Devices for Endovascular Interventions
technical advances and translational challenges
Foreword

Cardiovascular disease is the major cause of deaths in the Western world, of which vascular disease is a main contributing factor. Current endovascular repair involves guiding special shaped catheters to a specific target in the aorta and auxiliary arterial vessels combined with different treatment options including stenting, embolization and ablation. For each of the treatment regimes, both clinical challenges and new technological advances are discussed. A major part of this report is focused on the development of new devices for endovascular interventions. These include devices that can provide intraoperative imaging and sensing, as well as implants that can be used for functional restoration and monitoring the efficacy of treatment processes.

This report also addresses the role of robotics for endovascular intervention and the current commercial state-of-the-art and emerging technologies. Steerable catheters incorporate flexible structures and special actuating modes are used to vary the shape and direction of intervention to provide consistent actuation, master-slave manipulation, with improved accuracy and safety. It is anticipated that there will be significant future developments in this area.

In this report, the use of the endovascular approach for delivering new therapies including focused energy, drugs, or new gene and cell therapy is also discussed. It further outlines translational challenges with recommendations for technical developments, regulatory considerations, funding, market access and better collaboration between the clinical and engineering communities.

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Executive summary

This report on Medical Devices for Endovascular Interventions was commissioned by The National Institute for Health Research (NIHR) Clinical Research Network (CRN) and supported by the EPSRC-NIHR HTC Partnership for Technology Network on Devices for Surgery by the EPSRC-NIHR HTC Partnership for Research Network (CRN) and supported commissioned by The National Institute Endovascular Interventions was

• To collect expert views on technologies
• To review the current and emerging analyses to support and guide NIHR-CRN and Rehabilitation to provide expert Technology Network on Devices for Surgery with the greatest potential impact on NHS care; with the academic perspective and a large developments for devices in endovascular UK clinical trial.

1. Endovascular Treatment

1.1. Stenting

Endovascular Intervention is a minimally invasive method for treating cardiovascular diseases via the vasculature. With this approach, the use of stenting is common. A stent is a small scaffold that can be implanted into the blood vessels in order to maintain the blood flow, as well as to reinforce the vessel wall. Most stents are made of biocompatible metals and those lined with fabric are called stent grafts. Stent grafts are widely used for treating aortic aneurysms. Once deployed, they form an inner lining of the aortic wall, restore the regular lumen geometry and prevent the vessel from rupture. Some stents are made with drug eluting capabilities; they gradually and continuously release medicine to prevent restenosis. The performance of endovascular stenting is usually under the guidance of X-ray fluoroscopy to provide the visualisation of blood vessels and confirmation of successful deployments.

1.1.1. Endovascular Aneurysm Repair

Although open surgery for aneurysm repair remains the standard of care, it is associated with lengthy procedure time, the need for general anaesthesia, and prolonged hospital stay and recovery. Endovascular Aneurysm Repair (EVAR) has now become a promising alternative. The goal of EVAR is to deploy made-to-measure stent grafts to restore vessel geometry and normal flow patterns, prevent further weakening of the vessel wall that can lead to aortic rupture. Successful implantation relies on careful pre-operative planning and ideally customised stent grafts that conforms to patient-specific vessel geometry. Common imaging modalities used include CT angiography, magnetic resonance imaging (MRI)/MR angiography, and duplex ultrasonography (US). Clinically, contrast-enhanced CT is the most commonly used technique for pre-operative planning of EVAR (Erbel, Aboyans et al. 2014). A typical stent graft system consists of three components: 1) a delivery mechanism; 2) a self-expandable metallic mesh tube that supports the vascular attachment; and 3) a fabric coating on the mesh to exclude the aneurysm and conduct blood flow. The most common stent graft is built with a self-expanding nitinol scaffold supported with a polyester or polytetra-fluoroethylene membrane. In practice, preoperative aneurysm morphology scoring is also important to define the difficulties of the procedures. The neck morphology of the aneurysm is a crucial factor for predicting long-term outcomes.

