The Technological Advancement to Engineer Next-Generation Stent-Grafts: Design, Material, and Fabrication Techniques

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Endovascular treatment of aortic disorders has gained wide acceptance due to reduced physiological burden to the patient compared to open surgery, and ongoing stent-graft evolution has made aortic repair an option for patients with more complex anatomies. To date, commercial stent-grafts are typically developed from established production techniques with simple design structures and limited material ranges. Despite the numerous updated versions of stent-grafts by manufacturers, the reoccurrence of device-related complications raises questions about whether the current manufacturing methods are technically able to eliminate these problems. The technology trend to produce efficient medical devices, including stent-grafts and all similar implants, should eventually change direction to advanced manufacturing techniques. It is expected that through recent advancements, especially the emergence of 4D-printing and smart materials, unprecedented features can be defined for cardiovascular medical implants, like shape change and remote battery-free self-monitoring. 4D-printing technology promises adaptive functionality, a highly desirable feature enabling printed cardiovascular implants to physically transform with time to perform a programmed task. This review provides a thorough assessment of the established technologies for existing stent-grafts and provides technical commentaries on known failure modes. They then discuss the future of advanced technologies and the efforts needed to produce next-generation endovascular implants.

1. Diseases of the Aorta

Diseases of the aorta can affect any segment of the vessel, from the aortic root to the bifurcation, and typically manifest as either the formation of an aneurysm or dissection (Figure 1). An aneurysm occurs when part of an artery wall weakens, allowing it to balloon outwards. The widening and weakening increase the risk of aortic rupture, which may burst if left untreated, causing major internal bleeding and often death. Aneurysms commonly occur in the abdominal aorta but can also form in the thoracic aorta, and as major vessels branch from the aorta, the aneurysmal disease often includes these important regions. Clinical guidelines recommend treating the aneurysm when the maximum diameter exceeds a certain threshold, beyond which the risk of rupture then outweighs the risk of surgery. The repair should be performed for all patients with acceptable perioperative risk with an abdominal aortic aneurysm (AAA) ≥5.5 cm in diameter and all patients with symptomatic aneurysms or rapid growth.

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DOI: 10.1002/adhm.202200271
AAA incidence in 65 years old men increases by 6% per decade. According to a predictive modeling assessment, there might be more than 1 million people in the United States by 2010 with AAA.\(^4\) Thoracic aortic aneurysm (TAA) is less common than AAAs, yet is still diagnosed in more than 6 to 10 cases per 100,000 patients.\(^5\) The incidence rate for ruptured or surgically treated aneurysms per 100,000 patient-years at risk in a 20 year follow-up study (median 16 years) was 27 in AAA and 9 for TAA.\(^6\)

Aortic dissection occurs when a tear is formed in the innermost lining of the aortic wall allowing blood flow to be redirected down a “false” lumen where pressure is often higher, as well as the “true” lumen (Figure 1). Pressure and force from the flowing blood further separate the wall’s layers and cause rupture through the wall or compromise flow through branches to end organs, including the brain, heart, gut, kidneys, legs, and spinal cord.\(^7,8\) The false lumen expands in a dissection as the mean pressure relative to the true lumen is higher due to reduced relative run off, causing higher diastolic pressures. This is also why the true lumen can become compressed, and branch vessels off the true lumen are annularly compressed, leading to target organ ischemia.\(^9\) Aortic dissection is the most common and catastrophic disease within the acute aortic syndrome spectrum. Aortic dilation is a common feature of dissection as the wall is weakened and can bulge outwards, and aneurysm development is common over time.\(^7,8\) In a 20 year follow-up assessment of 30,412 middle-aged men and women, the risk for aortic

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**Figure 1.** Schematic of aortic disorders. Illustration of the aorta with type B aortic dissection (TBAD) and abdominal aortic aneurysm (AAA). i) Cross-section of the lumen for TBAD. ii) Cross-section of the lumen for AAA.

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Aortic dissection was reported as 15 cases per 100 000 patient-years, men having the majority of the portion with 67.5%. The most predominant age range for aortic dissection is in 65 to 75 years of age, with an incidence of 35 cases per 100 000 people per year. Aortic dissection in women is more lethal than men due to often presenting at an older age with atypical symptoms, delaying diagnosis.[7]

Before 1990, open surgical repair was the only treatment option for aortic disease and was associated with high perioperative morbidity and mortality rates (Figure 2a,b).

Parodi and co-workers[10] changed the treatment paradigm in 1991 and were the first to exclude an AAA successfully by minimally invasive delivery of a covered stent. Since then, this method of treatment has evolved in terms of procedural guidelines, equipment and devices and has been applied to other aortic pathologies such as dissection. In this minimally invasive procedure, an endoprosthesis, known as stent-graft (SG), is placed transluminally through a catheter to exclude the disorder by sealing the diseased wall from
the blood pressure and, thus, prevent rupture. The approach is now the gold standard for many patients over open repair, especially for those with comorbidity, the elderly and frail and those with a hostile abdomen.[1]

1.1. Endovascular Aortic Repair

Standard endovascular aneurysm repair (EVAR) is suitable for aneurysms that begin below the renal arteries, where an adequate length of healthy aorta exists for a reliable seal of the SG without leakage of blood around the device (Figure 2c,d). Patients will be offered elective repair of their aneurysms when it reaches a critical size diameter (typically greater than 5.5 cm) where the risk of rupture is greater than the risk of surgery.[11] Clinical trials revealed fewer early complications and a lower mortality rate with EVAR compared to open repair.[12] There is, however, a significant reintervention rate of 20% to 30% with EVAR,[13,14] which is the result of ongoing endoleak and lack of long-term durability in currently available devices.[15]

Thoracic endovascular aortic repair (TEVAR) is now considered the first-line treatment for isolated aneurysms of the descending thoracic aorta. TEVAR is recommended acutely in the treatment of complicated type B aortic dissection (TBAD) and can be considered in the post subacute phase in uncomplicated aortic dissection to reduce the risk of long-term aortic-related mortality from ongoing expansion and aneurysm development[10] (Figure 2c). Technical success of TEVAR is defined as the successful deployment of a SG with complete coverage of the primary entry tear and no signs of type I endoleak (leak at the proximal sealing zone) at the end of the procedure. Access is usually achieved by a retrograde approach from the femoral artery. The success rates of TEVAR and procedural mortality rates are favorable in comparison to open thoracic surgery, where mortality is much higher.[17] TEVAR is typically performed with one or more overlapping tube SGs, and device selection relies on anatomic characteristics and surgeon/institution experience and preference.[1]

With the shift toward minimally invasive surgery, the range of endovascular medical devices is rapidly growing. Common endovascular medical devices comprise of SGs and/or covered stents and can also consist of ancillary and fixation components like modular SGs, stents, cuffs, foams, EndoAnchors, and staples.[18] An aneurysm sealing system, called an endovascular sealing device, has recently been introduced to solve the leaking problem for abdominal aneurysm cases where there might be a neck dilation due to the progression of the disease.[18] Apart from guidewires and sheaths for the delivery process, catheters have played a significant role in endovascular treatment to enable vessel cannulation. Ancillary devices and techniques have widened what is possible; for example, diagnostic systems, introducer systems, closure devices, grasping systems (e.g., snares), mechanical thrombectomy, optical coherence tomography, valvulotomy devices, thrombus aspiration devices, atherectomy devices and drug-coated devices.[18,19] Embolization can be performed using coils, plugs, liquid/gel embolic agents, intravascular flow disrupter, embolic particles/foam or beads.[18] Herein, we focus our attention on SGs and the associated manufacturing technologies as the most widely used device for endovascular aortic repair.

2. Historical Background of Stent-Graft Development

It is essential to first realize the application of a SG to better study the structure and materials employed for different models. SGs exclude aortic aneurysmal dilating disease and are mostly impermeable (e.g., commercial SGs), which makes their application and function unlike other products which are designed for occlusive narrowing disease. However, coronary stents are made to reopen the blocked lumen (e.g., small arteries) with scaffold-like structures in a percutaneous coronary intervention. grafts are to replace a blocked vessel using open surgery.

SGs are typically comprised of two main components: a flexible membrane “graft” designed to act as a conduit for blood circulation; and the supporting metal frame “stent,” which is connected to the graft, to provide the required patency for the expected device lifetime and maintain radial force.[20] The SG attaches to the wall either by auxiliary fixations using hooks, barbs, anchors, or staples that embed into the aortic wall, or by radial force fixation, in which the SG is oversized, either by balloon or shape memory behavior, relative to the aorta to create an outward (radial) force and thus a stable attachment.[21]

The concept of a SG was initiated as a “covered” stent idea and as a result of clinical trials, has undergone several design iteration processes to become the devices we use commonly today. Early SGs were custom-designed for a particular patient by the assembling of off-the-shelf components by the operating surgeon at the time of the procedure.[10,22] The concept behind the development of a SG was simple: implant a new artificial conduit that would relieve any pressure on the weakened diseased aortic wall and maintain the blood flow within this new conduit. Despite an understanding of the biomechanics of the aorta (i.e., pulsatile blood flow through an elastic artery), the choice of suitable materials was limited and could not mimic the biomechanics of the native artery. For instance, a commercial woven Dacron graft is 24 times stiffer than a healthy human aorta.[24] The mismatch in compliance between the SG and aorta can trigger local hemodynamic disturbance after implantation[24–27] with subsequent increase in cardiovascular load and deterioration in aortic Windkessel function (i.e., a term used for explaining the response of outflow arteries to blood pressure variation, where arterial elasticity helps to reserve a proportion of the stroke volume from each systolic pressure wave and unloads that volume with diastole).[28–30] However, regardless of these drawbacks, SGs were overall a major advance in a condition that was otherwise only treatable by major open surgery, and therefore, innovation has continued.

After initial experiences through the 1990s, the commercial potential of SGs began to gain attention, and in the late 1990s, development in Perth, Australia, resulted in the creation of the modern-day fenestrated SG, licensed by COOK Medical (Figure 3a).[31,32] The first animal trials were in 1997, followed by first-in-man in 1998, and the first SG that used branching iliac artery regions was implanted in 2001.[33] This SG provided a stable and secure proximal fixation using a bare stent with hooks and barbs, which mitigated the problem of distal migration (i.e., slippage of the graft) and further improved the initial Gianturco (i.e., a type of early stent design made of stainless steel wire bent
Figure 3. Design of current state-of-the-art stent-grafts (SGs). a) Perth early device. b) Commercial SGs for the thoracic aorta. (i) COOK standard profile TX2. (ii) GORE thoracic branch endoprosthesis. c) Commercial SGs for the abdominal aorta. (i) COOK Zenith Flex. (ii) Vascutek Anaconda. d) COOK ZFEN SG customized for fenestrated endovascular aneurysm repair (FEVAR) operation. e) Commercial SGs for small arteries. (i) iCAST Atrium. (ii) GORE VIABAHN. (Note: there might be some design variations compared to the original device).
in a zigzag fashion to create a cylinder) stent design to prevent breakage of the material and ensure durability.

3. Current State-of-the-Art

The modular COOK Zenith SG came together with an endovascular delivery system for minimally invasive procedures that provided controlled and precise deployment. This design and material technique have encouraged other manufacturers to introduce their models to the market.

Over the last two decades, we have witnessed a boom in innovation and device diversity from the global collaborations between vascular interventionists and bioengineers and currently, several commercial SGs exist with varied stent designs and distinct materials, fabric architectures, fixation methods, deployment processes, and delivery systems many of which show acceptable long-term outcomes. The modern variability and availability of such devices have increased the accessibility of treatment, allowing the selection of the most appropriate device for each patient and their anatomical limitations.

