Challenges to the development of the next generation of self-reporting cardiovascular implantable medical devices.

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(Clinical Application Review)

***Abstract* - Cardiovascular disease (CVD) is a group of heart and vasculature conditions which are the leading form of mortality worldwide. Blood vessels can become narrowed, restricting blood flow, and drive the majority of hearts attacks and strokes. Reactive surgical interventions are frequently required; including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Despite successful opening of vessels and restoration of blood flow, often in-stent restenosis (ISR) and graft failure can still occur, resulting in subsequent patient morbidity and mortality.**

A new generation of cardiovascular implants that have sensors and real-time monitoring capabilities are being developed to combat ISR and graft failure. Self-reporting stent/graft technology could enable precision medicine-based and predictive healthcare by detecting the earliest features of disease, even before symptoms occur. Bringing an implantable medical device with wireless electronic sensing capabilities to market is complex and often obstructive undertaking.

This critical review analyses the obstacles that need to be overcome for self-reporting stents/grafts to be developed and provide a precision-medicine based healthcare for cardiovascular patients. Here we assess the latest research and technological advancement in the field, the current devices; including smart cardiovascular implantable biosensors and associated wireless data and power transfer solutions. We include an evaluation of device that have reach clinical trials and the market potential for their end-user implementation.

***Index Terms*—Biosensor, Cardiovascular, graft, impedance, implantable medical devices, smart, stent, Precision Medicine.**

I. Introduction

A. Cardiovascular Disease - In-Stent Restenosis and Graft Failure

Cardiovascular disease (CVD) remains the leading form of mortality worldwide that will affect 1 in 3 of us[1]. CVDs preferentially affect Western Europe, North America, Australia, New Zealand and increasingly China with less than 10% afflicting sub-Saharan Africa, rural India and South America[2] CVDs costs the EU economy €210 billion per annum according to the European Heart Network [3]. Atherosclerosis is a progressive form of CVD characterised by silent development of intimal fatty plaques caused by the proliferation of vascular smooth muscle cells (VSMC), and an influx of inflammatory cells and proteins [4]. This results in narrowing of blood vessels and restriction of blood flow, driving the majority of hearts attacks and strokes. Narrowing of vessels in the heart often requires surgical intervention including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Despite successful opening of vessels and restoration of blood flow, often a wound response termed in-stent restenosis (ISR) occurs requiring repeat interventions. Peripheral vascular diseases such as chronic kidney disease affects 10% of the global population (CKD), 2 Million patients alone in the USA require frequent renal dialysis that damages sections of conduit vessels. Indeed, CKD account for 1% patient's yet consume 5% ($64 Billion) of the Medicare budget. These can be replaced with synthetic expanded polytetrafluroethylene (ePTFE) grafts but where these sections join the native artery and vein a similar ISR wound response occurs. This results in vessel occlusion, thrombosis and costly patient complications associated with increased morbidity and mortality. In contrast PCI uses a tubular mesh called a stent on a balloon catheter which is guided through a peripheral vessel to the site of the blockage or narrowed artery. The balloon is inflated at the lesion site and the stent expanded reopening the vessel and remains permanently *in situ* after the guide catheter is withdrawn. Stents can be classified into coronary, peripheral (carotid, iliac, femoral, retinal), and neurovascular [5]. ISR occurs as a result of cell overgrowth within or around the stent by disruption to the endothelial monolayer and vascular smooth muscle cell (VSMC) hyperplasia. As a result, the luminal area is re-blocked partially or fully within the first six months after surgery. To diagnose ISR it can be costly with in-patient coronary angiography or intravascular ultrasound [6].

CABG procedures utilises arteries or veins, often from the left internal mammary (thoracic) artery and/or the greater saphenous vein, and uses them as grafts to bypass blocked arteries [7]. Graft failure also manifests from VSMC migration from the muscle wall layer of the vessel into the graft lumen due to mechanical disruption at the site of anastomosis (joining) and the new haemodynamic blood pressure environment. This results in thrombosis and progressively leads to neo-atherosclerotic plaque formation requiring surgical re-intervention [8]. Early reports from 1990's suggested that stent

failure due to ISR occurred in 15-20% of stent placements within 6-12-month post implantation[9] To reduce ISR, stents made of stainless steel and cobalt chromium were developed as a bare metal stent (BMS) option. This evolved to prevent restenosis but ISR continued to be prevalent in 17-41% of implants[7]. Even the last designs can affect rates as high as 15% of stented patients[10]. With a million patients in each of USA, China and Europe territories per annum this remains an urgent medical problem.

B. Next Generation of Stent Technology

After the first generation of bare metal stents (BMS) were introduced a new design used anti proliferative drugs eluted off the stent (DES) to prevent ISR. DES with a pharmacological drug-coated surface inhibited ISR by preventing inflammation, VSMC proliferation and migration and consequent platelet aggregation [11]. Despite delayed onset and a lower risk of ISR with DES, shortcomings of these stents included long-term safety and initiation of late stent thrombosis [11]. More recently, bioresorbable stents (BRS) that degrade over time to protect the endothelial layer, were developed by Abbott such as Absorb™. However, randomised controlled trials have shown BRS have not yet proved efficacy over DES and were recently withdrawn from the market [9, 12, 13].

A predicative rather than reactive approach of remotely detecting the onset of pathological changes rather than waiting for symptoms to occur could prevent these fatal complications. To date there are no self-reporting implantable medical devices (IMDs) capable of diagnosing the earliest changes associated with the development of ISR or graft failure. With up to 1 in 10 patients suffering complications from even the newest design of stents [6] and patency rates as low as 50% for bypass procedures [8], there remains a pressing clinical need to advance this technology.