The most common complications of EVAR are stroke and endoleaks. An endoleak is the perfusion of flow to the excluded aortic pathology and it can be classified according to the site of perfusion. A Type I endoleak happens when there is a continuous perfusion due to loose fixation at the proximal and distal attachment sites. A Type II endoleak occurs when there is a reverse blood flow through a branch vessel arising from the aneurysm sac, which is the most common type of endoleaks. Type III endoleaks are related to the defect of the device itself, such as the breakdown of the fabric coating, hence causing perfusion to the aneurysm sac. Type IV endoleaks happen when blood leaks from the fabric coating due to the porosity of the grafts. Finally, Type V endoleaks are usually caused by the expansion of stent grafts caused by increasing pressure inside (Erbel, Aboyans et al. 2014).

Patient preparation and intervention before the procedure is necessary to prevent Contrast medium–Induced Nephropathy (CIN) since iodine contrast agent is introduced during the catheter angiography. Intravenous sodium bicarbonate and preoperative hydration are useful to prevent CIN. EVAR is performed in a dedicated sterile operation room equipped with C-arm fluoroscopy or CT fluoroscopy. Considering the significant radiation involved, particularly for long procedures, the imaging modalities should also provide dose reduction technologies such as variable-rate pulsed fluoroscopy. Geometrical adjustment of the imaging view relative to the anatomy is important to the surgical outcomes. The use of the iodine contrast agent needs to be carefully regulated in order to prevent CIN (Walker, Kalva et al. 2010). The access of the endovascular instruments is achieved by percutaneous access at the femoral artery for EVAR. An angiography catheter is initially introduced to visualize the arteries. This is followed by endovascular catheterisation, which introduces a stiff guidewire by using a combination of elongated instruments such as a catheter and sheath. The next step is to insert the stent graft delivery tool over the guideewire that has been previously introduced to the target region. After the placement of the stent graft, endoleaks can be examined intraoperatively by carefully evaluating the images from the arteriogram. Type I and Type III endoleaks, if observed, should be immediately treated (Erbel, Aboyans et al. 2014).

After an uncomplicated operation, the patient needs to stay in hospital overnight. Observation and monitoring methods include pain management, monitoring the access site and cardiopulmonary status.
For complex procedures, post-operative CT scans are often required. Lifelong imaging surveillance of patients after endovascular interventions is critical for monitoring implant status and detecting endoleaks. Renal function should also be monitored after a catheter-mediated intervention. CT remains the most common modality for postoperative imaging surveillance. However, for renal protection, this could be replaced by MR angiography and ultrasound. Implantable telemetric pressure sensor is another way of surveillance for monitoring the pressure inside the aneurysm sac, which has the advantage of being real-time, continuous, and low-cost (Walker, Kalva et al. 2010).

In clinical practice, there are further complications other than endoleaks. Mechanical injury of the endothelial lining of the arterial wall may happen during navigation. This can initiate platelet aggregation, causing blood clots to form, and stimulate neointimal hyperplasia. In severe cases, this may lead to vessel perforation and dissection. Excessive pressure could rupture the blood vessel with dire consequences. Although stent graft infection occurs very rarely, but failure to detect infection can result in serious conditions. Antibiotic treatment is needed to mitigate the infection risk. Furthermore, to avoid ischemic complications and limb occlusion due to blockade of arteries by endovascular components, secondary interventions are required to treat these conditions. A Type II endoleak due to reverse blood flow through a branch vessel arising from the aneurysm sac is the most frequent reason for re-intervention. Selective catheterization, embolization, direct sac puncture and extra stenting are typical re-intervention techniques (Walker, Kalva et al. 2010).