3.1. Design Principles for Developing Efficient Stent-Grafts

3.1.1. Aims and Challenges

The evolution of SG design has focused on addressing both short- and long-term aims. In the short term, designs aim to promote the easy implantation of the device, mainly through challenging iliac anatomy and accurate positioning and deployment, which, if accomplished, is termed “technical success.” Short-term expectations are the minimization of vessel trauma, impacts on end-organ blood supply, risk of embolization, and conversion to open surgery. In the long-term, the aim is to enhance the performance of the device through better flow dynamics, reduce late migration and disconnection or other device-related failures that would lead to secondary interventions. As such, facilitating delivery and deployment accuracy for the operator and establishing practical means for SG adjustment are considered essential design requirements. In the future, the best SG should be the one that can be modified according to individual patient anatomy, applicable to all anatomical variations and achieve durability in the long term.

The placement of current SGs inside a vessel introduces compliance mismatch and can create flow disturbances. To overcome these issues, different SG designs have aimed to mitigate the foreign body reaction while balancing the critical technical requirements, as mentioned in the previous section, radial force with potential tissue trauma (e.g., endothelial trauma and ongoing neck dilatation) and considerations for proper seal and fixation through distal and proximal end designs. These also can influence deployment site (or landing zone) choice to avoid late migration through extending the disease treated length with uncovered stents (e.g., in the limbs for AAA) or by the addition of proximal anchoring hooks. These responses are more difficult to ameliorate when considering fenestrated and branched SGs, which are inserted into diseased aortic segments where maintenance of branch vessel flow is crucial and landing zone lengths are limited.

There is now a wide range of commercial SGs available to treat different regions of the aorta, including thoracic, abdominal, peripheral, as well as different lengths of disease with tubular, bifurcated, or fenestrated/branched. Composite components are often required over long sections such as with TBAD, and tapered designs enable seals between sections over a changing diameter. Most SGs for the aortic disease are self-expandable compared to SGs for peripheral vascular (or occlusive) disease, where a balloon-expandable option with greater radial force may be more appropriate. Deployment techniques can differ, for example, expansion from end to end or expansion from the middle to end, designed to cope with high flows in the aortic arch, and radial fixation is enhanced in some devices by proximal hooks or barbs.

3.1.2. Stent Design

Stent design is key to keeping strut thickness down while maintaining sufficient radial strength. Stent architecture, namely stent height and diameter, the number of peaks, wire thickness, oversizing, axial length, and material type, determine how much radial force is produced. Theoretically, the force per peak (i.e., radial force divided by the number of peaks), the overall radial pressure (i.e., radial force divided by the stent area), and the overall force are distinct design matters, which may solely influence migration, fixation, tissue trauma, or even tendency toward retrograde aortic dissection. Thus, overall force should be low enough to avoid vessel trauma and ongoing vessel expansion over time in the seal zone yet should be high enough to provide adequate sealing and migration resistance.

Although Z-shaped patterns are the most common design used, there is no consensus on the most ideal stent design. According to numerical and experimental studies on commercially available SGs, the design of metal stents can influence the mechanical performance of the entire device. As one of the key design factors to facilitate delivery and deployment, SG flexibility is preferred, but it opposes a more effective seal from a stiffer graft with higher radial force. This, however, can be partially mitigated by increasing the radius of the stent apex arc. Various configurations of the metallic skeleton have developed, such as continuous patterns (e.g., Z shape or diamond) or interrupted rings and helical shapes. Although the former has limited flexibility, interrupted rings and helical shapes can reliably conform to curved anatomy. An interrupted ring design has little flexibility in the discrete segments where the individual stents are attached, resulting in excessive kinking and flow disturbance. Plus, due to the infolding from the kinking, narrowing of the lumen might result. A helical design, on the other hand, evenly dissipates the length discrepancy and avoids the convergence of multiple stent struts. If superior sealing is required, a sinusoidal stent design might be preferable where the number of apexes reinforces the circumferential attachment, and a higher number of apices lead to more surface area pressing the graft onto the artery wall. Spiral and circular shapes showed greater flexibility and lower stress values than Z-shapes, especially for challenging and tortuous anatomies (Figure 3b–e).
3.1.3. Graft Design

The structural design of the graft plays an essential role in the variation of biological, biomechanical, and hemodynamic parameters at the implant site. For instance, whether in fiber or fabric form, the suitability of textiles lies in their structural and design flexibility, where the emulation of native aortic mechanical properties (e.g., strength, stiffness, elasticity, permeability) becomes possible. The structural heterogeneity of the native artery promotes a unique mechanical behavior in the vascular wall, such as non-linearity, anisotropy, viscoelasticity, and compliance, which altogether make design optimization of the graft a sophisticated task. In conjunction with radial compliance, known as an essential design property for a vascular implant, successful mimicking of natural artery behavior relies on the incorporation of other elements such as nonlinearity and anisotropy.[50]

The use of polymer-based fabrics or laminates in endovascular grafts evolved from their applications in open surgical repair, where either woven fabrics using fabrication technologies like weaving,[51] knitting,[52,53] braiding,[54,55] or nontextile fabrics through extrusion forming[56] and electrospinning[57,58] have been employed. Based on the fabrication technology, the material and design of the graft can differ. Nontextile fabrics inherently have a complex design process where the resulting structures mostly exhibit random patterns. For instance, expanded polytetrafluoroethylene (ePTFE) grafts microscopically have a porous morphology with node-fibril composition whereas, woven fabrics are mostly made of polyethylene terephthalate (PET) with controllable microstructures.

To have an optimal woven textile for SG fabrication, the saturation index is one of the determining factors that characterize both the percentage of spatial yarns in the structure (weft and warp directions) and their connections. A woven structure with a low saturation index (i.e., less dense than the theoretical maximum) can be described as a deformable textile with high porosity. On the other hand, a high saturation index defines a structure with more rigidity and cohesion of the SG fabric, where porosity is the lowest. This may cause areas of wearing, leading to the creation of holes at the contact of the stent extremities as the stents are tightly sutured to the fabric. Although a high saturation index brings improved wall sealing, it can also impact the crimping of the SG within the delivery system. The reduced porosity/increased rigidity of the SG might trigger displacement, especially where slow aneurysm sac shrinkage or neck dilatation may increase the chance of migration from enhanced caudal displacement forces. As such, a trade-off must be made between a high and low saturation index based on the desired properties and long-term effects.[59,60]

Permeability is another crucial feature in the design of a textile conduit, representing the liquid penetration through the grafts’ fabric, where early grafts needed precutting (if water permeability is above 600 mL/cm²/min).[61] Unlike surgical implants, endovascular implants are rarely precutted with patient blood. Thus, they must be impermeable to exclude flow outside the device.[43] Successful biological sealing, however, is a recent trend that is created through controlled permeability of the fabric, promoting tissue ingrowth and an effective endothelial monolayer to reduce the risk of thrombus formation.

Graft design can employ either monofilament or multifilament fabrics, with various densities and thicknesses of the warp and weft fibers, and be postprocessed to modify fabric density. Such differences contribute to excluding blood flow, resisting blood leakage, and conforming to tortuous anatomy.[43] The constructions of commercially available SGs (e.g., Anaconda, Zenith) are restricted to 4/4 twill weave (i.e., diagonal-like pattern) with monofilament yarns and 1/1 plain weave multifilament yarns. Although the mentioned structures are thin and deployable with adequate water permeability, the long-term resistance to biodegradation, especially with monofilament yarns, is unacceptable. Moreover, the fabric structure does not promote cell ingrowth and allows the transfer of nutritional components and metabolites. Fabric structures with multifilament yarns and twill weave hold essential design features (e.g., yarn and weave type) to fabricate a functional textile conduit for SGs.[61] The combination of multifilament warp yarns and multifilament weft yarns could enable novel textile designs with superior water permeability, thickness, and porosity similar to that of commercial SGs.[61]

3.2. Materials Used for Stent-Grafts

3.2.1. Aims and Challenges

The aorta is a challenging environment subject to approximately 35 million cardiac cycles per year, making it essential to design a device with enough resistance to bear intraluminal pulse pressure deformations.[62] Thus, the material system used must be concomitantly optimized for durability and flexibility, whereas the stent system must be strong and conformable to keep the SG in place, but compressible for device deliverability. The graft must endure radial and axial forces from the hemodynamic load while being flexible and compliant to regulate pressure and flow. The surface must be smooth, nonpermeable and inert to avoid thrombus formation and excessive host response. Radiopaque markers (typically platinum, platinum-iridium, tantalum, and gold facilitate accurate deployment[41]) and the process of attaching the stent to the graft must be effective and durable. Often, grafts are sewn to the stents using polyester or polypropylene sutures, or bonded through thermal processes, or less commonly, have stents sandwiched between graft layers.

Although aortic SGs currently employ the self-expansion technique for deployment, covered SGs (e.g., for coronary arteries or visceral vessels) can either use self-expansion or balloon dilation. Balloon-expandable SGs are manufactured to a deliverable configuration and are balloon-dilated to the final diameter inside the vessel. These materials should be plastically deformed on inflation, followed by a slight recoil caused by the elastic portion of the deformation. Thus, materials with low yield stress are preferable to ensure deformability at controllable balloon pressures and high elastic modulus for minimal recoil. On the other hand, self-expanding SGs are fabricated in the expanded configuration, compressed, and then crimped into the delivery system. Upon deployment, the self-expanding SG springs back to the predetermined diameter. In addition to the controlled mechanical performance, materials need to be radiopaque, have corrosion resistance, and be magnetic resonance imaging (MRI) compatible.[41]
3.2.2. Stent Material

Nitinol is the most prevalent self-expandable stent material, a superelastic shape memory alloy exhibiting superior features like remarkable biocompatibility, similar deformability and elasticity to biological materials, durability, resistance to corrosion, fatigue, and MRI compatibility.[43] Furthermore, Nitinol has been chosen for medical device construction due to the practical features, including thermal deployment, constant stress (i.e., Nitinol allows due to their flat loading and unloading curves over large strains can resist constant stress over a wide range of architecture), dynamic interference (i.e., long-range nature of stresses in Nitinol allows the expansion to preset diameter without recoil in self-expanding stents), stress hysteresis or biased stiffness (i.e., stent exerts low outward force while resisting deformation with a much higher force), and temperature dependence of stress.[63] Its shape memory behavior enables it to be crimped into a small diameter within a sheath and then self-expand to the preset vessel size simply through thermoregulation, without additional manipulation.[43]

However, according to the Stent Design Pyramid, a published classification system,[64] it is clear that properties like resistance to fatigue and corrosion are likely to depend on material forming (e.g., wire, tubing), fabrication technology (e.g., laser machining, braiding, knitting) and stent design (e.g., Z-shape, M-shape, rings, helix, coil, unconnected, open cell, etc.).[64]

Other stent material compositions are stainless steel (316L) and cobalt-chromium (Co-Cr) alloy (e.g., Elgiloy).[65] Elgiloy (or Phynox) is a trade name for a biomedical grade cobalt-chromium–iron–nickel–molybdenum alloy, which holds promising properties, such as nonmagnetic, highly corrosion-resistant (i.e., does not corrode by organic acids), and a superior reaction to inorganic acids compared to stainless steel, with the metal oxide layer building resistance to corrosion.[66] Plus, Elgiloy has excellent in vivo passivity (i.e., biocompatibility). Due to having outstanding mechanical features like high Young’s modulus, high yield strength, and favorable fatigue strength in the stress-controlled environment, it can withstand high stress and large deformations. This makes Elgiloy a practical choice for stenting applications since it provides noticeable spring properties. A relatively small amount of iron makes Elgiloy ferromagnetic and also compatible with MRI. Typically, Elgiloy stents are designed based on braiding techniques where flexibility is warranted through the strut design, as well as providing an intrinsic outward spring force to the stent.[67] However, image artifacts during MRI have been detected, which may be due to the clustering of magnetic elements, which prevail in Co–Cr alloys, causing the atomic scale heterogeneity of the material. Thus, the cons might outweigh the pros, especially as most patients require lifelong imaging-based surveillance.[68,69]