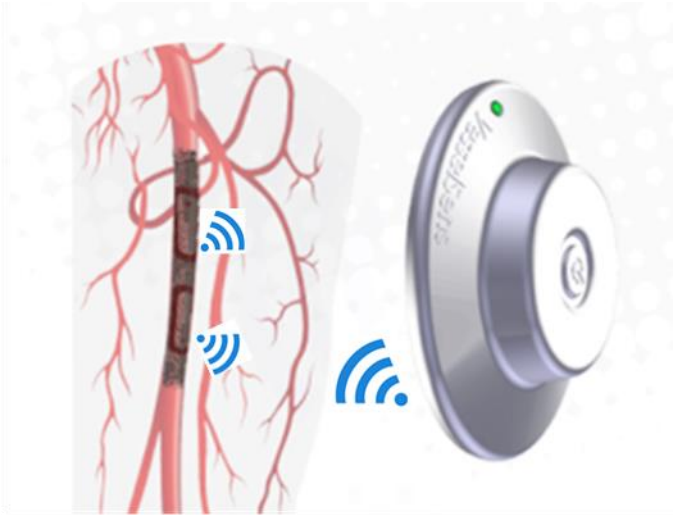

Figure 1) *Example of self-reporting vascular stent by Vesselsens that provides two-way communication for predictive medical response to vascular disease of restenosis. (VesselSens,GmbHLudwig, Bonn).*

C. Precision Medicine

Precision medicine (PM) and associated terms such as stratified and personalised medicine, focusses on predictive and preventative healthcare. In particular, this newest form of medicine has created the field of biosensing technologies. Biosensor innovation has and will advance clinical diagnostic and intervention practices. Although the concept of sensing technologies for the detection of physiological biomarkers has pre-existed before now. For example, successful glucose monitoring devices such as wearable biosensors have been commercially adopted for the management of diabetes [14]. FreeStyle Libre is Abbott's continuous glucose monitoring device worn on the back of the upper arm [15]. Cardiac monitors have also been marketed such as AliveCor's "KardiaMobile" for ECG home monitoring [16].

Clinical practice is entering a new era of implantable and wearable sensors which can wirelessly report physiological and pathological outcomes through 'cloud-based learning' health platforms. CardioMEMS HF™ promoted by Abbott is a commercially established IMD for heart failure patients that wirelessly captures pulmonary artery pressure for remote monitoring [17].

These so-called SMART sensors complement the pathway to PM by actioning interventions to the right patient at the right time. Using companion diagnostics at a molecular and physiological level to detect the onset of disease before symptoms occur, healthcare can transition from outdated empirical medicine to a more stratified personalised approach.

II. Fabricating SMART Cardiovascular Implantable Sensors

A new generation of cardiovascular implants medical devices (IMD) that can sense flow, pressure and vessel occlusion has growing interest. Wireless hemodynamic data capture could allow for the earliest intervention, disease prevention, reduced healthcare costs, and a better lifestyle for patients through remote home monitoring. Combining the study of engineering and cardiovascular research, a multidisciplinary approach has advanced the development of implantable biosensors for cardiovascular indications. Implantable biosensors with real-time monitoring capabilities could provide point-of-care diagnosis and early intervention for better targeted health care.

SMART stents and grafts will reshape healthcare procedures by having remote diagnostic and therapeutic capabilities. One sensing approach is to measure the increase in key electrical properties within an IMD caused by a build-up of cellular material. By using custom fabricated sensors with integrated telemetry circuit technology this decentralised approach to healthcare becomes possible. For example biosensors could monitor cell adherence and growth, while Bussooa *et al* has shown these can function as both diagnostic and provide a therapeutic function through the same sensor by inducing a controlled electromediated form of cell death [18]. The proposed device would not only detect ISR but would actively target disease pathology. The development of this and other types of cardiovascular sensors will prevent mortality and further surgical interventions before the onset of patient symptoms [10].

A. Advances in IMD design

Several advancements in technology design such as: electronic sensors, 3D printing, wireless powering techniques, and internet-of-things (IoT) approaches have pushed the development of medical SMART devices. Electronic sensors have been established for IMD including microelectro-mechanical systems (MEMS); where physical forces are sensed and integrated devices are created. Other sensors being utilised include capacitance resonator sensors, magnoelastic resonant sensors, and doppler ultrasonography which detect pressure, flow, and velocity [10].

The selection of biomaterials both for the device and the sensor is one of the crucial and the most important factors while designing implantable medical devices. Implant material should

be biocompatible without inducing any undesirable effects to the body. It should also have the ability to assist the body to heal after implantation, providing a stable connection between body and the implant surface. Materials must be tested for toxicity, carcinogenicity, hermeticity and material degradation over time. Further, it is essential to examine the biomaterial compatibility based on surface morphology, crystallinity, and other mechanical parameters within the human body.

For example Iridium, cobalt-chromium, nitinol, titanium, platinum, polydimethylsiloxane (PDMS), polymethylmethacrylate (PMMA), Parylene C and polyimide[19],[20], all show good biocompatibility and are found in across a variety of IMDs. Materials such as SU-8 polymer, Silicon, Silicon-dioxide (SiO2), Silicon-Nitride (Si3N4), Silicon-Carbide (SiC) and polysilicon have also been investigated under FDA guidelines and found appropriate for medical usage[21].

B. Advances in IMD fabrication

Conventionally, cardiovascular stents are fabricated using chromium-platinum compounds and nickel-titanium alloys (nitinol). A smart stent would require a wireless sensor node consisting of a transducer, associated readout electronics and communication infrastructure. Transducers can be used to detect various signals within the stent; ranging from blood pressure, volume flow or cell growth. While materials can be used to fabricate the transducers themselves, the interface electronics is almost always designed as silicon chip (or integrated circuit). In order to miniaturize the overall sensor dimension and integrate it with the stent/graft, it is necessary to fabricate the transducer on the same substrate as the electronics. Furthermore, due to advances in silicon technology in creating MEMS (micro electromechanical systems) devices and sensors, it is one of the best candidates for transducer fabrication. Placing active electronics within the device will require the addition Application Specific Integrated Circuits (ASIC) and the careful encapsulation of these silicon chips and all but the sensing elements.

C. Printing technologies for IMD sensors

Numerous 3D printing methods have evolved including high resolution techniques such as stereolithography (SLA). These printing technologies have advantageously brought the ability to design conductive nanomaterials into complex geometries which are biocompatible, flexible, and miniaturised. For example Jordan *et al 2020* have used an aerosol jet deposition to produce wireless resonant marker on polymer catheters for use in interventional magnetic resonance imaging (MRI)[22]. They used a water-based silver nanoparticle flake and dielectric polyimide ink deposited into a double helix. The inclusion of capacitor plates with a 60 µm tolerance and 4 µm trace thickness created a resonant L-C tank circuit than allows both catheter tip tracking and placement using magnetic resonance.