Thoracic Endovascular Aneurysm Repair
Patients with thoracic aortic aneurysm are often asymptomatic. Clinical signs include chest pain and compression. Diagnosis can be achieved through imaging such as chest CT, X-ray and MRI. Access to aorta is achieved either by open surgery or by percutaneous intervention. From the contralateral femoral side access, a pigtail catheter is typically used for angiography. Then a stent graft is delivered over a stiffer guide wire. A great proportion of thoracic aneurysm happens at the descending aorta, a slightly angled tubular stent graft can be deployed to exclude the lesion from blood flow. In cases when important branches of the aortic arch is involved, branched or fenestrated stent grafts are used to maintain the blood flows through these branches. However, the branches should not be over-stented in order to prevent complications including stroke. Common complication associated with this procedure is endoleak. Type I and III endoleaks are regarded as treatment failure, while Type II is less serious and the solution tends to be conservative. For Type IV and V endoleaks, re-intervention and treatments is immediately required to prevent further expansion and tissue rupture (Erbel, Aboyans et al. 2014).

Ablominal Aortic Aneurysm Repair
For Abdominal Aortic Aneurysm (AAA), early diagnosis is difficult and aneurysm repair is often indicated when rupture actually happens or obvious symptoms such as back pain occurs. AAAAs are classified according to their anatomic relationship to the renal arteries. The aim of endovascular abdominal aortic aneurysm repair is to deploy a stent graft with image guidance, securing device fixation to the wall covering the diseased aneurysmal sections, thus eliminating AAA sac pressurization. Deploying stent grafts for AAA needs two access sites from both femoral arteries in order to delivering a single branched stent graft. The fixation of stent grafts may be divided into suprarenal and infrarenal fixation depending on the difficulties of the anatomy. The shape of the grafts can be customized based on patient specific anatomy, all FDA-approved stent grafts come with modular design that allows preprocedural configurations (Walker, Kalva et al. 2010).

1.2. Coronary Artery Stenting
Percutaneous Coronary Intervention (PCI) is the most common therapeutic procedure in cardiovascular intervention. Stand-alone coronary balloon angioplasty has been replaced by coronary stent implantation nowadays due to reduced chance of acute vessel closure and restenosis. The major difference of coronary stents compared to other stents is that they are deployed over a balloon at the lesion site (Howard-Alps, de Bono et al. 2007). There are two main categories of coronary stents, bare metal stents and drug-eluting stents. The traditional bare metal stents have relatively high rates of restenosis and 20%-20% of those need re-intervention. Drug-eluting stents were first introduced in the 1990s. The idea is to gradually release anti-proliferative agents to the vessel in order to slow down the process of neointimal hyperplasia, which causes restenosis (Stefanini and Holmes 2013).

1.3. Peripheral Artery Stenting
For high-risk patients, long-term systemic atherosclerosis could lead to peripheral artery disease in lower limbs and upper limbs. For Superficial Femoral Artery (SFA) disease, stenting shows lower rate of restenosis, leading to significant improvement in functionality of the lower limbs compared to standard treatment such as Percutaneous Transluminal Angioplasty (PTA). However, there is a high risk of stent fracture in peripheral artery stenting. The choice of stents therefore highly depends on the location of the specific peripheral artery in order to prevent fracture. For example, coiled stent is favoured in Common Femoral Artery (CSA) as it is more resistant to bending compared to a mesh tube stent. Studies involving translating technologies from coronary artery interventions have shown promise. For example, drug-eluting stents for coronary artery can be used in tibial artery, with preliminary results showing reduced chance of restenosis (White and Gray 2007).