3.2.3. Graft Material

Given that complete healing of the diseased region being excluded by the SG is unpredictable, the long-term durability of the selected material is critical. Thus far, many polymers have been utilized, including Dacron, Teflon, Nylon, Ivalon, Orlon, and polyurethanes (PUs).[70,71] However, all currently available grafts employ either polyethylene terephthalate (PET), with the commercial name “Dacron,” or polytetrafluoroethylene (PTFE) with the commercial name “Teflon,” due to their outstanding features like biostability and long-term resistance to wear and degradation.[72,73]

PET is a highly durable thermoplastic polyester that can be processed into synthetic fibers. Historically, weaving and knitting have been adopted to fabricate tubular conduits from Dacron fibers due to sufficient rigidity.[73] PTFE is a fluoropolymer that is biochemically stable, hydrophobic, and mechanically durable. The graft surface is electronegative, which favorably limits reaction with blood components. Today PTFE is predominantly processed into ePTFE tubes by means of stretching a melt-extruded solid polymer tube, which then cracks into a non-textile porous structure. Macroscopically, the surface of ePTFE is smoother, and the grafts are soft and pliable. ePTFE, microscopically, has a porous morphology consisting of islands of solid nodes linked by fine fibrils that occupy close to 20% of the total volume (Figure 4a). However, ePTFE grafts have considerably smaller void space than PET woven or knitted grafts, and due to the innate hydrophobic nature of the fluoropolymer, a natural barrier to water is produced, preventing blood permeation.[73,74]

ePTFE fabrics can have better endothelialization than PET, depending on pore size, which contributes to long-term integration and graft patency as well as relatively better handling with their thin-walled fabrics due to improved graft compliance.[74] Enhanced conformability should let the material collapse or “accordion” easily, while relative rigidity of PET in comparison to ePTFE may promote the chance of kinking and flow disturbances.[48]

Recently, attention has shifted to using alternative materials like PU and ultrahigh-molecular-weight polyethylene (UHMWPE). PU grafts were developed to improve the weak compliance behavior in ePTFE and PET grafts. PU is a biocompatible and comparatively elastomeric copolymer with different monomers that provides strength and flexibility at normal body temperature. By changing the composition of the monomer repeat units, the mechanical properties of PU grafts can be fine-tuned.[73,74] The UHMWPE membrane technology, developed as Dyneema Purity® (DSM), is a promising alternative to common graft materials in that the higher ratio of strength versus volume compared to ePTFE enables the development of SGs with a smaller profile. Apart from being self-lubricating, this material has low friction and nonstick surface coefficient, making it possible to fabricate smooth and slippery medical devices.[41] In a recent attempt,[75] a covered stent with UHMWPE membranes sandwiching a nitinol frame was developed and implanted into an ovine peripheral artery model. Data revealed that UHMWPE could be regarded as a suitable alternative to the current synthetic graft materials for use in low-profile covered SGs. Also, compared to PET, UHMWPE fibers showed fewer inflammatory responses while promoting equal or even better healing.[41]

3.3. Current Technologies for Stent-Graft Production

3.3.1. Aims and Challenges

Despite their use as a modern-day life-saving device, SGs are still typically fabricated using traditional methods. Due to the current
Figure 4. Materials and Fabrication of SGs. a) PET graft design pattern. (i) SEM image of plain weave (scale bar: 100 μm). Reproduced with permission. Copyright 2012, SAGE Publications. (ii) SEM image of warp-knit (scale bar: 200 μm). Reproduced with permission. Copyright 2011, Springer Nature. (iii) SEM image of ePTFE for node-fibril microstructure representation (scale bar: 10 μm). (b) Schematic of the braiding process (blue line denotes PET fibers and red line denotes covered NiTi yarns) and fabricated SGs with different parameters. Left: Reproduced with permission. Copyright 2018, Elsevier Ltd. Right: Reproduced with permission. Copyright 2017, SAGE Publications. c) Production of the small caliber electrospun SG and SEM image of the graft (scale bar: 10 μm). Reproduced with permission. Copyright 2016, JoVE. d) Merit WRAPSODY SG. (i) Three-layered electrospun membrane. (ii) Comparison of the cross-section of the three-layer SG with a commercial SG through animal histology at 180 d where the layered SG (right) showed neointimal layer formation and cellular migration across the ePTFE layer (scale bar: 2 mm). Reproduced with permission.
acceptable patient outcomes, it is still a question whether new manufacturing techniques are worth the investment. While late failures can usually be treated using additional minimally invasive approaches and explantation of SGs is now rare. Therefore, the major indication for the development of new generation devices is probably to reduce the cost of surveillance and frequency of reintervention, which are not without patient-related and financial impacts.

3.3.2. Stent Fabrication

The established metal stent production technologies are laser cut sheet forming, laser cut tube forming and wire forming (welding/joining), where the latter two are used for making large stents. Metal stents are structured into the functional shape and then assembled through stitching and weaving to the graft. Careful attention should be taken at the fabrication stage due primarily to the sensitivity of the solid-state transition; enhanced profile due to filament crossing when wire forming may lead to fretting corrosion or wear at cross-over points, while laser-cut stents can provide a more effective crimping and complicated shaping. Laser-cut forming requires additional post-processing steps to remove the thermal stress of the “heat-affected zone” and residual burrs along the edges. Electropolishing has been employed to dissolve a small amount of the metal alloy, rounding all edges and smoothing the surface. Moreover, electrical discharge machining and water jetting are among the less frequent production methods of tube-form stents.

3.3.3. Graft Fabrication

The technologies to manufacture endovascular grafts are mainly categorized into woven forming and nontextile forming techniques. Woven forming uses a loom to weave PET fiber into a tubular film and is widely employed by SG manufacturers as it enables a compact structure, stable size, and controllable thickness. Woven textile fabrication techniques, like weaving, knitting, and braiding, produce endovascular grafts in most commercial and research-based applications. However, mimicking the properties of the native artery remains a challenge. Among the established nontextile forming methods, extrusion forming and electrostatic spinning are used for graft fabrication.

Weaving: Weaving is a production technique whereupon the interlacement of warp (longitudinal) and weft (crosswise) yarns perpendicular to each other produce the graft fabric (Figure 4a). Different types of weave designs are plain, twill, and satin, with plain and twill weave being the most common. Parameters that determine fabric behavior are weave type, thread spacing, linear density, and twisting trend of the warp and filling yarn. The distinct characteristics of these grafts are a smooth surface, water permeability, ease of handling, nonreactivity, burst strength, biological healing response, and suture retention strength. Although the production of thin profile fabrics is possible, the tendency to wrinkle and the dissimilarity to a natural artery are limitations. Plus, the organized structures (i.e., orthogonal arrangement) promote poor radial compliance and low axial elongation, which are unsuitable for long-term in vivo applications. Crimping might be a useful technique to provide the desired axial elasticity as well as keep the tubular shape of the graft while bending. To improve the inferior radial compliance in woven grafts, the principles of the multilayered morphology of native arteries have been adopted to design textile vascular prostheses. A bilayered woven graft prototype was developed with the inner layer made of low modulus circumferential yarns (poly-trimethylene terephthalate) and the outer layer made from high modulus yarns (PET), stitched in a crimped form to the inner membrane. The inner layer is responsible for absorbing the strain at low normal physiological pressures (diastolic), while the crimping of the outer layer occurs due to a further increase in pressure (systolic). Altogether, the joining process of the layers increases the overall elastic modulus of the graft. Despite the high pressure-induced radial compliance with this design, the disadvantage is the reduced bending flexibility or kink resistance due to the crimped outer layer.

Knitting: Knitting employs a looped filament construction enabling a continuous intertwined chain of yarn loops twisting circumferentially around the graft (Figure 4a). In comparison to weaving, knitting makes softer, flexible, radially distensible, and compliant structures. By modifying the density, pore size, and distribution, knitted structures can be effectively controlled. However, high porosity and the tendency for rapid dilatation have been reported as issues, with graft preclotting able to resolve the porosity problem. There have been some efforts to improve the mechanical behavior of knitted fabrics, but they still fail to match native artery mechanics. A novel knitted SG design that better mimicked the native artery has been proposed based on longitudinal structural segmentation or metamerism, which appeared to respond effectively to applied stress like a natural artery as a result of multiple low and high modulus segments. The biomechanical behavior was improved through structural segmentation due to a 3D volumetric expansion feature when SG was under hoop stresses. Thus, the orthotropic elastic property of the native aorta was obtained.

Braiding: Braided structures may effectively replace SGs due to their high structural flexibility and ability to maintain their original shape post-implantation, making them favorable for hostile anatomies (Figure 4b). However, the axial shortening in response to the radial expansion and the stent failure (wire breakage) at suture sections under in vivo conditions limited their use to braided metallic frames with no graft covering and controlled porosity. Braided stents are typically helix wires interlaced into cylindrical tubes, with crossings connected through friction. The low porosity in the braided structure can play the shielding role of the SG without the need for a graft cover. Due to the increased stent stiffness (radial and longitudinal), host artery hemodynamics can be negatively influenced by the non-compliant behavior of the implanted region, resulting in an overall pressure drop and an increase in pulse-wave velocity. The concept of a braided stent entered a new era with the commercialization of the multilayer flow modulator (MFM; Cardio, Isnes, Belgium), bringing a new paradigm and shifting the focus of treatment from traditional aneurysm exclusion (physical barrier) to reconstruction of the parent vessel (functional barrier). The MFM is an uncovered, self-expanding multilayer interlocked bare-metal stent, capable of providing high radial force and flexibility, which is made of fatigue- and corrosion-resistant
cubalt-alloy wire (Phynox). Due to porosity in the range of 65%, MFM channels flow to the branching vessels, altering blood flow from turbulent to laminar and inducing positive shear stress that fosters thrombus formation inside the aneurysm sac.\[83–87\]

Although long-term clinical data have not been published yet,\[83–86\] the use of braided stents in treating intracranial aneurysms, thoracoabdominal aortic aneurysm (TAAA), TRAD, juxtarenal aortic aneurysm, and peripheral and visceral artery aneurysms have been reported across the literature.\[85,86\] The one-year results of MFM use in the management of TAAA and TBAD revealed 93.7% technical success and aneurysmal-related survival.\[88\]

Put differently, according to a clinical assessment on various aneurysm conditions,\[87\] perfusion into covered aortic branches encouraged thrombosis, and aneurysm shrinkage was observed gradually and intermittently in complex aortic aneurysms. The authors stated that due to the insufficient protection from rupture after stent placement (especially for the first months), it is advised to use MFM for the patients unfit for EVAR, TEVAR, or fenestrated endovascular aneurysm repair (FEVAR) and even open repair.\[87\] Other studies reported that continued aortic enlargement had been observed,\[85,89,90\] representing the lack of strong evidence of the technology’s effectiveness to avoid aneurysm rupture and aortic-related morbidity longer than the initial one-year postimplantation.\[86\]

Following these attempts, sutureless SGs with different designs were made in 2017\[71\] through a braiding technique composed of Nitinol wires and PET multifilament yarns (Figure 4b). Superior radial force, axial flexibility, and torsion resistance were achieved in which the suitable yarn friction confined stent elongation and enhanced the compactness for easy delivery through tortuous diseased vessels. In the authors’ later attempt\[91\] to improve the mass transfer performance (i.e., blood and microthrombus transfer through graft wall) of braided SGs, they found that although the porosity and pore diameter can positively influence the mass transfer behavior, the thickness can promote adverse effects. Thus, enhancing the density of yarns and adopting multifilament with fine single filaments brought lower risks of endoleak and blockage.\[91\] The controlled mass transfer is essential to encourage vessel healing, avoid blood leakage and microthrombus protrusion through graft material.