Fused deposition modelling (FDM) is the standard melt extrusion 3D printing for commercial rapid prototyping of devices. [23, 24]. The heated liquefier (print head) melts the filament and pushes it through a nozzle and the nozzle then deposits the melted filament on XY plane on the printing platform, these can be rotating or Z-axis controlled for stent fabrication[25]. After depositing exactly one layer of material thickness, the printing platform moves in Z direction and the process starts over [26]. This process is repeated until the desired structure is built. The low melting point of polymer filaments that are used in FDM include polylactic acid (PLA), a biocompatible material used in the 1st and 2nd generation of the Absorb™ series of bioabsorbable stents. Acrylonitrile butadiene styrene (ABS), polycarbonate (PC), and polyamide (PA)[24] are all common substrates, which while their availability is widespread and their cost is low their biocompatible is questionable.

FDM technology contains drawbacks, such as weak mechanical properties, layer-by-layer appearance and poor surface quality and limited resolution that makes their suitability of most IMD limited[23]. Some of these drawbacks can be overcome with fibre reinforcement as it improves the polymer matrix of the materials, which enhances the overall mechanical properties. However, 3D printed composite parts have their own difficulties such as fibre orientation, bonding between the fibre and matrix and void formation[23].

D. Photolithography.

Photolithography is a mainstay of micro fabrication sensor techniques which allows the light patterned creation of 2D features on a microscopic scale. Traditional photolithography is a subtractive process using light patterns through an optical mask to pattern a photo resist which can then be used as a physical mask in an etching process to produce suitable high resolution sensors that can be encapsulated and mounted on suitable IMDs[18]. In contrast stereolithography 3D printers ~~however~~ provide an additive process that in the future can be used to make the IMDs as they use photopolymerization of a photo sensitive liquid placed in a reservoir by a computer aided-positionally programmed laser beam or a digital light projector with computer-aided platform. This laser cures the resin and from liquid to solid via chemically crosslinking it [27] while following the pattern of the structure desired to be built. Once the first layer`s polymerisation is completed, the platform is moved away in order to for build layer to be recoated with liquid resin and this process is followed until the desired structure is achieved[28]. Having a precise fabrication accuracy and the ability to print structures as small as 20 µm compared to other printers (50-200 µm) makes SLA one of the most useful 3D printing technologies for fabricating small structures[29]. However, the limited number of resins that are commercially available for SLA is one of the drawbacks of the ~~SLA~~ technology as well as fact it is time consuming and the mechanical properties of printed structures is often inferior to components machines by subtractive processes [27],[29]. However, SLA provides a strong, rigid advantage in biomedical engineering applications due to its ability to utilize CAD files from magnetic resonance imaging (MRI) and computed tomography (CT); an ability to provide biodegradable, patient specific implants will improve with ever increasing technological advancements[29].

E. Metal powder bed fusion (PBD) printers and latest print technologies

PBD printers includes a number of methodologies including direct metal laser sintering (DMLS), Electron beam melting (EBM), select heat sintering (SHS), selective laser melting (SLM) and selective laser sintering. These methods use a laser or electron beam to melt and fuse material together in a vacuum and is suitable for metal and alloy parts. The sintering still requires a layer-by-layer approach with 100 µm thickness. The advantages of this method are that it is relatively expensive, and not suitable for small technology integration prototypes such as stents but does have a large range of available materials. Their other disadvantages are that they are relatively slow and their resolution does not yet meet the high precision required for stent manufacture.

F. Power Transfer solutions

Wireless powering transfer (WPT) is particularly appealing for implantable reporter sensors due to weight, limited battery space and cytotoxic leak considerations. In this way, energy can

be transferred from an external coil to a receiver coil on the implanted device on demand. Energy transfer can be transmitted through radio-frequency (RF) electromagnetic waves, ultrasound, or a biological source [30]. Several techniques for transferring power wirelessly to implantable devices have been suggested. These techniques can be classified into five main categories: near-field, mid-field, far-field, solar and ultrasound ([31]. Near-field and mid-field transmits energy using electromagnetic induction mechanisms whereas far-field transfers power based on electromagnetic radiation. Solar based implantable devices harvest photovoltaic energy from light [32], and ultrasonic based devices uses ultrasonic (sound) waves to transmit energy wirelessly[33] but due to the nature and depth of the implant solar is deemed too impractical. For a more detailed evaluation we refer the reader to Mohammad Etemadrezaei work on WPT in Power Electronics Handbook 4th Edition, 2018 and the work of M. Kod, "Wireless Powering and Communication of Implantable Medical Devices," *PhD Thesis , University of Liverpool,* 2016.

III Suitable vascular IMDs for smart self-reporting technologies.

A. Stent-grafts for Haemodialysis Patients

Self-reporting vascular devices will have universal medical appeal as stents are placed throughout the body. For examples stents are frequently used in the heart, brain, kidney renal and carotid arteries as well as ureters and oesophagus to name but a few. Synthetic grafts are used as native vessel replacements are clinically ubiquitous and used for peripheral access such as for blood exchange in haemodialysis patients *(Figure 2).* Being relatively large bore vessels and surface mounted may make these the most suitable targets for the next generation of SMART devices. The endovascular Viabahn Graft and HeRO graft have been designed for haemodialysis patients who suffer from venous stenosis. These are the most common cause of haemodialysis vascular access dysfunction which is usually treated through percutaneous transluminal angioplasty (PTA) and the use of stents is becoming increasingly popular to provide longer patency when compared with PTA alone [46]. A study conducted by Carmona et al, 2016, reviewed graft patency in patients who were treated with PTA alone and PTA with Viabahn Endoprosthesis (Gore) stent grafts and found that after 12 months, 87.8% of the grafts with stents continued to work successfully as opposed to a low 36.4% with PTA alone[47]. Previous studies have trialled using stents with haemodialysis patients and shown low success rates due to reported complications associated with the implantation of stents. This includes stent fracture which can occur at various locations such as the costo-clavicular junction as the stent collapses between the clavicle and the first rib[46]. Infection is also another complication that can lead to cardiac events as it has been reported 16.3% of stents placed in arteriovenous accesses failed due to stent infection (El Kassem et al., 2015). A complication of stenting in haemodialysis patients is the placement of stents in cannulation sites as repetitive cannulation can damage the stent strut. This is perhaps due to the nature of stents used previously as this recent study by Carmona et al, 2016, uses the Viabahn stent instead of a BMS used previously. The Viabahn stent is reinforced, heparin bonded, self-expanding and has a polytetrafloroethylene (PTFE) liner which is attached to an external nitinol stent structure [47].