1.4. Venous Stenting
Venoplasty/angioplasty and venous stenting is commonly applied to chronically thrombosed veins. Venous angioplasty initially opens the blockage of the vessel, then stents are required for maintaining the blood flow because of the low intravascular blood pressure of the venous system. Swelling is a common syndrome of obstructed venous system including inferior Venous Cava (IVC), Superior Venous Cava (SVC), Infernal Jugular Vein (IJV), Innominate Veins (IVN), iliac veins and subclavian veins. Self-expanding stents are the best for interventions in the venous system. Balloon expandable stents are poor choices since deformation may cause severe restenosis. For typical IV/C SVC stenting, long-term outcomes have shown that the patency rate can be as high as 95%. The complications associated with venous stenting are rare. The examination and visualization of the procedure can be done by Intravascular Ultrasound (IVUS), CT and MRI (Bjarnason 2010).

1.5. Cerebral Stenting
Atherosclerotic intracranial arterial stenosis is one of the most common causes of stroke. There are two major treatments available: aggressive medication and Percutaneous Transluminal Angioplasty and Stenting (PTAS). PTAS is a relatively new strategy for treating ischemic stroke, the procedure is operated by neurointerventionists by deploying self-expanding stents to intracranial arteries (Novotzki 2009). Intracranial angioplasty may be introduced before the deployment in order to open the stenosis. However, PTAS does not show superior outcomes compared to medical therapy. It has a higher rate of periprocedural stroke, death and restenosis (Chimowitz, Lynn et al. 2011).

Stent retriever technology is a recent method that shows promising results for acute ischemic stroke treatments (Gasco, Lobotesi et al. 2014). A stent retriever device is a non-permanent stenting system that removes the plaque in cerebral arteries. The procedure starts with introducing a microcatheter and a storable microwire to the occluded site. Then the stent retriever delivery system is introduced over the microcatheter and into the vessel over the thrombus. After the stent retriever is fully expanded, angiography is performed to confirm plaque aspiration. Then stent retriever will be recovered and pulled back with the guiding catheter. A CT scan is typically performed at the end of the procedure to screen for haemorrhagic transformation, which is a major complication after the procedure. Further image examinations are performed for the same purposes.

1.6. Carotid Artery Stenting
Carotid Artery Stenting (CAS) is a minimally invasive treatment whereby embolic agents are delivered via a catheter into a blood vessel to block blood flow. The procedure is performed under X-ray fluoroscopy guidance. Access to the site is via guidewires and catheter and successful deployment of the embol is confirmed through digital subtraction angiography.

1.2. Embolisation
Catheter embolisation is a minimally invasive treatment whereby embolic agents are delivered via a catheter into a blood vessel to block blood flow. The procedure is performed under X-ray fluoroscopy guidance. Access to the site is via guidewires and catheter and successful deployment of the embol is confirmed through digital subtraction angiography.

1.2.1. Emboli
A range of embolic agents can be delivered via a catheter embolisation (Leyon, Littlehales et al. 2014). These range from liquids to particles that have varying degrees of cost, availability and possible side effects. All these agents are designed to deliberately cause ischaemia and necrosis. Mechanical occlusion devices include snares and balloons. Particulate agents can be classified as spherical or nonspherical, also available in various sizes. Liquid agents are designed to solidify once in place. Scelerosing agents induce tissue necrosis directly.

A summary of the different types of embolization agents available is presented in Table 1.
Cyanoacrylates solidify on contact with ionic fluid such as blood or saline. Low cost. Prior training required. Liquid. Coils are avoided as they preclude further embolization.

Adhesive

Polyvinyl Alcohol Provided as a powder to be reconstituted with contrast agent and saline to allow for delivery through a catheter. Permanent occlusion. Particle clumping and blockage of catheters can occur due to differing particle sizes. Difficult to predict level of embolisation.

Sclerosing

Absolute Alcohol Low cost but side effects are common. Cause pain and thus may require general anaesthetic. Peripheral AVMS.

Sodium Tetradecyl Sulfate Foam. Provides sonographic and fluoroscopic contrast. Low cost. Low risk of transient visual and neurologic symptoms. Vascosity, varicoceles, gastric bleeding, peripheral venous malformations.

Table 1: A summary of the different embolization agents currently available.