**Electrospinning:** Electrospinning is an established nontextile fabrication technology that emerged to provide a nanofiber porous membrane with superior biocompatibility, nonthrombogenicity, and the ability to mimic the extracellular matrix to encourage faster injury site healing\[92\] (Figure 4c). This technology involves the application of high voltage through a charge-to-charge and electrostatic attraction between the syringe needle and the earth to make an electrified viscous fluid jet (in the form of a solution or melt) being drawn via the air towards a static or rotating collector (at a different electric potential) to produce a nontextile mesh of fibers.\[93\] The deposition of layers with different polymer components makes layer-wise control over the mechanical graft response possible.\[94\] Properties like deposition and thickness of the nanofibers can be modified by changing the polymer concentration to make thin and flexible membranes. However, solution electrospinning is a highly dynamic process with further technical complications, making the control of fiber deposition challenging.\[91\]

The main advantage of this technique is the possibility of rapid SG production on a laboratory scale. For instance, a small-caliber electrospun SG was developed, in 2016, by enveloping a balloon-expandable stent between two electrospun PU layers\[92\] (Figure 4c). Mechanical assessment of the SG showed sufficient flexibility of the nanofibrous PU membrane during the crimp and expanded phases while staying patent with no signs of de-lamination or tearing in the membrane. The fabricated SGs were delivered through standard size guide catheters.\[92\]

A commercial electrospun SG with a unique design has been studied clinically (Wrapsody; Merit Medical systems) (Figure 4d).\[57\] The structure of this SG includes a Nitinol stent frame enveloped within a three-layer graft structure, including an abluminal ePTFE layer (internodal distance of 5–15 μm), an intermediate nonporous fluoropolymer layer, and a porous luminal electrospun PTFE layer.\[57\] The patency, tissue response, and thrombogenicity of the SG were comparable to a commercially available ePTFE SG (Fluency endovascular; Bard Peripheral Vascular) with a Nitinol stent frame encapsulated between two layers of ePTFE graft material (internodal distance of 15–30 μm) with no impermeable barrier membrane, in a nonatherosclerotic external iliac artery ovine model. The novel layered structure exhibited significantly lower diameter stenosis at 180 d and lower mid-device neointimal coverage scores at 30, 90, and 180 d. The investigated SG avoided transgraft cellular migration due to the impermeable barrier and resulted in small luminal neointima without any thrombus formation on the exposed spun PTFE graft surface (Figure 4d). This demonstrates that layered graft designs with varying porosity should be the primary consideration for next-generation SGs.

### 3.4. Covered Stents and Clinical Applications

Covered stents are a type of SG composed of a thin membrane that either shield the luminal side or the abluminal surface of the metallic part or completely sandwich the stent inside. Covered stents enable controlled radial pressure, confined in-stent restenosis, and prevention of embolization via a physical barrier between the vessel wall and the bloodstream, limiting tissue ingrowth. Covered stents employ the same production technique as SGs, where some of the large-scale SGs have evolved from small caliber covered stent prototypes. They also play an essential role in laboratory-based studies to investigate scientific ideas on animal case studies. Covered stents can be effective in the treatment of conditions like fistulae, congenital vascular disease, neureovascular disease, and coarctation of the aorta.\[58,95,96\] To prevent restenosis in smaller arteries, covered stents can act as an effective drug delivery platform for the localized release of therapeutic agents.

Most current efforts are aimed at the material science of the membrane rather than the design and mechanical characteristics of the metallic section. PTFE, PET, PU, and polylvinyl (PVA) cryogels are among the synthetic polymers used as cover materials, as well as biological materials such as heterologous pericardium, autologous venous or arterial grafts, scaffolds loaded with endothelial cells, chitosan-based polymers, collagen, fibrin, and tissue-engineered vascular grafts (TEVG). More
recently, synthetic nanocomposite polymers were employed. Electrospinning (e.g., Solaris SG by Scitech Medical[58]), casting and Langmuir–Blodgett techniques, layer-by-layer assembly, and polymer sleeve braiding are some of the techniques used to make low profile covering membranes.[95]

In a ten-year clinical study of commercially covered stents (i.e., Wallgraft; Boston Scientific, Jostent; iCast; Atrium Medical, Fluency; Bard, and Jostent Graft Master; Abbott Vascular) to treat superior mesenteric artery pseudoaneurysms, technical and clinical success with mid-term stent patency was reported.[97] In a comprehensive review[98] of commercially covered stents, iCast and Advanta V12 (Atrium) showed a primary patency rate of 74.7% at five years, suggesting covered stents are favorable over bare-metal stents (BMS) for complex aortoiliac lesions.

3.4.1. Bioengineered Stent-Grafts (BioSGs)

Biological incorporation may improve the attachment between the native aorta and the implanted SG and brings excellent long-term conformability, even in angulated or short landing zones. BioSGs are composed of a metallic stent sandwiched or attached to a TEVG, aimed to improve postoperative outcomes (e.g., no risk of graft infection or aortoenteric fistula developing, and anti-thrombogenicity from early endothelialization).[99–101]

To enhance the overall sealing performance, a unique graft system was developed[99] by compounding degradable polyglycolide (PGA, core) and nondegradable PET (sheath) fibers (Figure 5a). This configuration encouraged tissue ingrowth from the aortic wall into the graft fabric, where late migration and endoleak post-deployment were effectively avoided. PET/PGA and PET grafts had similar mechanical properties (i.e., tensile strength and flexibility), with a somewhat better water permeability for the proposed PET/PGA graft. The biodegradable filaments were replaced with host tissue (including a mixture of α-SMA-positive cells and other host cells) after the PGA fibers degraded in the animal over two months (Figure 5a).

A BioSG was developed in 2015 by harnessing the body’s ability to encapsulate foreign material[100] (Figure 5b). Dorsal subcutaneous pouches were made in beagles, and then the stented molds were placed into each pouch under anesthesia. The obtained BioSGs after four weeks showed a complete encapsulation of the stent by connective tissue with notable neovascularization. Despite having a low profile, the BioSG had an elastic modulus almost twice as high as that of the native beagle abdominal aorta. Next, the BioSGs were implanted as allografts into infrarenal abdominal aortas via the femoral artery of three other beagles using 10-Fr delivery sheaths[101] (Figure 5c). After one month of implantation, no stenosis or aneurysmal changes were detected. They observed that the luminal surface of the BioSGs was covered entirely with neointimal tissue, including endothelialization, without any thrombus formation.

3.4.2. Biodegradable Stent-Grafts

The degradation phenomenon is critical to in vivo medical applications. Although the terms “Biodegradable,” “Bioresorbable,” and “Bioabsorbable” are often used interchangeably, the term “Biodegradable” is perhaps appropriate here since degradation is the main process occurring in some implantable products. However, bioabsorbable products are the ones destined to be fully absorbed with no by-products. Biodegradable devices could eliminate the need for surgical intervention and avoid possible long-term health risks associated with permanent devices. While biodegradable polymers (e.g., natural and synthetic) exhibited suboptimal performance in clinical trials due to their weak mechanical properties, biodegradable metals have found their way into the clinical arena, with promising results achieved through nontoxic by-products that do not trigger a marked inflammatory response.[102]

The concept of the biodegradable stent was proposed to reabsorb over time and restore native vessel functions. Such a stent must maintain mechanical integrity for 3 to 6 months and degrade within 12 to 24 months in vivo (i.e., degradation rate < 0.02 mm per year), and be biocompatible (i.e., nontoxic, no harmful by-products, and noninflammatory response).[103] Synthetic polymers like poly(l-lactic acid) (PLLA), desaminotyrosine polycarbonate polymer, salicylates, polycaprolactone (PCL), and poly(lactic-co-glycolic acid) (PLGA) have been employed as stent materials. For coatings, layers have been made of poly(d,l-lactic acid) (PDLA), PLGA, and PLLA due to their extensive drug delivery use. However, attention switched to biodegradable metal stents due to the weaker mechanical properties of polymers. It has been claimed that since metals are present as biological ions in vivo, implanted devices containing such metals would tend to corrode their by-products, avoiding systemic toxicity by being safely metabolized.[104] Due to their favorable clinical results, Mg-based, Fe-based, and Zn-based alloys have been used as metal stents.[105] Alloying, microstructure design, and coating are reliable methods to enhance the performance of biodegradable stent materials where mechanical properties and corrosion profile can be controlled.[106,107]

There have been recent attempts to develop biodegradable covered stents for aneurysm repair. The long-term (12 months) efficacy of magnesium alloy-covered stents in an aneurysm model was investigated in the rabbit common carotid artery (CCA),[108] and was claimed to have distinct advantages compared to commercial counterparts. In a recent study to investigate the efficiency of fully biodegradable SGs, four different biodegradable SGs were developed and tested in animal studies (e.g., pig and rabbit). They reported encouraging in vivo results with a fully biodegradable system (Electrospun graft and magnesium stent) with a favorable rate of restenosis and patency.[109]

3.5. Device-Related Complications

The main disadvantage of endovascular treatment of aortic disease with SG is the high rate of reintervention, predominantly due to device-related complications such as endoleaks, migration, device integrity, limb occlusion, and graft infection.[110,111] Comprehensive knowledge of the SG design, material, and fabrication process leads to a better understanding of the incidence of complications,[8] enabling the development of a more stable SG with better clinical outcomes.[37]
Figure 5. Covered stents. a) SG with a composite graft structure. (i) Woven structure of the graft with a double-layered yarn made of PET and PGA filaments and SEM image of the double-layered warp yarn (scale bar: 1 mm). (ii) Luminal surface of the PET/PGA and PET grafts after two months of the implantation (scale bar: 5 mm). (iii) Histological evaluation of the explanted SGs after two months, stained with α-smooth muscle actin (α-SMA) (top: thin-walled woven polyester graft, bottom: PET/PGA graft, scale bar: 100 μm). (iv) Cell viability of the PET/PGA and polyester grafts, represented as the mean number of cells mm$^{-2}$. Reproduced with permission. 

b) BioSG. (i) BioSG produced through the assembly of a self-expandable stent and a cylindrical acrylic rod. After four weeks, the mold was covered entirely with the connective tissue of the beagle. (ii) Histological images of the cross-section of the BioSG where complete incorporation of the stent strut within the connective tissue was achieved (stained with hematoxylin-eosin) (scale bar: 5 mm (top), 100 μm (bottom)). Reproduced with permission. 

c) Intraluminal surface of the graft after 30 d of BioSG implantation was flat with no thrombosis, and the BioSG wall was tightly integrated within the native aorta circumferentially. Reproduced with permission.
3.5.1. Endoleak

Successful endovascular repair of aortic aneurysmal disease is dependent on isolating the diseased region properly from the systemic circulation. Incomplete exclusion results in persistent blood flow within the sac but outside the SG, which may gradually increase sac pressure, resulting in expansion and increased risk of rupture again. There are five types of endoleak that differ from each other according to the source of the communication between the SG region and the blood circulation: In type I endoleaks, the blood flows between the vessel wall and SG due to an inadequate sealing at the proximal (type Ia) or distal attachment sites (type Ib) or around an incompetently sealed iliac occluder plug (type Ic). Type II endoleak is caused by a continuous blood flow into and out of the residual aneurysm sac through patent aortic side branch vessels like visceral and lumbar arteries. Type III endoleak occurs due to structural failure of the SG in which blood flows through a graft defect, for example, a modular disconnection (type IIIa) or through a fabric tear (type IIIb). Type IV endoleak takes place when blood flows through the graft wall due to the high porosity of the graft material and occasionally due to numerous suture holes holding the graft material to the stent. Type V endoleak is associated with persistent residual aneurysm sac expansion with no evidence of a demonstrable leakage, known as endotension, which is frequently reported in ePTFE grafts. The term “endoleak” can also be defined for endovascular repair in TBAD cases. Endoaneurysms are mostly reported after EVAR in 15% to 30% of patients in the first 30 d and less commonly seen after TEVAR in 4% to 15% of the patients. Additional intervention after EVAR secondary to endoleaks is essential in 11% to 25% of patients.

