.

Laser-cut stents (LCS), used largely in coronary artery disease where rigidity is required, are less adaptable for implantation into more compliant, low-pressure venous environments. Conversely, braided-structure stents (BDS) have mainly been used over the last decade to treat peripheral arterial lesions such as those in the carotid and popliteal arteries or intracranial vessels. The advantage of BDS stents is that they are much more flexible because of the discontinuity of the braided wire structure, combining the flexibility and strength of textile structures.

Our group compared the radial behavior of both LCS and BDS stents in a preliminary study performed at GEPROVAS, the European Research Group on Applied Prostheses for Vascular Surgery. Two models of BDS were compared to two commercially available venous LCS from two different manufacturers (LCS 1 and LCS 2). The companies are not cited here for confidentiality reasons. Two designs were considered for BDS stents: the first was constructed with one metallic wire (13 summits, 0.22-mm gauge) and was highly deformable (BDS Soft), whereas the second was made from 13 wires (13 summits, 0.22-mm gauge) with a specific interlacing technique that limited wire movement within the structure to restrict deformation (BDS Rigid). The main characteristics of the tested devices are summarized in Table 1.

The crush resistance of the devices was tested globally and locally. For that purpose, specific compression configurations were designed on the MTS extensometer device (MTS Insight electromechanical testing system, MTS Systems). For global crush resistance, the stents were compressed up to 50%

Figure 2.
Testing of local compression. The stents were compressed with a 9-mm diameter rod up to 50%, in the middle and at its extremities, at a compression rate of 2 in/min.
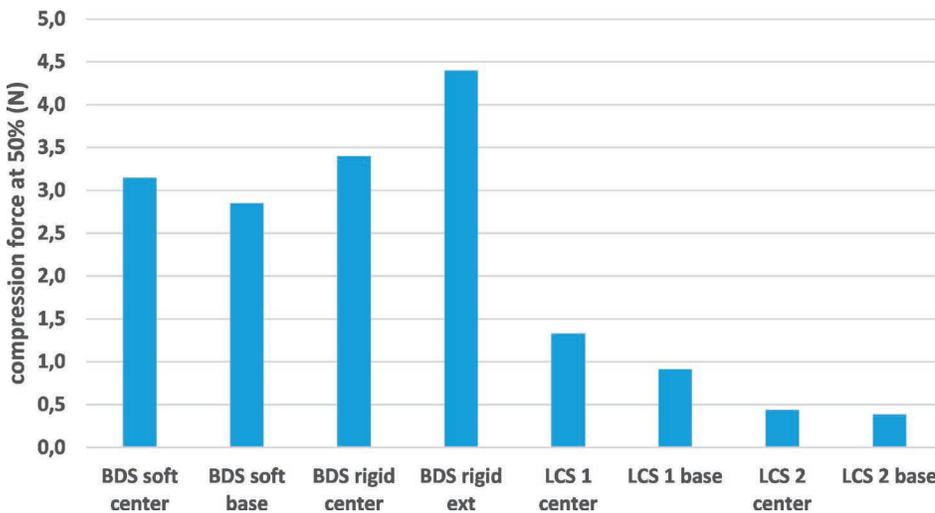
Figure 4.
Results of global compression testing for the four stents. BDS: braided-structure stents; LCS: laser-cut stents
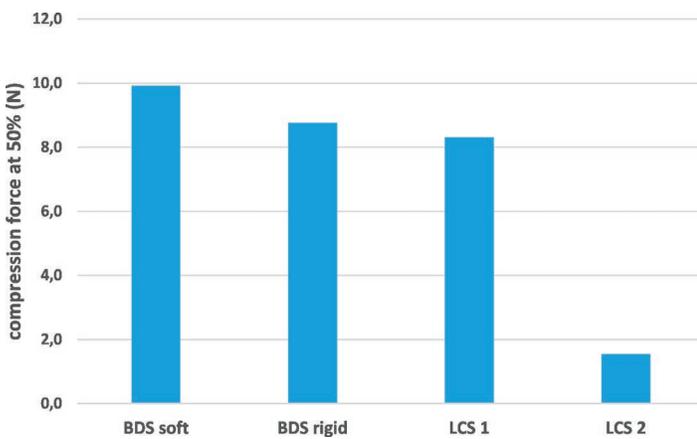
KEY POINTS

- There is a growing need for dedicated endovascular devices to treat pathologies specifically affecting the venous system.
- The multiplicity of forces applied on the venous wall/stent system creates a relatively complex system for study.
- Stent material and structure, mechanical properties, deployment method, visibility, and coating are crucial features that must be analyzed and developed specifically for venous use and may differ depending on whether the lesion is nonthrombotic, acute thrombotic, or chronic thrombotic.

device (LCS 2) appeared to have limited mechanical properties, with a crush resistance below 2N at the global level and 0.5N at the local level. This preliminary study shows that braided structures comprise potentially promising mechanical properties that combine crush resistance and flexibility, making them strong candidates for venous stenting applications.

CONCLUSION

Compared to arterial diseases, venous diseases are under-researched and thus poorly understood. As a result, many venous interventions use arterial devices that are not optimized for venous pathologies. There is a need for development and testing of vein-specific devices that meet the specific conditions of each venous pathology. If we want to truly improve patient outcomes, it is time for real venous focus and research.

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