Mechanical Occlusive

Balloons No longer in common use. Can be used as a temporary occlusion device. Large vessel embolization.

Coils Permanent occlusion. Firmer coils used for anchoring while softer coils for packing. Detachable or non-detachable systems. Available in a wide range of sizes of delivery catheter. Easily available and relatively low cost.

Amplatzer Vascular Plug Based on the amplatz device used in interventional cardiology. Highly effective and safe. Good control over positioning and can be repositioned. More expensive than coils. Risk of device migration if incorrectly sized.

Particulate

Polyvinyl Alcohol Provided as a powder to be reconstituted with contrast agent and saline to allow for delivery through a catheter. Permanent occlusion. Particle clumping and blockage of catheters can occur due to differing particle sizes. Difficult to predict level of embolisation.


Autologous Clot Used where the clot can break down to restore circulation within hours. Rarely used today.

Gelatin Foam or powder forms. Low cost and relatively temporary. Possible reflux and nontarget embolization.

Liquid

Adhesive

Cyanoacrylates solidify on contact with ionic fluid such as blood or saline. Low cost. Prior training required. Any.

Onyx Nonadhesive and solidifies from outside to inside. Overcomes some of the difficulties with adhesives. Expensive. Mainly in neurointervention.

Sclerosing

Absolute Alcohol Low cost but side effects are common. Cause pain and thus may require general anaesthetic. Peripheral AVMS.

Sodium Tetradecyl Sulfate Foam. Provides sonographic and fluoroscopic contrast. Low cost. Low risk of transient visual and neurologic symptoms. Vascosity, varicoceles, gastric bleeding, peripheral venous malformations.

Table 1: A summary of the different embolization agents currently available.

Microspheres


Vascular

Cerebral Arteriovenous Malformations (AVMs)

The first embolisation of a Cranial Arteriovenous Malformation (AVM) is credited to Alfred J Lussenhop (Maiti, Bir et al. 2016). Cerebral AVMs are complex networks of abnormal arteries and veins within the brain that lacks an intervening capillary bed. This results in high flow that can result in haemorrhage and thus neurological injury (Ellis and Lavine 2014). Treatment options include microsurgical resection, stereotactic radiosurgery, and endovascular embolization; a combination of these approaches is usually used. Embolisation is typically performed pre-microsurgery or pre-radiosurgery and less usually delivered alone. Liquid agents, particulate agents, and coils are normally used in these procedures. The risks of this procedure can be substantial - with rates of 5%-15% reported in the literature.

Cerebral Aneurysms

The gold standard for the treatment of cerebral aneurysms is currently microsurgery (Rosenwasser, Chabouli et al. 2014) although endovascular techniques have evolved considerably, with coils, stents and flow diverters now available for placement. Endovascular treatment is also suitable for ruptured aneurysms. While endovascular coiling appears to have a lower complication rate than microsurgical clipping. The rate of reintervention is higher, indicating a lower long-term durability. Whether endovascular treatment should be attempted in the first place will depend on the location of the aneurysm, its clinical grade and configuration, as well as medical comorbidities.

Bleeding

Epistaxis (Nose Bleeds)

Epistaxis is the acute haemorrhage from the nostril, nasal cavity, or nasopharynx and spontaneous epistaxis that requires embolisation is idiopathic in nature (Krajina and Chrobok 2014). Causes can include a tumour blush, telangiectasia, aneurysm, and/or extravasation. Embolisation using a microcatheter and microparticles decreases the flow to the bleeding nasal mucosa while avoiding damage to the nasal skin and palate mucosa. Coils are not recommended. The success rate of embolisation for epistaxis is 71-94%.