3.5.2. Migration

The pulsatile nature of blood flow through the aorta exerts a downward force on the SG. When displacement forces exceed friction forces, SG migration occurs, defined as a proximal displacement of the SG by more than 5 to 10 mm from the original position. Device migration has been reported after TEVAR in 1 to 2.8% of patients and 1% to 10% of the cases after EVAR at 1 year postintervention. The risk of SG migration increases over time and can result in the return of disturbed blood flow into the diseased region and thus an increased risk of rupture again, which usually requires urgent treatment. If untreated, this can later lead to kinking or occlusion, even with small displacements. Severe neck angulation, short landing zones, inadequate proximal sealing, and short overlaps are considered the leading causes of early device migration. Furthermore, ongoing disease progression in the aortic neck can result in slow expansion over time, perhaps augmented by the radial force of the SG inside, causing migration and Type Ia endoleak.

3.5.3. Infection

SGs, like any other implants, present a risk for infection. They generally exhibit lower bacterial resistance and greater bacterial adherence, with the latter dependent on the SG sealing length and degree of endothelialization of the SG surface. Bacteria within the thrombus in an aneurysm sac are excluded from luminal blood circulation but not that from vasa vasorum or the lymphatic circulation. Possible causes of SG infection are perioperative contamination, hematogenous seeding, mechanical erosion (e.g., into the overlying duodenum), and secondary intervention. Infection is one of the most challenging and threatening complications in vascular surgery and may lead to graft/arterial interface disruption, hemorrhage, or sepsis. SG infection has been observed in 0.4% to 3% of the patients following EVAR. Due to the high mortality and morbidity risks, complete SG removal offers the only hope for cure but is associated with very high mortality rates, ranging from 25% to 50.

Infection risk of SGs has also been related to mechanical erosion, which can result from the biochemical degeneration of foreign material through inflammation (i.e., a foreign body response). An excessive release of metallic ions into the surrounding tissues due to corrosion will alter the local tissue environment, promoting an inflammatory reaction, although the link with infection is yet unclear. Either way, the release of metallic ions might accelerate the degradation rate in a septic environment leading to late device failure. Most importantly, approximately half of the elemental composition in Nitinol-based implants is nickel, which can cause allergic reactions, carcinogenicity, and nephrotoxicity at various doses.

3.5.4. Device Integrity

Pulsatile blood flow can lead to fatigue loading on an aortic SG, which jeopardizes the device integrity. Graft and component separation defects can appear as graft fabric tears, suture breaks, and stent/hook/barb fractures. Furthermore, all modular SGs rely upon friction and radial force between overlapping components, without which the structure’s integrity may demise over time. Tortuous anatomy or excessive oversizing of the SG also affects device integrity by leading to device infolding or collapse.

3.5.5. Compliance Mismatch

Compliance, in theory, is the percentage change in diameter of a cylindrical conduit between diastolic and systolic pressures. Native vessels have dynamic compliance inversely proportional to blood pressure, with some likely to have effects on endothelial dysfunction and the resultant development of atherosclerosis. SG placement, meanwhile, may cause a more severe drop in compliance, increasing the risk of device failure from reduced device durability from repeated hemodynamic variation. Also, due to the altered hemodynamics, restenosis tends to result in areas of compliance mismatch, especially in small arteries.

3.5.6. Limb Occlusion/Stenosis

The underlying mechanism of graft occlusion or thrombosis in EVAR is mostly due to kinking of the unsupported SG limb, excessive oversizing (more than 15%), and extension with the SG.
limb into the external iliac artery. However, late limb occlusion can be accompanied by migration and dislocation of a SG component, causing a major hemodynamic disturbance and, eventually, limb or entire SG thrombosis, which can result in acute lower extremity ischemia.\textsuperscript{[110,124]} SG displacement from the distal or proximal anchoring sites has been observed to cause device kinking postimplantation. Kinking may also appear in the form of infolding due to the accordion effect, from deliberate forward pressure during deployment to ensure branched origins are not occluded unintentionally. Anatomical and aneurysm morphology changes like residual sac shrinkage once the sac is depressurized may also result in the form of a late kink.\textsuperscript{[115]} Iliac angulation (more than 60\degree) and extensive iliac tortuosity increase the risk of early kinking during deployment.\textsuperscript{[112,124,125]} Earlier studies reported much higher incidence rates for kinking to be higher than 50\% after a 4-year follow-up.\textsuperscript{[112]} However, improvements in SG technology have limited the kinking/occlusion rates to 2\% to 4\% after EVAR.\textsuperscript{[110]}

3.6. Device Quality Assessment

The quality of a SG can be examined against its designated primary goals: biodurability, biocompatibility, and biofunctionality. SGs should exhibit undisputable biodurability, aiming to increase the patient’s life expectancy through long-life performance, and is considered biodurable when it assures fatigue resistance, wear resistance, and corrosion resistance. SGs must also be biocompatible to avoid likely side effects that jeopardize the patient’s health, that is, to be chemically bioistoic, nontoxic, nonallergic, or carcinogenic, as well as not to promote thrombosis or hemolysis. Biofunctionality is another descriptor representing the device’s anticipated medium and long-term clinical performance.\textsuperscript{[41,126,127]} As previously revealed through explant studies,\textsuperscript{[62]} manufacturers have improved the quality of SGs by using more chemically stable materials, optimized designs, and efficient deployment systems. Despite such well-established explant programs, there needs to be more integration of engineering knowledge of materials and production to provide a deeper insight into why SGs may fail in vivo. Here, we present an analysis and critique of the failure modes of SGs based on these three primary goals using available literature from explant studies.

3.6.1. Biodurability

**Failure Modes:** Fabric damage is one of the very first concerns. According to a recent explant analysis,\textsuperscript{[138]} two primary sources for fabric failure are compression and abrasion. Due to the nature of the delivery procedure in endovascular treatment, medical implants like SGs radially compressed into a smaller size on a catheter. If the deformation infringes the material’s elastic limit while the textile material is under severe stress, a permanent wrinkle due to local creases (i.e., a bending or crimping phenomenon due to the ductile deformation of the fiber) appears on the graft surface. The textile construction gets locally fragile due to bending, while the fiber is less resistant, especially in contact regions with stents and sutures, where holes and tears eventually appear under severe crimping conditions.\textsuperscript{[129]} Moreover, the cyclic movement of the blood can create an abrasion between different parts. The process of cyclic stress is generated by the relative movements in the textile membrane, the suture yarns, frame segments, or other abrasive elements like calcification in the vascular tissue. Given that metallic parts are more resistant, polymeric sections like fabric and sutures fail first. The result is a SG with holes and tears within the fabric with a tendency to propagate over time.\textsuperscript{[128]}

Sutures as holding units can also be the center of SG collapse, mostly observed as several knots being cut in a row due to abrasion. Once one suture breaks after abrasion between the stent segment and the suture, more significant similar movements are likely to propagate the falling of the adjacent knots. This can lead to a local separation of fabric and stent. Time is also another determining factor in graft failure, as degradation gradually weakens the material.\textsuperscript{[128]} Various levels of defects were observed in explant studies because of longitudinal distortion and stress concentration on the sutures holding the Nitinol wires, particularly at the contact between the vertical bars and stents.\textsuperscript{[70]}

The failure of the metallic segments due to constant cyclical loading, unloading, and deformation appears as strain hardening and fracture (e.g., cracks), which is an alarming point for SG collapse. Defects can occur in localized stress regions, strain, surface irregularities, and asymmetric loading. The damage gets more pronounced when the mechanical properties of Nitinol stent wires deteriorate due to unpredicted corrosion in different forms. Pitting corrosion might appear in the form of an electrochemical process initiated by adherent bacteria or fibrinolasts and the current flow of metal ions. Other forms of corrosion are crater or large and irregularly shaped surface alterations observed in most explanted SGs. The nonsuperelastic oxide layer may crack under large strains (i.e., forward and backward mechanical strain), creating a conduit for nickel-rich exposure phases to the in vivo environment.\textsuperscript{[130]} Although rare, galvanic corrosion may also happen at stent-wire junctions due to the factors like humid environment, different material types of the stent wire, and the severe pressing process used to form the connectors. It was claimed that this phenomenon might exacerbate with time but would not be a significant damaging factor for the overall device integrity, at least over the early years.\textsuperscript{[128]} Moreover, fatigue fractures often begin at surface heterogeneities detected through high Ni content found on retrieved cardiovascular implants.\textsuperscript{[62,111]} For instance, a potential site for fatigue is the sharp angle at the apex where the frame is bent to shape the strut.\textsuperscript{[132]}

**Commentary:** Materials’ selection and processing are critical factors to create biodurable SGs. Degradation analysis can help understand the biodurability of the selected material before fabrication, where the rate of material degradation is technically a leading cause of complications and puts patients at risk.\textsuperscript{[110,113]} A SG is theoretically expected to function for over ten years in vivo without any secondary intervention.\textsuperscript{[111]} The re-intervention-free survival for the Zenith SG was reported to be 70\% at 16 years.\textsuperscript{[134]} The high Ni release phenomenon is due to insufficient surface treatment (e.g., passivation process) and uncontrolled heat treatment, which results in diminished corrosion resistance in most commercial SGs.\textsuperscript{[113]} As Nitinol stents are fracture-prone, better polishing has eliminated surface pitting, and superior stent design has resulted in a controlled strain within a tolerable
range.\textsuperscript{[37,60]} Surface treatments like mechanical and electropolishing, sandblasting, chemical etching, and oxidation have been suggested to enhance corrosion resistance. Other safer alternative approaches like coating the surface with polymers (e.g., PU, PTFE) and electroplating have been used. However, due to the “banana skin” or coating–peeling phenomenon, the in vivo reactions should be carefully monitored.\textsuperscript{[132]}

Although the material system is a determining factor for better biodurability in metallic parts, design optimization has been reported to improve durability. Topology optimization by generating distinct cell geometries for Nitinol stent design improved fatigue life by controlling the changing strain arising from pulsating blood pressure and radial supportive force to enhance the efficiency of the aortic SG for AAA treatment.\textsuperscript{[138]} According to parametric analysis,\textsuperscript{[136]} the proposed stress concentration-free lattice displayed superior anchoring performance and reduced risk of fatigue failure compared to present stent designs.

Mechanical reinforcement of critical regions is also useful. A novel fabric design with reinforced zones was proposed to enhance durability,\textsuperscript{[137]} prevent fabric abrasion, and thus reduce the occurrence of endoleaks (Types III and V), which had not been eliminated with even the M-shaped stent reconfiguration before. The reinforcement area was considered at the proximity of the sharp apices (Z-shaped stents) and the area between two adjacent hoops where folding and creasing are dominant. Improved mechanical behavior (e.g., tensile and bursting stress) and fatigue resistance were achieved for the fabrics with locally reinforced zones compared to the commercial plain weaves.