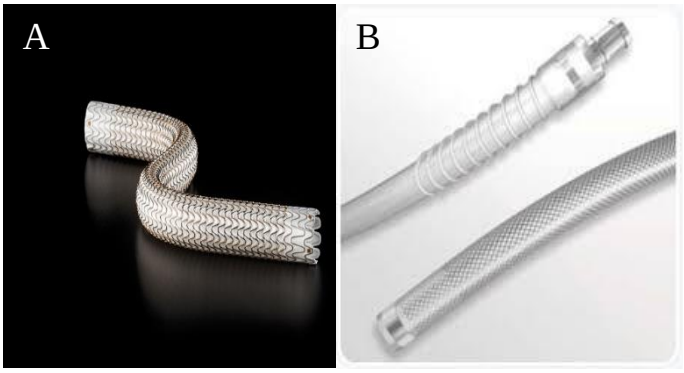

Figure 2) Implantable medical devices suitable for SMART technology. *A) Gore Viabahn Endoprosthesis graft (W.L. Gore & Associates, Inc., Flagstaff, AZ) B) Herograft (Merit Medical, UT, USA).*

The use of the Viabahn stent has been studied in treating cephalic arch stenosis in haemodialysis accesses which has been found to be a common cause of brachiocephalic arteriovenous fistula dysfunction. The cephalic arch is located in the section of the cephalic vein which crosses the deltopectoral groove in the shoulder and joins the axillary vein. The tortuous anatomical features of the cephalic arch make it highly susceptible to developing stenosis and also results in limited treatment options[48]. Previously, the treatment available has been PTA followed by a BMS; however, this has shown to cause ISR, axillary vein stenosis and occlusion therefore the best treatment is yet to be selected[48]. A study conducted comparing the treatment of BMS to the Viabahn stent graft in the treatment of cephalic arch stenosis showed a major increase in six-month patency rate of 82% in stent grafts compared to only 39% in BMS, one-year primary patency was also higher in stent grafts at 32% compared to 0% in BMSs[46]. Although this study had a small sample size, it shows potential in the future of treatments with greater success rates in stent grafts as a better alternative.

The HeRO Vascular Access Device was also designed for haemodialysis patients suffering significant outflow stenosis which provides continuous blood flow directly from an artery into the central venous system. Unlike a conventional graft, this device has no venous anastomosis which is the common site of stenosis. This device has two components, the arterial graft component composed of polytetrafluoroethylene, and the venous outflow component which is a silicone catheter reinforced with nitinol. The two components are joined together by a titanium connector and the end of the arterial graft component is anastomosed to the brachial or axillary archery to allow subcutaneous tunnelling to the upper arm[49]. The venous outflow component is placed percutaneously into the right atrium through the internal jugular vein or subclavian vein. For haemodialysis, the HeRO device is cannulated by inserting the dialysis needles into the graft component. A study conducted by Perry et al, 2017, reviewed 10 haemodialysis patients from 2013 to 2016 who received a modified HeRO dialysis system with an ACUSEAL graft (W. L. Gore & Associates, Newark, Del) as the arterial graft component to allow immediate cannulation[50]. All patients displayed early cannulation without complication; however, 2 patients suffered thrombosis requiring reintervention but this is attributable to a hypercoagulable disorder and repeated hypotensive episodes (Perry et al, 2017). Primary and secondary patency rates were 70% and 90% at 6 months, and 50% and 70% at 12 months which is higher than with CVCs as

well as displaying increased dialysis adequacy and decreased infection rates[50]**.** Merit Medical have stated that the HeRO graft is the only subcutaneous arteriovenous access solution clinically proven to maintain long term access for haemodialysis patients with central venous stenosis and has been classified by the Food and Drug Administration as a vascular graft prosthesis.

IV Commercialisation

The technology adoption pathway in healthcare of new innovative technologies can be viewed as one of the most complex for a commercial product. Considerations are needed during the technology research and development phase to assess if smart devices for cardiovascular health can be developed and marketed feasibly. Technology road mapping is a method used by many industries to form a business model that strategically forecasts the environmental landscape, including threats and opportunities in technology development [51]. An entrepreneur-based approach to analyse product feasibility would also be valuable before venturing on a potentially barricaded commercialisation process.

A. Risks and Rewards

The opportunity of developing new types of implantable medical device can be considerable but comes with new risks. While there is temptation to make compromises and tackling the lack of self-reporting devices by opting for purely wearable technologies, these "lower hanging fruit" fail to realise the benefits which can only be achieved by fully implantable devices. Specifically, by identifying and reporting the earliest cellular changes, can only be detected by the unique physical interactions of the cells of interest with the sensor. To mitigate these risk implantables should be designed with the fewest parts necessary to complete the design. The implant should surgically handle as close as possible to the current "gold standard". In the example of AVGraft the same ePTFE material can be used and an external telemetry kept extra-vascularly and away from the circulation to reduce risks of complication. To ensure uptake of these new device they must also reach stringent regulatory compliance.