Recurrent Hemothysis

Hemothysis is the coughing up of blood or blood-stained mucous from the respiratory tract and causes can include bronchietasis, chronic obstructive pulmonary disease, tuberculosis, and malignancy (Ramírez Mejía, Méndez Montero et al. 2016). Bronchial artery embolization, introduced in 1974, is the main endovascular therapy for hemothysis although it does not deal with the underlying cause; recurrence is therefore frequent. Embolic agents used include polyvinyl alcohol (PVA) microspheres, cyanoacrylate and gelfoam. Coils are avoided as they preclude further embolization if necessary.

Gastrointestinal Bleeding

In major nonvariceal upper gastrointestinal bleeding, the use of embolization has increased over open surgery. A recent literature review on existing studies comparing the two showed that while there was no difference in the mortality rates after both procedures, embolization appeared to show an increased risk of rebleding (Beggs, Dillworth et al. 2014). Further studies are required to confirm this finding.

Endoleak Management

The most common endovascular complication after endovascular abdominal aortic aneurysm repair (EVAR) is type II endoleak, whereby the sac refills via a type II endoleak. For post-EVAR embolization, the feeding artery and/or the aneurysm sac may be embolised. However, a review of studies looking at prevention of endoinkocele via embolisation has shown variable success rates and identified a number of disadvantages to embolisation (Brown, Saggu et al. 2016). Likewise, with treatment of post-EVAR endoleaks, there exist relatively high reintervention rates that necessitate a careful risk versus benefit review.
Trauma Haemorrhage

Whilst there are no clear guidelines for the treatment of traumatic pelvic injuries, one possible procedural intervention is angiographic embolisation (Mauffrey, Cuelar Ill et al. 2014). Studies have shown a success rate of 85-100% in the use of interventional angiographic embolisation for the treatment of unstable pelvic fractures. However, while success of the procedure is high, the mortality rate remains high, making the use and role of embolization in cases of pelvic fracture controversial. The pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma recommends that patients with ongoing haemodynamic instability undergo treatments including angiographic embolisation (Rossaint, Bouillon et al. 2016).

Oncology

Embolisation can be used for the delivery of regional therapies for the treatment of cancers – these include chemoembolisation and radioembolisation. One key area of embolisation for oncology is in the treatment of liver masses (Molvar and Levandovski 2015). Randomised control trials have shown a survival benefit of conventional transarterial chemoembolisation in patients with hepatocellular carcinoma. Retrospective data and noncontrolled prospective studies have shown that both chemoembolisation and radioembolisation are safe and effective for the treatment of primary and metastatic liver disease and benign liver lesions.

Women's Health

Uterine fibroid embolisation is a well-established treatment for symptomatic uterine fibroids and is performed by the embolisation of the uterine artery (Lopera, Suri et al. 2013). Particulate agents are used; PVA used to be the standard but this is now Embospheres (Biophase Medical, Rockland, MA).

The technical success rate is 84-100% while the clinical success rate is 90% - the fibroid will shrink as well the uterus.

Postpartum haemorrhage is the main cause of pregnancy-related maternal death worldwide and may also be treated with uterine artery embolisation, similar to the treatment of fibroids. Bleeding can be controlled to the order of 80-90% and the uterus can be preserved. In this case the embolic agents used are partcurate or adhesives, with coils occasionally used. Pelvic Congestion Syndrome (PCS) causes chronic pelvic pain in women. Its causes are varied but can be associated with the presence of ovarian and pelvic varicose veins. It can be treated by transcatheter pelvic varicose embolization, with a technical success rate of over 95% and with 68-100% of patients reporting a relief in symptoms. Scarring or liquid embolic material is chosen for this procedure; coils are avoided due to their potential to migrate.

Men's Health

Prostate artery embolization is becoming more commonly used for treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia.

While large, randomised studies are required to establish the efficacy of the technique, current evidence suggests that it is a promising method, especially if pharmacotherapy is not fully successful (Jones, Rai et al. 2015).