Fabric structure can also be an essential factor in enhanced biodurability, where yarn organization might lead to rapid deterioration and the eventual demise of the graft integrity. For example, monofilament yarns can rapidly fail, while multifilament yarns are less prone to damage.\textsuperscript{[70]}

Potential Stent-Graft Failure Conditions:

a) Creep failure

Although it has not been studied in detail in aortic SGs, creep failure is common to many implanted medical devices over the long term. Creep is the material deformation due to permanent stress that might lead to a collapse if not controlled. One possible explanation is when degradation starts in vivo, physical aging and hydrolysis simultaneously weaken the SG leading to creep resistance.

Once the SG is implanted, it should be designed in a way to avoid creep failure. The SG must have enough radial strength to counteract vessel elastic recoil and the cyclic load from pulse pressure. Otherwise, vessel patency may be compromised, and sealing may be lost, bringing potential complications like migration, compliance mismatch, and thrombosis or vessel rupture. In the long term, degradation would eventually cause the SG to break apart, and device by-products may enter the bloodstream. Therefore, parts must exhibit sufficient creep resistance during degradation, not only to reduce gradual device recoil but also to avoid clinical risk to patient health. Fatigue failure is also possible in post-creep failures in biodegraded materials.\textsuperscript{[138]}

Some of the commercial SGs passed the in vitro creeping test.\textsuperscript{[139]} This test evaluates the long-term durability of the graft attachment to the stent (and stent to the graft); the device must withstand a transient hypertensive physiological, clinical pressure of 320 mmHg after the equivalent of 10 years while maintaining a load equivalent to a physiologic clinical pressure of 110 mmHg.

b) Stress Corrosion Cracking

Any implanted material needs to have adequate resistance to cracking or fracture in vivo. The most important mechanism for implants to lose their functionality is stress corrosion cracking. Although it is not explored in detail, one of the likely failure modes for SG is stress corrosion cracking, which occurs due to the combined influence of tensile stress and a corrosive environment (i.e., a biological environment rich in chlorides).

As discussed in detail, corrosion processes from electrolytic behavior release ions.\textsuperscript{[131,140]} Corrosion is the likely result of the ions reacting electrochemically with the surface of the metallic biomaterial, which may cause inflammation, tissue deterioration, and weakening in the mechanical properties of the device.\textsuperscript{[106,141]} On top of that, stents are exposed to stresses due to contact with graft or blood vessel (depending on the SG design), the blood flow, and pressure applied for stent expansion.\textsuperscript{[142,143]} The occurrence of these two simultaneously increases the chance of stress corrosion cracking phenomenon.

Among the practical solutions, surface modifications such as superhydrophobic surface coating\textsuperscript{[144,145]} or optimizing water repellence and biomimetic techniques\textsuperscript{[146,147]} may enhance corrosion resistance.

3.6.2. Biocompatibility

Failure Modes: Fabric microarchitecture can change the overall biocompatibility of the SG by avoiding cellular interactions. In one of the retrieved clinical SG cases, intracellular communication through the graft wall (between the internal and external capsules) was observed not to happen through the woven structures with monofilament yarns.\textsuperscript{[158]}

Corrosion of metallic sections can be attributed to biological factors, which then negatively influence the in vivo stability of the entire device. Due to the inflammatory cells releasing oxidative factors, like free radicals, hydroperoxides, and reactive oxygen species, environmental stress cracking (i.e., material degradation) might accelerate in vivo.\textsuperscript{[60,135]} It was observed that although there was no detectable endothelialization on the luminal side of the SG, inflammatory cells were abundant, even for four years after deployment, a sign of persistent, acute inflammation.\textsuperscript{[135]}

Although luminal narrowing due to the accumulation of fibrous and cellular substances on the surface of the SG has not been widely reported in the aorta (large vessels), a different reaction was observed with smaller arteries. Adverse reaction to the host artery due to poor biocompatibility is reported with small-sized SGs, making the patency the primary concern. For instance, occlusion of small arteries with severe inflammatory reactions was observed in the swine model with synthetic polymers like PU and PET. The local toxic reactions pertinent to the material residues left from the production stage (such as heavy metals, oligomers, antioxidants, nitrogen-containing aromatic compounds) are believed to be the possible reasons.\textsuperscript{[149]}

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\textsuperscript{[132]} Surface modifications such as mechanical and electropolishing, sandblasting, chemical etching, and oxidation have been suggested to enhance corrosion resistance. Other safer alternative approaches like coating the surface with polymers (e.g., PU, PTFE) and electroplating have been used. However, due to the “banana skin” or coating–peeling phenomenon, the in vivo reactions should be carefully monitored.

\textsuperscript{[137]} Although it has not been studied in detail in aortic SGs, creep failure is common to many implanted medical devices over the long term. Creep is the material deformation due to permanent stress that might lead to a collapse if not controlled. One possible explanation is when degradation starts in vivo, physical aging and hydrolysis simultaneously weaken the SG leading to creep resistance.

\textsuperscript{[138]} Some of the commercial SGs passed the in vitro creeping test. This test evaluates the long-term durability of the graft attachment to the stent (and stent to the graft); the device must withstand a transient hypertensive physiological, clinical pressure of 320 mmHg after the equivalent of 10 years while maintaining a load equivalent to a physiologic clinical pressure of 110 mmHg.

\textsuperscript{[139]} Although luminal narrowing due to the accumulation of fibrous and cellular substances on the surface of the SG has not been widely reported in the aorta (large vessels), a different reaction was observed with smaller arteries. Adverse reaction to the host artery due to poor biocompatibility is reported with small-sized SGs, making the patency the primary concern. For instance, occlusion of small arteries with severe inflammatory reactions was observed in the swine model with synthetic polymers like PU and PET. The local toxic reactions pertinent to the material residues left from the production stage (such as heavy metals, oligomers, antioxidants, nitrogen-containing aromatic compounds) are believed to be the possible reasons.
Commentary: The biocompatibility of the sealing zone can be improved through an appropriate design of the fabric structures. For instance, woven architecture with multiflament yarns provides slight encapsulation, and knitted structures promote tissue encroachment. Moreover, the optimization of graft porosity can improve the endothelialization of the graft’s luminal side. The concept of biological sealing where endothelialization will reduce adverse outcomes from graft blood interactions is now believed to be critical in avoiding late luminal thrombus formation.

The chemical nature of the graft and stent surface plays a significant role in regulating cell–material interactions to promote biocompatibility. Postsurface treatment is considered for stent corrosion, while the common practice for the graft surface is to precoat it with the desired protein (e.g., collagen, fibronectin, and laminin) or blend the protein within the polymer matrix. In addition, angiogenic growth factors can augment graft surface biochemistry by accelerating endothelialization. Biomimicry (e.g., coating the surface with phospholipids that mimic cell membranes) may also diminish the intensity of the foreign body reaction leading to improved biocompatibility.

Biocompatibility can also be improved through surface modification by adjusting the shear stress at the endoluminal surface of the device from blood flow which creates healthy neointima and reduces the risk of atherosclerosis. Surface functionality will be distorted when the shear stress is larger than the adhesion strength of endothelial cells, resulting in a prothrombotic surface. Moreover, developing graft architectures with a blood-compatible interface is essential, through which the surface design should encourage the creation of an endothelium monolayer, which then reduces thrombus development. The monolayer of stable endothelial cells in the intima produces anticoagulant factors to stop further thrombus formation. As such, generating polymeric structures that replicate the nano-to-micrometer scale of the extracellular matrix (ECM) is a proven method for modulating the behavior of adherent cells. Thus, substrate topography (i.e., porous surface) is a crucial regulator of many critical endothelial cell behaviors, including adhesion, migration, proliferation, and gene expression during in vitro culture. Among all established fabrication techniques, the fibrous nature of electrospun scaffolds more closely resembles the cell’s native environment of the ECM. However, the current texture design has not advanced for decades, either in woven or nonwoven approaches. This may be due to the use of traditional fabrication methods that cannot manufacture sophisticated design structures.

3.6.3. Biofunctionality

Failure Modes: Various failure patterns due to poor functionality have been reported. The repetitive movement between the apex of a stiff, immobile stent and the overlying soft mobile graft material erodes the softer component. Thus, ensuring the simultaneous movement of the stent and graft as a single unit is an essential step to creating a flexible SG. According to a comparative analysis of different design functionality, Z-stents showed a considerably lower endurance limit to buckling in the fatigue test. The contact between the apexes of adjacent hoops led to fabric damage. Conversely, ringed stents did not cause any significant fraying in the polymer fabric, making this a favorable choice for complex cases reducing the likelihood of tears and holes. However, an increased risk of thrombosis secondary to fabric creasing and consequent turbulence is yet to be fully understood with ringed designs.

Compliance is one of the complex issues connected to the poor SG flexibility to conform to the complicated anatomy that often involves calcified, tortuous, or narrow-access vessels, insufficient landing zones, high neck angulation, or the presence of thrombus. Theoretically, the reduction in compliance affects blood flow patterns and von Mises stress in the arterial wall, which triggers arterial dysfunction and pathophysiology such as neointimal hyperplasia. Explanted SG analyses showed that a layer of pseudointima covered most of the internal surface of the early SGs. However, in kinked areas, the covering could be thin or broken, revealing bare stent wires and the outer polyester textile, which might be the cause of late occlusion. Most importantly, the potential risk of “bird beaking” (i.e., the malformed placement of the proximal SG where a wedge-shaped gap forms between the device and the wall) is high due to compliance mismatches in regions like the aortic arch.

Design variation in the SG microstructure might negatively impact flexibility. The relationship between SG architecture and flexibility was studied by measuring bending and spring-back forces to see why current stent shapes exhibit weak stability, sealing, and delivery precision. Structural factors like energy loss due to the inter-fiber friction, stress–strain fiber behavior, and Nitinol stent deformation were observed to affect flexibility. Moreover, continued twisting and bending of SGs in angulated regions contribute to a loss of friction in the landing zone, thus losing the proper sealing. Twisting may further change the length of the entire device, while bending is likely to cause fabric tears or stent breakage. Altogether, the stented region may elongate in an angulated aorta, where modular SGs can get disconnected, causing Type III endoleak. This is influenced by high intersegmental slipping coefficients where the SG components do not have much overlap.

Commentary: SGs should improve the patient’s life expectancy by mimicking the aorta’s mechanical and biological properties to withstand the dynamic environment. However, current devices cannot adjust their structure and functionality to respond to the environment. Ideally, the structure should exhibit functional in vivo flexibility to curtail flow resistance and pressure drops while maintaining an adequate seal with the host artery.

Advantageous neck anatomy and technically accurate deployment within the target zone are key initial sealing requirements, signs of successful design-wise biofunctionality, which provides a permanent circumferential barrier to any leakage into the aneurysm sac. The technical success comes with proper SG oversizing and optimized stent radial force. Although the amount of adequate oversizing is typically calculated on vessel diameter only, diseased vessel wall due to the presence of heterogeneous tissue in the landing zone means that radial force is a sophisticated element to be determined precisely per patient. This gets more prominent, especially in the presence of thrombus and calcification, where poor radial force can lead to neck...
dilatation over time, causing early migration and, if untreated, late endoleak.

We no longer consider columnar bars in commercial SGs architectures, while enhanced columnar stiffness provides sufficient resistance to longitudinal displacement and better positing the SG. Columnar stiffness is currently adjusted through correct stent spacing and fabric stiffness.