B. Regulatory Framework

The regulatory framework required to take these devices from bench to marketplace is complex and beyond the scope of this article but is addressed here briefly. Implementation of a quality management system (QMS) is of critical importance for reaching regulatory compliance; either through the USA Food and Drug Administration (FDA), the UK Medical Health and Regulatory Authority (MHRA) or the European Medical Device Regulation (MDR). Medical devices are classified from Class I (wearable) to Class III (implantable) with each having their own distinct requirements. The purpose of these standards is to provide a design framework with quality standards and a presumption of conformity. There are a number of essential standards that must be met which requires submission of a risk management report to a certified notified body such as the British Standards Institute (BSI) that will lab test compliance of the device to the regulations and implement a quality assurance conformity assignment and compliance as part on an on-going technical file that records the devices design, fabrication, specification (ISO13485), useability (IEC62366), biocompatibility (ISO10933), electrical safety (ISO60601), sterilisation (ISO11737), medical software and data protection (ISO62034) as well as labelling, packaging (ISO15738) with of course reference to good manufacturing practice (GMP) of the final device. Only then a product be given the seal of approval with a UK Conformity Assessment mark (UKCA) or European CE mark. There are ongoing maintenance costs associated with maintaining the technical file and this conformity and any changes to the design must be notified, with reclassification checked every 3 years. Further details can be found at the following hyperlink of the European Commission for Harmonised standards: New 2020 lists of harmonised standards for medical devices are now available | Internal Market, Industry, Entrepreneurship and SMEs (europa.eu). Often overlooked regarding regulation is data protection. With predictive monitoring and the addition of algorithms, it is imperative for the safeguard of patient data, whether that be managed by device designers or clinical practices themselves.

C. Market Outlook for SMART Stents/Grafts

The road to commercializing a smart Stent/Grafts is a high risk undertaking but the recent COVID-19 global pandemic has shown how remote monitoring of patient could make a fundamental difference to stratifying clinical need. An outlook specifically on the coronary stents market from 2020-2027 is predicted to jump over $11.3 billion, rising at a compound annual growth rate (CAGR) of around 4.7%. The report by Research and Markets also stated that DES is the lead generation of stents and Asia Pacific geographically will experience the highest growth rate. Additionally, the dominant companies in the coronary stents market are; Abbott, Medtronic, Boston Scientific, Terumo Corporation, Biotronik, and Microport Corporation [52].

A promising report of the vascular graft market forecasts market size to increase by a CAGR of 6.4% from 2019-2026. Endovascular grafts are thought to continue to capture the market and peripheral vascular grafts will be the fastest-growing product segment. North America followed by Asia Pacific are expected to be the main regional markets for grafts. Leading firms in the graft market include Medtronic, LeMaitre Vascular Inc, Terumo Corp, Cook Medical, and Gore and Associates [53]. Most importantly, and with an ageing population, from 2018-2025, it is estimated that the global market for implantable remote patient monitoring devices will reach $10.1 billion at a CAGR of 20.1% [54].

The individual technological components of the implantable sensor are also on an upward market trend. Between 2017 and 2025, the medical device market is predicted to reach $2.77 billion, growing at a CAGR of 16.8% with Asia-Pacific witnessing the highest growth [55]. The medical IoT market size is projected to increase from $72.5 - $188.2 billion from 2020 to 2025, at a CARG of 21.0% [56]. Additionally, the global wireless power transmission market is expected to reach $29.23 billion by 2027, also growing at a CAGR of 21% [57]. Similar increase in market share is probable with medical sensors; market is worth $1.2 billion in 2020 and rising to $1.7 billion by 2025, at a CAGR of 6.8% [58].

D. Drivers of Change

To help imagine the future and viability of implantable smart vessel devices, the forces and drivers behind technological and medical changes must be identified. According to a market research report by Grand View Research, the main drivers for IMDs for the forecasted period 2019-2026 were; an increase in demand for less invasive procedures, growth of coronary arterial diseases prevalence, and an increase in geriatric population [59]. The world health organization states that from 2015 to 2050, an increase in elderly of >60 years old will almost double from 12% to 22% [60].

As part of the United Nations "sustainable development goals", goal 3.4 aims to reduce "one third of premature mortality from non-communicable diseases through prevention and treatment,

and promote mental health and well-being" by 2030 [61]. There is an urgent need to prevent CVD before symptoms occur. The SMART stents/grafts intend to reduce surgical procedures through its diagnostic and therapeutic abilities for CVD patients.

PM is evolving and expanding. In 2015 President Barack Obama publicized that the US was initiating a government funded infrastructure, now named "All Of US", to aid PM [62]. Further economic incentives put in place have driven a paradigm shift in healthcare; the need to prevent diseases at a molecular and physiological level. With this new era of healthcare, comes 'patient-centered' medical care where patient reported outcomes (PRO) are frequently being adopted [63]. The role of the patient opens innovation opportunities for patient-clinician remote connection as projected through the smart app. A novel diagnostic device is required to individually personalize therapy for patients and involve them in the decision-making process.

Interestingly, the current COVID-19 pandemic has pushed the use of telehealth for remote monitoring up the agenda. Forced lockdown has opened a portal for efficient patient surveillance without face-to-face interactions such as GP services, therapy and counseling from mental health professionals, and maternity telehealth care. Interestingly, severe COVID-19 complications are associated with CVD [64] and it is recommended that cardiovascular patients are monitored remotely through telehealth in order to mitigate the effects of quarantine [65]. No doubt this will further the use of remote monitoring and cloud-based healthcare moving forward. COVID-19 has also brought waves of technological innovation in the IoT, machine learning, and artificial intelligence for screening and tracing uses [66]. Together, these drivers and signals prompt the need-of-concept for smart technology for CVD.

E. Value Creation

Value propositions are used in business pitches to show a novel product or service will provide value to its end user. Often, technological products intended for entering a healthcare system fail due to poor analysis of the value it will create. Osterwalder et al developed a 'value proposition canvas' whereby the method is to analyse gain creators and pain relievers for the end user [67]. Gain creators can be explained as the beneficial outcomes the customer will receive from the product and pain relievers describes the customer obstacles which are alleviated [67]. In the case of smart stents/grafts, value will be created for healthcare systems and patients. A proposed value proposition canvas can be illustrated (*figure 3)*. Healthcare systems will gain a decrease in the number of surgeries and appointments, and in turn this will reduce the economic burden. Patient reported outcomes will facilitate knowledge generation to the clinician for making informed decisions and lead to better QoL for the patient. In turn better QoL through less invasive procedures and open access to own health data will enhance patient motivational adherence and management of health outcomes (37).

Furthermore, value co-creation considers stakeholder involvement such as the patient in providing quality of care. The research on innovative medical technology to date has tended to focus on value created for healthcare rather than for the patient. A recent empirical study combats this by evaluating the role of advanced technologies in designing a value co-creation environment for the patient [68]. The author proposed that in order to encourage patients to participate in the co-creation process of their care, fundamentals including reliable accessible technologies, socioeconomic considerations, and satisfaction are required [68]. Future smart IMDs will allow patients to input symptoms and experiences to an accessible mobile app with efficient data protection.