Obesity

With the increase in obesity around the world, there have been growing interests in catheter driven treatments, including embolisation (Anton, Rahman et al. 2015). Initial evidence suggests the promise of this technique for weight management though the first animal studies showed a possible risk of post-embolisation gastric ulcer formation. Further trials are required to elucidate the role of embolisation for obesity.

1.3. Ablation

1.3.1. Cardiac Catheter Ablation

Ablative therapy in the heart is used for the treatment of complex arrhythmias unresponsive to medication and life-threatening to the patient. The most common method of choice is the delivery of radiofrequency (RF) energy waves from the tip of a flexible catheter at precise myocardial positions in order to cause irreversible lesions in the arrhythmic tissue. Nowadays, a myriad of conditions are treated by these means, including atrial and ventricular tachycardias (Klein, Shih et al. 1992, Stevenson, Khan et al. 1993, Tracy, Svartt et al. 1993, Kallman, Vanhara et al. 1996, Poty, Sassudi et al. 1996, Sacher, Roberts-Thomson et al. 2010), Wolff-Parkinson-White syndrome (Calkins, Sousa et al. 1991, Jackman, Wang et al. 1991, Calkins, Langberg et al. 1992), and more recently atrial fibrillation (Jaíl, Halászeguerré et al. 1997, Nadermame, McKenzie et al. 2004, Pappone, Vicedomin et al. 2006).

In addition to RF energy, there has been extensive interests in using laser ablation for cardiac application. Laser energy has already been used in destroying cancerous tissue, such as liver carcinoma (Gough-Palmer and Gedroyc 2008). Its benefit compared to RF energy is that lesions are potentially not influenced by the quality of the contact between the tissue and catheter tip (Anton, Rahman et al. 2015). Previous studies (Anton, Rahman et al. 2015) looked into ablation bovine myocardium with an irrigated laser catheter (RytmoLas, Lasticor GmbH, Taufkirchen, Germany) with promising results for dynamic procedures such as cardiac arrhythmias. Khurram et al (Khuram, Canzaro et al. 2015) discovered no statistical difference between postablation scar in RF, laser, and cryoablation, as shown in late gadolinium enhancement MRI.

Another alternative is the use of microwave energy. Potential benefits include controlled heating of large volumes and reduced charring, one of the main issues with traditional RF catheters (Chiappini, Di-Bartolomeo et al. 2003). Moreover, the ablation lesion is deeper for the same tissue surface temperature; lesions not deep enough are a common issue, as they do not contribute to arrhythmia suppression. Despite some of the advantages, microwave ablation has a limited use for the current cardiacology practice.

Qian et al (Qian, Barry et al. 2015) described a first attempt at designing and using a microwave catheter for pulmonary vein isolation in vitro. They reported good results and emphasised the need for an in-vivo contactless ablation technique with results that are less susceptible to cardiorespiratory motion.

Additionally to RF, laser and microwave ablation, cryoablation has been described as therapeutic means for curing heart rhythm disorders (Heart Rhythm Society 2017). Similarly to laser catheters, the delivery device have a balloon at the tip containing refrigerant. The balloon technique is used for single ablation of each of the pulmonary veins in vivo. Cryoablation technology consists of temporary reversible alteration of the tissue as opposed to permanent damage. This is in particular useful for confirmation of the intended ablation site (Beggs, Dilworth et al. 2014, Brown, Saggu et al. 2016). While it can be argued that electroanatomical mapping is already used for establishing the target, short-term cryoablation can be a secondary source of information and can be used in conjunction with electrical mapping to simulate the effect of permanent ablation. This is not available yet in any of the electroanatomical mapping software versions on the market. However, because of the possibility of reversible ablation, there have been several cases of tachycardia circuit recovery and need for redo procedure (Heart Racing 2017). Further investigations showed that the catheter thickness is positively correlated with the efficiency of the procedure. Secondly, it was reported that cryoablation causes less intraprocedural complications than RF energy (Heart Racing 2017). Among these advantages are less charring, blood clots (common complication in ablation ablation) and in general better outcome even in regions with reduced blood flow.