Intercomponent sealing in areas of overlap is another essential sealing element acquired by proper friction, radial force, and sufficient surface contact. Correct tapered designs/ratios (e.g., tapered or reverse tapered SG) are fundamental to successful sealing in treating conditions such as aortic dissection where diameter varies to avoid potential migration scenarios. In vivo flexibility is a broad term that can solve compliance concerns. Providing close compliance to the native artery is a challenging task, in which current technology is unlikely to resolve the problem. Current solutions include antiproliferative drugs incorporated into the device (to limit the chance of overproliferation of the smooth muscle cells resulting in narrowing of the luminal area) and further research into layered structures that mimic the native vessel. In a recent attempt to improve the flexibility through stent design modification, the optimal flexibility was obtained with a Z-type strut structure with long stent spacing and a large stent apex angle (fewer struts per hoop), mainly due to lower force with the same number of struts per hoop. Z-stent grafts could help reduce rigidity, unlike M-stented grafts, because of the higher number of continuous fabrics in Z-stented grafts with the same number of struts per hoop. Material change might also help control compliance. For instance, PET and PU grafts exhibited a 15-fold increase in compliance however, despite promising results in the compliance-matched regions, restenosis was observed elsewhere. Thus, optimum compliance is complicated and is further compounded by varying blood pressures in different patients.

4. Next-Generation Stent-grafts

Although many commercial devices have been developed in recent years to limit the complications, unfortunately, functionality is still hard to achieve with the conventional approaches. Hopefully, recent technological advancements support the growth of next-generation SGs, shedding light on the treatment of sophisticated aortic diseases for all patients. As such, scientists in this area should obtain comprehensive multidisciplinary knowledge to create practical endovascular implants.

4.1. Functional Design Approaches

4.1.1. Origami

Origami, the art of paper folding, is an inclusive term for all folding practices. With recent advances in shape-changing architectures, origami has found its way to medical device design and can be applied to SG architectures to achieve low insertion profiles. One of the exciting aspects of the folding pattern is that it causes the SG to fold and deploy both longitudinally and radially, ensuring enhanced flexibility. In 2006, a cylindrical tube was divided into a series of identical elements with “hills and valleys” to act like hinges capable of longitudinal and radial manipulation. The developed SG was made of a Ni-rich TiNi shape memory alloy implantable in body temperature where the crimped origami shape could be triggered through thermoregulation and superplasticity. Following a similar approach, the first practical origami SG was developed in 2012 having a foldable sutureless self-expanding SG comprised of a polymer nanocomposite (polyethylene oligomeric silsesquioxane–poyl(carbonate-urea) urethane) and Nitinol stent. The fabricated SG showed superior properties like compliance, viscoelasticity, antithrombogenicity, and MRI compatibility. However, this design lacked significant improvements in architecture and fabrication processes despite using the origami approach since the structure did not comply with the severely cramped deployment condition.

4.1.2. Biomimicry and Bioinspiration

Biomimicry means using naturally occurring principles (e.g., the movement of sea creatures) to solve human design challenges and has achieved success in the creation of advanced medical devices. For instance, bioinspired medical device designs have shown great potential in soft robotics, for example, octopus’ tentacle, elephant trunk, squid tentacle, snake movement kinetics, and even designing biomedical polymeric systems from the footpads of a gecko. Recently, an artificial tissue construct was developed from dissociated rat tissue (i.e., neonatal rat ventricular cardiomyocyte) and silicon polymer to mimic the swimming behavior of jellyfish, with potential applications in the development of cardiovascular and muscular pumps as well as cardiac pacemakers. Inspired by the nepenthes pitcher plant, a slippery, liquid-infused, porous surface was proposed to address vascular clotting issues on devices. The developed nonadhesive, antithrombogenic interface stopped thrombogenesis for up to more than eight hours when implanted in pigs. In the context of SGs, inspired by the caterpillar cuticle, a novel hydrokeleton SG design with promising biomechanical properties was developed in 2014. The design was based on structural segmentation with the aim of controlling device migration. The improved levels of structural distensibility had optimized features such as volumetric compliance, radial compliance, Petzner elastic modulus, and stiffness index. The proposed SG design better matched the native aortic biomechanics and significantly surpassed the performance characteristics of a commercial Z-type SG.

4.2. Smart Materials for Endovascular Applications

Smart materials, also called intelligent or responsive materials, inherit the potential for versatility in behavior and may enable significant progress in the next-generation SG. These materials are designed to have one or more properties that can be transformed in a controlled manner by external stimuli like stress, moisture, electric or magnetic fields, light, temperature, pH, or chemical compounds. These transformations could be reversible and repeatable, which opens new avenues to designing smarter devices.
As a type of smart material, shape-memory materials (SMMs) have the potential to be transformed and fixed in a temporary shape, from which they recover their original shape if subjected to an appropriate stimulus (e.g., heat, light, pH, etc.). The shape change process happens by preprogramming the shape via mechanical deformation to fix the temporary shape. Since shape memory can be defined from a combination of material morphology and specific processing, it is possible in SMMs to have the cycle of programming and recovery in a repetitive manner, with different temporary shapes in subsequent cycles.

Compared to shape memory alloys or ceramics, shape memory polymers (SMPs) offer superior properties like greater recoverable strain (up to 400%), lower density, easy processing and fabrication techniques, more straightforward adjustment of material treatment properties (e.g., transition temperature, biocompatibility, biodegradability, stiffness, functional gradient), programmability and controllability of recovery behavior, low-price, and flexibility.

According to the literature, there has been an ongoing effort to employ the benefits of SMPs in cardiovascular implants. For instance, a laser-activated SMP was developed with a unique combination for endovascular treatment of ischemic stroke and cerebrovascular aneurysms (e.g., thrombus removal). The optical fibers were embedded into thermoset PU, which could sense optical energy by specific wavelength, triggering the shape memory effect via gradual heating.

Acrylate systems also have attracted attention due to their ability to undergo facile chain-wise or stepwise polymerization

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**Figure 6.** Potential design approaches for the production of next-generation SGs. a) Metallic origami SG, TiNi foil SG; b) Origami SG with a novel polymer material. (i, ii) fully expanded shape and modified design with less hostile behavior; c) Bioinspired design of monarch caterpillar. (i) Segmental construction of cuticle based on the spring-mass model (longitudinal stiffness constants are represented via $k_{td}$, $k_{tv}$, and $k_{av}$ which are dorsal abdominal, dorsal thoracic, ventral thoracic, and ventral abdominal spring factors, respectively); (ii, iii) structural geometry of produced SGs with and without PU graft covering. Reproduced with permission. Copyright 2014, Elsevier Ltd.
reactions, primarily because of their “click” nature. The dual-curing processes give distinct and temporarily stable sets of properties at each curing stage, upon which promising procedural functionality can be achieved. A dual-cure shape-memory polymer system was created based on nonstoichiometric thiol–acrylate systems with a set of initial thermomechanical properties ($T_c = 33{ }^\circ C$, a modulus of 20 MPa) favorable for facile programming of shape change for medical device implantation. The second stage activation of the curing process, post-implantation, yielded another set of properties ($T_g = 38{ }^\circ C$, a modulus of 1500 MPa) desirable to acquire functionality in a longer period of the device in vivo.[185]

SMPs have been processed using electrospinning to make smart cardiovascular grafts. It was demonstrated that the electrospun nonwoven shape memory PU (SMPU) nanofibers could be triggered by temperature, and the shape recovery was 98% after several cycles.[186] SMPU microfibers also showed a much quicker shape recovery compared to bulk SMPUs.[187] Fibrous membranes with adaptive reactions to external stimuli to cope with complex in vivo alterations are highly beneficial for biomedical applications. The size change of nanopores/micropores in SMPU membranes ranged from 150 to 440 nm by electrospinning with a two-way shape memory effect based on temperature stimulation.[188] However, one of the most significant investigations showing the versatility of electrospun SMP grafts was the development of a device for controlled peripheral nerve regeneration that aimed to simplify the challenging surgery process.[189] (Figure 7a). A trisegment smart nerve conduit was fabricated from a PLGA copolymer system by electrospinning with specific properties (e.g., tailorable glass transition, tunable body-water responsive shape-recovery behavior, and suitability for electrospinning). As illustrated in Figure 7a, the device gradually recovered during an in vitro experiment under stimulated physiological conditions.

Reversible shape changing with the multishape definition is an attractive feature of electrospun membranes. This is possible by enriching novel shape memory fibrous composites with functional fillers like Nafion or synthesizing the polymer with special groups.[190,191] The incorporation of Fe$_2$O$_3$ (i.e., Iron (II, III) Oxide) into cross-linked cPLC as the matrix and multiwalled carbon nanotubes as the reinforced filler resulted in composite fibers with the ability to be stimulated by both hot water and magnetic field alteration, a promising approach for noncontact actuation in biomedical devices.[191] (Figure 7b). In another work, a special polymeric device was developed by imprinting covalently cross-linked PCL fibrous meshes with a reversible bidirectional SMP actuation (Figure 7c). This system showed a tendency to repeat the changing behavior between two different programmable shapes under stress-free conditions when triggered by an external stimulus (i.e., heat), leading to porosity alterations.[192]

Finally, acquiring optical features alongside shape memory behavior is also possible. An electrospun near infrared-emitting shape memory web was developed by incorporating poly(vinyl acetate) polymer with indocyanine green[193] (Figure 7d). Combining contrast agents in this manner could enable in vivo visualization, which would have great potential in internal suturing, sensors, feeding tubes, and catheters. It could also be used in next-generation SGs to facilitate long-term monitoring of treated patients.

### 4.3. Additive Manufacturing

To overcome current challenges facing SG performance in vivo, progress in materials and design is needed, and this may not occur until there is a shift towards newer fabrication techniques like additive manufacturing (AM). Fabrication of physical 3D models is an established cardiovascular AM application that can help diagnose, plan and develop optimized management and interventional procedures.[194] Cardiovascular implants at the research scale have been pursued using different AM technologies like fused deposition modeling (FDM) but currently lack real application through minimally invasive surgery. Further, due to the inherent limitation of the method, it is not feasible to print organized micrometric polymeric fibers through traditional extrusion-based AM techniques.