Here, a landscape has been shaped to provide; need-of-concept for implantable cardiovascular sensors, a vision of the complex integrated markets and the value the IMD will create. This outlook will aid in supporting decision making investments in this field.

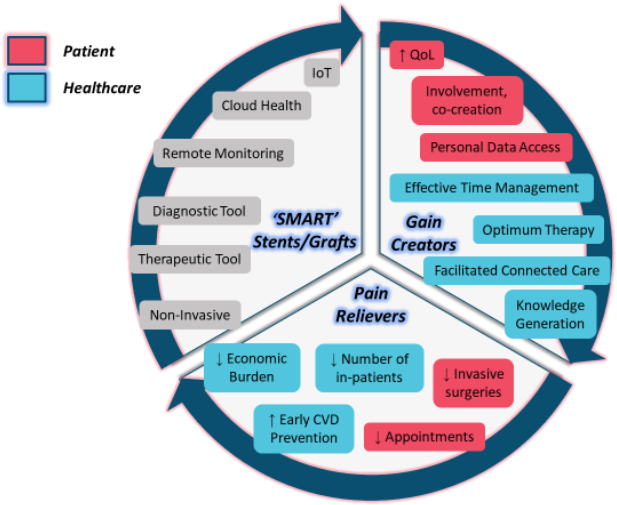

Figure 3. *Proposed value proposition canvas of SMART Stents/Grafts for adding value to healthcare (blue) and patients (pink).*

F. SMART Stents/Grafts for Precision Medicine

Implementation of a self-reporting implantable stent or graft could help bring PM to cardiovascular patients. A useful example of how this device can provide care to the right patient at the right time, is by the development of clinical prediction and risk models. The ability to screen high-risk individuals would assist medical decision making. The current predictive models for ISR such as PRESTO-1, PRESTO-2, and EVENT, have low predictive power of 0.31, 0.27, and 0.18 area under the precision-recall curve (AUC-PR) respectively [69]. There is a need for more powerful and accurate prediction. Recently, Sampedro-Gómez *et al* performed machine learning to create a 12-month risk score for ISR which had superior power than previous models (0.46, AUC-PR) [69]. This is proof that machine learning, possibly combined with the IoT, can aid clinical decision making for restenosis. The proposed self-reporting device would have the capability to utilise physiological and pathologically collated data, along with baseline characteristics such as demographics, genetics, and lifestyle parameters to create more effective models.

Furthermore, wireless remote monitoring would allow stratification of patients for early intervention. An example of efficient stratification from a diagnostic implantable device can be shown from a cardiac resynchronization therapy defibrillator (CRT-D). A convincing paper using clinical data presented that heart failure risk-stratification from a CRT-D device was able to risk-stratify CRT-D patients using the Medtronic Optivol® algorithm. The authors suggest the next step is to evaluate if treating high-risk patients first through risk-stratification will improve patient outcomes [70].

G. Effectiveness of Remote Monitoring

To date there is no self-reporting implantable devices capable of detecting early ISR or graft failure, although several have been proposed by research groups (see section 6). To forecast the performance and implementation of smart stents/grafts, previous exemplar studies from cardiovascular remote

monitoring (RM) IMDs can be used to evaluate if this style of device would be effective.

The CHAMPION trial showed remote pressure monitoring using the CardioMEMES system had efficacy over standard of care, including a decrease in the number of hospital admissions during an 18-month follow-up [71]. The secondary aim of a recent first in human study (NCT03850327) investigating an implantable cardiac monitor (BIOMONITOR III), was to evaluate home monitoring transmission success using the CardioMessenger® mobile device. Messages from 45 patients included in the end study successfully transmitted 98.0% ± 5.5% of days with a RM message after the first message [72].

In contrast, a systematic review and meta-analysis of randomised controlled trials estimating the effects of implantable cardiac devices found that RM was less effective in reducing all-cause mortality or heart failure related hospitalisations. However, the study conducted a subgroup analysis and found benefit in RM in reducing hospitalisations when using pulmonary pressure monitoring only [73]. This suggests that RM outcome differences may occur between devices depending on which parameter is being tested – pressure, flow, occlusion, and that critical investigation will be needed to address the efficacy of smart stents/grafts.

From a healthcare standpoint it is imperative that new IMD does not only improve patient outcomes but also have long-term economic benefits. Previous evidence of economic value from cardiovascular IMD examples can give insight into the feasibility of adopting 'SMART' stents/grafts. Using the implantable CardioMEMS device as an example, two studies concluded positive cost-effectiveness of the remote pressure monitoring system compared to standard care. Both studies measured cost-effectiveness as an incremental cost-effectiveness ratio (ICER). ICER can be calculated by the difference in cost between the two interventions divided by the difference in quality-adjusted life year (QALY). If the ICER is less than $50,000/QALY it is classified as having high economic value. The first study using data from the CHAMPION trial and NHS (UK) health system costs stated that CardioMEMS therapy increased cost compared to standard of care by £10,916 and increased QALYs by 0.57, giving an estimated ICER ratio of £19,274/QALY [74]. In contrast, Schmier et al evaluated cost-effectiveness in a Medicare American health system from the CHAMPION trial data. Results suggested that remote monitoring of heart failure was cost-effective with an ICER ratio of $44,832/QALY [75].

A strong meta-analysis and systematic review assessing the economic difference between remote monitoring of implantable cardiac defibrillator and standard of care showed positive outcomes for the French Health Authority cost guidelines (ICER ratio €14,136 /QALY) [76]. A further study assessing implantable cardiac defibrillator feasibility found remote monitoring was favourable with an ICER ratio of $10,752/QALY using data from the PREDICT RM database [77].

The studies reviewed so far have limitations due to different healthcare systems around the globe and have varied hospital and care costs. Considerations when commercialising smart stents/grafts include who the beachhead market will be – public or private systems - for wide adoption. Additionally, some models do not include all cost considerations such as staff training and time expenditure. Nevertheless, the above economic studies suggest that implantable cardiovascular remote monitoring devices are cost-effective for the management of patients and gives perspective of willingness adoption of smart stents/grafts into a health setting.

H. Patient centred

Achieving PM will require patient involvement. Barriers that need to be addressed include the ethical considerations of implantable biosensors, data protection, biohacking, and the patient's acceptability and views. Would patients accept being monitored through an IMD as part of the treatment regime? Patient validation so far has been positive for this patient-centred new health care. When breast cancer patients were interviewed about their views regarding implantable biosensors within a tumour microenvironment for the personalisation of adjuvant radiotherapy, 90.6% of participants were supportive of the use of sensors. Despite the majority of them being unaware of biosensors, 87.5% of patients had a strong preference for wireless powering [78].

In a cardiovascular context, a study assessing patient psychological and behavioural changes after implantation of a wireless hemodynamic monitoring sensor, found a decrease in cardiac anxiety and a drop in fear of the patient's condition [79]. Wireless remote monitoring may be advantageous in aiding psychological effects. A thematic synthesis study interpreting qualitative studies recurrently reported that patients positively had confidence and a sense of safety with remote monitoring. It was noted that RM increased shared-decision making, disease-specific knowledge, and self-management. Widespread concerns regarding remote monitoring include fear of being lost in data and losing face-to-face interactions [80].

Additionally, a study comparing clinical and remote monitoring for the management of cardiac arrest through an ICD showed that informants reported they favoured clinic visits compared to remote examination due to the increased interaction with clinical visits [81].

V Current Research on Smart Vasculature Technology

Commercialising biotechnology requires open innovation, often driven by academic researchers who converge disciplines and advance innovative technologies. The idea of sensing post-surgical vessel environments through a wireless reporter device with therapeutic capabilities is now being investigated. Various methods of device development include utilising different circuit design, powering, and sensing technologies. The following provides an up-to-date understanding of the recent cardiac wireless implantable discoveries from university and research institutions. Within this review of basic research, new stent, graft, and other cardiovascular smart technologies will be discussed.

A Current Commercialisation of Vasculature smart Technology: Innovative Companies

Academic and research institutions are advancing design and proof-of-concept for smart stents/grafts. However, it is essential to address demand and progress from the private sector. Despite pioneering contributions from basic scientist's towards development, it is the role of established medical device and spin-out commercial companies to take these products from experimental validation to clinical trials and, eventually regulatory approval. This may be achieved through investment rounds, mergers/acquisitions, and widening clinical pipelines. Some smart vascular products have exceeded the research and developing stage and moved onto clinical investigation, or further. Examples of innovative companies who are actively commercialising smart vasculature technology are listed in *Table 1*.

Vectorious has developed an implantable sensor for left atrial pressure monitoring in patients with heart failure [82]. After success of ex-vivo and animal model investigation [83], the V-

LAP™ device *(figure 4)* is currently being tested in its first human clinical trial (74). A recent case study has shown the device successfully prevented hospitalization by telehealth of a patient who was self-isolating from COVID19 (Feickert et al., 2020). Additionally, Synchron is a company formed in 2012 who have developed a stent to diagnose and treat neurological conditions such as paralysis, epilepsy, and depression. Their Stentrode™ product is implanted non-invasively into the vasculature and detects brain activity over a range of frequencies [84]. A study in 2018 showed that the Stentrode™ when implanted into the superior sagittal sinus of sheep, induced motor responses by cortical stimulation [85] and has now moved onto a clinical feasibility study [86]. This is an example of treating neurological conditions from a smart vasculature implant.

Table 1. *List of innovative companies with their products in the pipeline.*

Company	**Synchron**[84]	**Endotronix**[87]	**Profusa**[88]	**Vectorious**[82]	**VesselSens**[89]
Device Type	Stent - Motor Neuroprosthesis	Implantable Sensor and Patient Kit	Implantable microsensor and Wireless Patch	Implantable Sensor and external belt	Implantable Sensor (Stent) and external wireless readout unit
Product Name	Stentrode™	Cordella™	Lumee™	V-LAP™	VesselSens™
Health Condition	Neurological Disorders • severe paralysis • epilepsy • depression	Heart Failure	• Peripheral Artery Disease • Influenza • Diabetes	Heart Failure • Acute/Chronic HF • mitral regurgitation • arrhythmias diastolic dysfunction • atrial fibrillation	Arterial Disease • Restenosis
Function	Neural Stimulation. implanted into the superior sagittal sinus that converts thoughts into command functions, controlling an external device.	Pulmonary Artery Pressure Sensor. Detects worsening of early heart failure by capturing fluid filled pressure measurements.	Monitors local Tissue Oxygen levels by inserting microsensors in the subcutaneous tissue and placing an external detector on the skin.	Left Atrial Pressure Monitoring System which sends heart data to the cloud. Clinicians and patients can monitor pressure trends and amend medication/intervention.	Wireless Restenosis Detection through a passive device to measure pulse wave velocity of the impacted vessel segment.
Stage of Development	Clinical Trial	Clinical Trial	Clinical Trial	Clinical Trial	Seed funding
Advantages	Minimally invasive procedure which does not require open brain surgery.	Handheld device measurements. Trend based heart failure management.	Wide clinical applications including chemical monitoring inside the body.	Direct daily measurement of left atrial pressure. Built in algorithms can also allow for additional cardiac conditions.	Company has moved onto building algorithms, cloud services and software for this passive device..
Challenges	Telemetry unit in the chest to provide wireless transmission which is invasive.	Multiple device accessory's required for the patient to use. t training.	Adopting the technology for home use in addition to surgical use.	Invasive implantation. After clinical efficacy is proved, proof of economic feasibility is needed.	Device is early product stage and requires further proof-of concept.
Clinical Trials	NCT03834857[86] Open-Label Feasibility Study	NCT04089059[90] Randomized, Controlled, Single Blind, Multicenter NCT04012944[91] Prospective, Multi-center, Open-label, Single-arm CE-Mark trial	NCT04514861[92] Open Label Single-arm Non-randomized Effectiveness and Performance Study	NCT03775161[93] Open Label FIH Multi-center Evaluate the Safety, Usability and Performance Study	N/A