Melt electrowriting (MEW) is a hybrid technology that emerged from integrating electrospinning technology with AM principles to enable the ejection of a stable molten electrified jet which is collected in a layer-by-layer manner[195,196] (Figure 8a). The controlled deposition with micrometric fibers through high voltage implementation enables the exquisite tuning of architecture to print biomimetic constructs and soft network composites with a very high surface to volume ratio, unlike the random fiber deposition obtained through electrospinning.[196]

Most importantly, MEW avoids any cytotoxicity-related complications associated with the presence of residual solvents, common in solution electrospinning technology.[197] MEW also makes it possible to translate sophisticated biomimetic architectures into physically printed fibrous networks, unlike other fiber fabrication approaches like solution electrospinning, weaving, knitting, and braiding.[198] Through controlling the process parameters like fiber winding angle, rotational velocity, and collector diameter, tubular MEW structures were printed with different morphologies.[199,200] A well-defined mathematical model was developed[201] considering the effective parameters like fiber placement, spacing, stacking, cylinder diameter and length, and winding angle to continuously direct-write porous tubular MEW structures onto a cylinder collector with varying porosity sizes and pivot points (Figure 8a). The change in the morphology showed a direct impact on the overall scaffold strength based on the mechanical analysis. The expansion of the range of processable materials suited for MEW[202] the addition of labeling agents compatible with clinically accepted methods of visualization upon implantation[203] and the improvement of the MEW systems will eventually produce innovative medical devices and implants with precise architectures.[204]

MEW has shown great potential for cardiac patch generation with well-ordered, hexagonal microstructures to support high tensile strains when placed on a contracting heart achieved through minimally invasive delivery[205] (Figure 8b). Furthermore, to enhance the mechanical and biological properties of the construct, this technique was also combined with extrusion-based bioprinting,[206] where cell-loaded hydrogels and aligned fine fibers were deposited within a single-step fabrication process in a spatially arranged manner (Figure 8c). The developed hybrid approach has brought promising improvement for the manufacture of complex hierarchical structures with better biomimetic properties close to functional native tissues. Recently, the applications of the MEW scaffolds have been further increased for
Figure 7. Smart materials to produce next-generation SGs. a) Smart nerve conduit (SNC). (i) Process of shape memory function for nerve treatment based on different $T_g$.\textsuperscript{[189]} (ii) permanent shape at room temperature and the temporary shape of the SNC at 20 °C.\textsuperscript{[189]} (iii) diagram for recovery rate to the recovery time of SNC.\textsuperscript{[189]} Reproduced with permission.\textsuperscript{[189]} Copyright 2016, Wiley-VCH GmbH; b) Images of the shape memory recovery process of the cPCL/Fe$_3$O$_4$@CD-M composite nanofibers in 46 °C water (top) and an alternating magnetic field with a frequency of 20 kHz and field strength of 6.8 kA m$^{-1}$ (bottom).\textsuperscript{[191]} Reproduced with permission.\textsuperscript{[191]} Copyright 2012, Elsevier Ltd.; c-i) sequential heating (bottom) and cooling (top) of a twisted electrospun specimen between 60 to 10 °C temperatures (scale bar: 2 cm).\textsuperscript{[192]} (ii) comparative assessment of pore diameter through SEM images of the cPCL after cooling and heating (scale bar: 20 μm).\textsuperscript{[192]} Reproduced with permission.\textsuperscript{[192]} Copyright 2019, IOP Publishing Ltd.; d) Evaluation of the PVAc fibrous webs.\textsuperscript{[193]} (i) Small circular sections were cut from a halo specimen, and recovery was observed for both water actuation at 25 °C and heating at 50 °C.\textsuperscript{[193]} (ii) NIRF performance of the fabricated specimen with an exposure time of 140 ms and the gain of 1.0 (ICG concentration: 0.0125 mg mL$^{-1}$, scale bar:10 mm).\textsuperscript{[193]} Reproduced with permission.\textsuperscript{[193]} Copyright 2014, Elsevier Ltd.
4.3.1. The Potential of 4D-Printing Technology for Stent-Graft Fabrication

Medical devices with flexible or even dynamic structures might open the next chapter for the future generation of aortic endoprostheses. Medical implants with morphing features can be created through 4D-printing technology, enabling future SGs to respond to the in vivo environment. The 4D-printing process enables innovative and fascinating applications that cannot be achieved with conventional manufacturing techniques.

In 4D printing, an additively manufactured object can transform itself into another structure due to the influence of external energy input (e.g., temperature, light, stress, and others). 4D printing has become a vibrant research area that combines manufacturing, materials science, and mechanics,[208–210] and current technology allows objects to change shape, directly off the print bed, to predefined target shape over time.[211] This technique offers a streamlined path from idea to reality with performance-driven functionality built directly into the materials. Therefore, features like self-assembly, multi-functionality, self-repair, time and machine dependency, and predictability can be tailored accordingly. Although it is still an emerging area of research in itself, 4D-printing has already been applied to tubular structures and blood vessels, whereby a porous self-folding tubular structure was 4D-printed[212] with encapsulated growth factors that were released in vivo by thermoregulation (Figure 8e). To improve and maximize the potential applications of the 4D-printing process, significant multidisciplinary research is required over the coming years.

4.4. Real-Time Monitoring

Embedding advanced optical properties could enable real-time diagnostics leading to the detection of endovascular implant deficits early. The integration of biosensors with SGs can provide remote monitoring of device performance and detection of internal changes, such as pH control, flow and pressure. Microelectromechanical system (MEMS) technology facilitates the fabrication of sensors for SGs. Following this concept, an implantable endovascular stent-electrode, “stentrode,” was developed in 2016, capable of recording intracranial neural activity[214] (Figure 9a). The stentrode was delivered successfully via catheter angiography, showed a successful self-expanding ability, and recorded vascular electrocorticography in animal models through wire-based connection. Following the trend, a remote self-monitoring graft system was made to diagnose hemodynamic changes through wireless data transmission capable of capturing signals within soft tissue under biologic conditions.[215] However, vascular implants with self-powering capability or battery-free sensing have recently revolutionized this concept to use a reliable infinite energy source, where polymer-based piezoelectric nanogenerators can convert the biomechanical energy in the human body into useful electricity.[216] A ferroelectric artificial conduit has been made to provide a battery-free real-time monitoring capability.[217]

A vascular conduit with in situ poled ferroelectric biocomposite (a blend of polyvinylidene difluoride polymer matrix and KNN (K0.5Na0.5NbO3) particles) has been printed using electric field-assisted FDM technology and showed a high piezoelectric response and superior pressure sensibility to occlusion monitoring (Figure 9b).

However, unlike most traditional electronic devices, sensors and electronic materials should have limited time frames in vivo. This is to avoid adverse effects from long-term implantation of foreign material or the need for surgical intervention. The emergence of biodegradable electronic materials allows engineers to generate safer medical implants. A biodegradable electronic implant has the potential to feature a predefined stable operation before it reaches a rate of degradation at which the functionality is lost in vivo. Promising features on the horizon include diagnostic or therapeutic functions, implantable pH sensors,[218] pressure sensors,[219] and electrocorticographic sensors.[220] An example of a smart biodegradable stent with integrated diagnostic and therapeutic capabilities was recently described.[221] They created a bioresorbable magnesium alloy electronic stent coated with polyactic acid (PLA) film, where the conductive metal enabled wireless transmission of data, and the coating made controlled drug release possible. Furthermore, the stent was integrated with a blood flow sensor, a temperature sensor and an antiproliferative drug stored in a nanoparticle shell. This is an excellent example of what may be possible in the future for mainstream SGs.
Figure 9. a) Real-time monitoring of brain activity through an intracranial stent-electrode array. (i) Process of stentrode deployment from a 4F catheter (green arrow), coming with $8 \times 750 \mu m$ electrode discs (yellow arrow) (scale bar: 3 mm).\cite{214} (ii) Schematic of endovascular stent-electrode array implanted in an animal case. Created with Biorender.com; (iii) Location of implanted stentrode in various animal models (red: limb motor, yellow: sensory areas, scale bar: 2 cm) and the corresponding 3D illustration of the electrodes within the environment (scale bar: 3 mm) as well as peak to peak amplitude recording (scale bars: 30 ms and 50 $\mu$m).\cite{214} (iv) Preimplantation_Left image: junction of sinuses and superior sagittal sinus (SSS) (blue arrows), imaged from a lateral projection cerebral venography roadmap of external jugular vein (scale bar: 20 mm); Pre-implantation_Right image: superior projection of SSS where blue arrows show the lumen diameter and cortical veins are pointed with the red arrow (scale bar: 10 mm). Postimplantation_Left image: lateral projection of stentrode in place in SSS where the electrode is shown with yellow arrow and the delivery catheter is pointed with green arrows (scale bar: 10 mm); Postimplantation_Right image: contrast study of stentrode in a superior projection where the electrode is pointed with a yellow arrow (scale bar: 10 mm).\cite{214} Reproduced with permission. Copyright 2016, Springer Nature; b) Battery-free real-time sensing conduit. (i) Electric-field assisted 3D printing process and final tubular conduit;\cite{217} (ii) Electric-field assisted 3D printing process and final tubular conduit;\cite{217} (ii) Illustration of the piezoelectric effect in the artery in response to blood pressure and partial occlusion (0%–80%) of the artery system through PDMS-simulated thrombosis;\cite{217} (iii) Peak to peak voltage change (top) as a function of artery blockage (data were expressed as mean ± SD (n = 3)), comparison of detailed single voltage envelope under different levels of occlusion (bottom).\cite{217} Reproduced with permission. Copyright 2020, John Wiley & Sons, Inc.
Material selection, however, is limited. Because the SG components are cramped and expanded during the deployment process, there is a risk of mechanical failure. Moreover, SGs are permanent prosthetics, so biocompatibility is a major consideration (i.e., resistance to chemical and biological reactions). Functionality must be maintained after degradation, even if by native tissues. Such a device may represent a paradigm shift in how we think of (and design) SGs for aortic repair, where autodiagnostic feedback would be combined with shape change through 4D-printing technology and controlled degradation of the components. As such, all devices would have in-built early warning systems with real-time feedback to a mobile phone, for example, when expedient intervention can be performed to reduce patient risk from what is commonly an asymptomatic device failure. As well as saving lives and limbs, this would change the face of long-term endovascular device surveillance from one of life-long screening to one of remote automonitoring and focused intervention.

5. Conclusion

Endovascular aortic repair began with the treatment of abdominal aortic aneurysm but rapidly evolved to the entire aorta. However, despite the advantages of this technique, it has complications and challenges that are still not fully understood. Device complications jeopardize patient outcomes, and as such, more engineering assessment is required to fully understand the current limitations and design solutions to create the next generation device.

The ideal SG has yet to be constructed. However, the optimum SG should be biocompatible, nontoxic, and noncarcinogenic, have a stable configuration, and be flexible, conformable, and durable. Materials for SGs should be resistant to wear, fatigue, and corrosion, be ductile and tough, and have optimal graft porosity. Devices must also be versatile enough to address complex anatomic intricacies while being compatible with standard angiographic techniques. Looking ahead, it is likely we will see more use of hybrid smart materials capable of controlled responses combined with real-time monitoring capabilities via biosensors. Based on current evidence, it is possible that future SGs will overcome established complications from existing designs by activating interconnected biological and mechanical dynamic elements, so the device can fully integrate into the body enabling the device to sense, respond and adapt to the changing environment. Functional structures within the SG could effectively seal and heal aortic pathologies such as aortic dissections and then degrade based on a controlled degradation profile. For instance, 4D-printed devices could have an adaptive radial response to hemodynamic changes or even a changing pore size with accompanying drug release to avoid thrombogenesis. The possibilities are endless and exciting.

Here we aimed to provide a holistic interrogation of SGs and device-related deficits so one can understand why traditional approaches have not been enough to reach the next level in SG design and development. Future perspective is bright as many inspiring new techniques are converging in the space; however, the route forward for commercialization is lengthy and not straightforward, especially when considering devices that can acquire data and even be manipulated in vivo by external stimuli. Nevertheless, with the intertwined and rapid advancements underway in materials, manufacturing and medical device design, the merging of these fields is leading to new devices that would not have been thought possible some years ago; opening up the possibility of developing the next generation of SG that can overcome the current problems with these life-saving devices.

Acknowledgements

Australian Government Research Training Program Ph.D. Scholarship from The University of Western Australia is gratefully acknowledged.

Open access publishing facilitated by The University of Western Australia, as part of the Wiley - The University of Western Australia agreement via the Council of Australian University Librarians. After initial online publication, the name spelling of author E.D.-J.-P. was corrected on July 6, 2022, due to a previous error. The affiliation order of E.D.-J.-P. was also corrected so that “T3mPLATE Harry Perkins Institute of Medical Research” is her second affiliation, and “School of Mechanical, Medical and Process Engineering, Queensland University of Technology” is her third affiliation. The editorial office apologizes for any inconvenience caused.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

4D printing, complications, endovascular treatment, smart materials, stent-grafts

Received: February 3, 2022
Revised: April 4, 2022
Published online: May 16, 2022

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