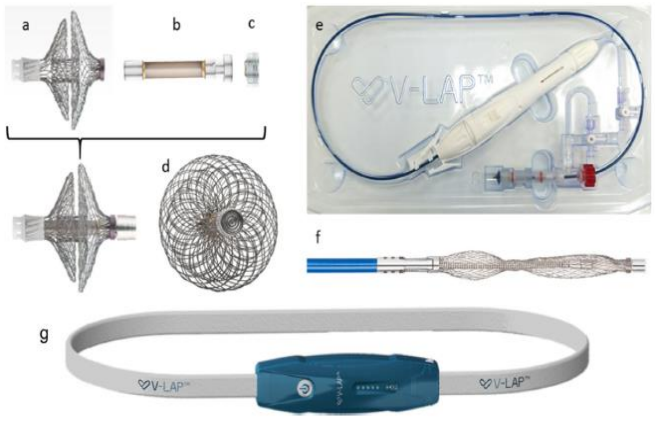

Figure 4. *Illustration of V-LAP™ device by Vectorious. [83]. The implant (a+d), electronic circuitry component and pressure cup (b+c), delivery system (e), nitinol anchor (f) and external belt (g).*

B. Recently Approved Devices

Cardiovascular wireless implantable biosensors are achievable. In addition to previously mentioned CardioMEMS, other monitoring devices have been approved and made it to market. Key competitors Abbott, Boston Scientific, and Medtronic have recently passed FDA approvals. Gallant™ is Abbott's ICD and CRT-D device for patients with heart rhythm disorders. The Bluetooth device, which has now achieved FDA approval and CE Mark in Europe, connects patients to its smartphone app – MerlinPulse™ [94]. LUX-Dx™ is Boston Scientific's implantable cardiac monitoring system for detecting arrythmias connected to an app called MyLUX™ [95]. Additionally, in the competitive field, Medtronic has achieved FDA and Europe approval for their insertable cardiac monitor – LINQ II™ which is also linked to a patient app named MyCareLink Heart™. Medtronic states that their improved algorithm can cut false detection by 79% [96]. These recent examples are proof that novel wireless implantable devices can move through the commercialization process and pass technological, clinical, and regulatory hurdles.

C. Key Stakeholders

The emergence of smart vasculature technology will require strategic alliances and open innovation (without destroying intellectual property value). Currently, basic research and pre-clinical studies outweigh the number of approved devices that make it to market. One of the dominant reasons for this is the clinical- translational barrier. To achieve the full potential of PM, fragmented stakeholders need to collaborate and integrate their own disciplines, whether that be science, medicine, regulatory policy, business, sociology, and economics. The development of bioelectronic medicine was recently discussed at an event in Geneva, 2019 funded by BioSig Technologies Inc consisting of academic, medical and private sector multidisciplinary stakeholders. A recent review summarizes the recommendations for molding a future of bioelectronic medicine through collaboration: [97]

1. Work towards a shared and unison set of goals and visions.

2. Together, build evidence that smart technology would be safe, effective, and cost-effective.

3. Physicians must ensure research results are credible and frequently connect with engineers.

4. Promote science communication and public engagement to gain trust in patients.

5. Policy makers and regulators should provide guidance during the development stage to aid navigation through regulatory pathways.

6. Incentivize the use of smart technology through reimbursement pathways and cost-saving predictions.

7. Develop the next generation of innovative leaders by incorporate engineering and bioelectronic medicine into medical education.

VI Discussion

The potential of smart-IMDs is driven by the prevailing market conditions, the need to innovate and the value new devices offer to clinicians and patients. Custom implantable devices offering remote patient monitoring, wireless data and power transfer for cloud-based learning are attractive elements. When combined they will provide clinically actionable data for predictive over reactive diagnosis. The next generation of medical device players will offer high risk but high growth opportunities and will need to define how their products will deliver value to end users. Cardiovascular RM-IMDs have already shown efficacy in certain sectors and appear cost-effective for global healthcare systems. Recent studies have conveyed that patients have good tolerance for these devices however increasing science communication and public engagement will increase their acceptability. With ever increasing advancement of technology, researchers are now producing proof-of-concept demonstrations for these devices with companies expanding the field's applications into clinical trials.

The work of Gray *et al*, 2018, describes how implantable biosensors can contribute to personalised medicine [98]. They comprehensively discuss the criteria for successful biosensors; however, attention was focused on biosensors for oncology. To our knowledge, this critical review is the first to specifically discuss a future outlook of cardiovascular implantable devices in a precision medicine-based context. Additionally, literature on the future ISR and graft failure diagnosis remains very basic research orientated. Not only does this discussion update the output from academic groups, but also begins to consider the clinical translation of these devices. This multi-disciplinary approach including comments from a scientific, technological, clinical, and business point of view hopefully will give insights for future collaborative partnerships in cardiovascular smart innovation. Entrepreneurs think of end users first and how a product or service can change the lifestyle or workflow of those customers, whereas basic scientists focus on proving the underpinning methodologies and technology work and how this could be implemented in a finalised working product. With the complex nature of this device, it is imperative to create a 'road-map' integrating multiple disciplines to strategically plan future viability. This 'out-side-in' perspective of examining the end implications of these devices, provides reassurance that embarking on a complex commercialisation process is worth it.

Considerations that are not always addressed are the ethical and security issues that these devices pose. Firstly, 'big' data collection and cloud platforms requires informed consent from patients, and protection of data from third parties is needed. Additionally, a fear of 'bio-hacking ' has emerged connected to electronic implantable devices. Further work is required to ensure these devices find a balance of safety and security.

In summary the challenge now for the development of smart stents and grafts for example is not one single technological obstacle but a series of interdependent challenges. To integrate and fabricate at scale all the components into the one device, the miniaturisation of integrated circuits that can relay data and power the device in a biocompatible format is clearly challenging. However, their ultimate success can only be validated through *in vivo* testing and stringent compliance with regulatory requirements. The main hurdle once technical and engineering challenges are met will be clinical translation to prove smart devices provide efficacy and cost-effectiveness over standard care in patients. The development of smart vascular real-time monitoring devices is starting to enter the precision medicine arena and their commercial and patient value will likely be bright.

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Conflict of Interest

The authors declare no conflict of interest.

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