In the general context of robotically assisted cardiovascular procedures, electromagnetic navigation has facilitated access and manipulation at anatomically difficult sites. For cardiac ablation in particular, the technology was implemented in the Niobe system (Stereotaxis, St. Louis, MO, USA) which uses two permanent magnets to generate a field in which the magnetic tip and flexible shaft of the catheter can move to any position (Figure 4).
One of the newest developments in magnetic navigation for cardiac ablation procedures is Aeon Phocos (Aeon Scientific, Zurich, Switzerland). The navigation system makes use of the company’s patented electromagnetic steering to provide easy access to any of the four cardiac chambers.

In a review of remote magnetic navigation outcomes for cardiac ablation, it was established that such devices were most often used in atri-o-ventricular re-entrant tachycardias (Oxley, Opie et al. 2016). Acute and intermediate success rates were as high as 95% and 93%, respectively. However, these figures can be achieved in the manual procedures as well. Looking into areas which can potentially benefit from the magnetic system’s catheter softness and higher stability, (Oxley, Opie et al. 2016) showed that for ventricular tachycardia, the manual success rate of 79% was improved to 97% by using a robotic catheter. Moreover, it was deemed that such a magnetic navigation system could be highly suitable for enclosed space applications such as epicaldial ablation.

Transcatheter Aortic Valve Implantation and Atrial Fibrillation

In the context of heart rhythm disorders, it is important to note that atrial fibrillation is a common complication of Transcatheter Aortic Valve Implantation (TAVI) (Saeed, Hett et al. 2012) proposed the presence of atrial fibrillation before TAVI as a predictor of the post-procedural mortality rate at 1 month. They also concluded that atrial fibrillation is more likely to be induced if the TAVI procedure is performed transapically. Their study showed that 30% of the patients with no previous episodes of atrial fibrillation experienced supraventricular rhythm disorders after the intervention.

1.3.2. Endovascular Ablation of Hepatocellular Carcinoma

In a broader sense, ablation is employed as therapy for several types of cancer (hepatocellular carcinomas, benign thyroid nodules, colorectal metastases to the liver, other liver, kidney, and bone tumours), with percutaneous access in most cases. While there is great potential in microwave and cryoablation for these particular applications, the lack of medical devices with endovascular access restricts the possibilities of therapy to RF, which is less effective in less conductive lung or bone tissue (Brace 2009). However, there has been an increase in these alternative treatments, with focus on standardised energy delivery for each application and organ.

One of the few endovascular systems based on microwave ablation is produced by EMcision (Department of Surgery, Hammersmith Hospital, London, UK (2017)). The company has been marketing several types of catheters, primarily for endovascular ablation of hepatic vein and other hepatocellular or gastrointestinal carcinoma. In Table 2, an overview of their most important and clinically approved devices is given. The bipolar RF catheters are shaped according to their intended application, but all of them are meant for a minimally invasive endovascular insertion to the targeted site.

1.3.3. Treatment of Chronic Venous Insufficiency

Chronic venous insufficiency is the result of reflux from the saphenous veins into venous segments which hamper the normal blood flow. Very often, the reflux is caused by the failure of the saphenofemoral junction valves (Weiss and Weiss 2017). Traditionally treated surgically, this condition has been managed with laser ablation of the saphenous vein junction and subsequent elimination of the abnormal segments. Both laser and RF ablation are in use (Khilkani and Winokur 2017). Additionally to ablation, recurrent cases are also treated with stenting of the iliac arteries (Eberhardt and Raffetto 2005).

One of the most popular endovenous laser treatment systems is VenaCureEVLT (Angiodynamics, Queensbury, NY, USA), whose principle is presented in Figure 6. The procedure is guided by intraoperative ultrasound.

It has been reported that despite very good outcome of ablative treatment for chronic venous insufficiency, there is a significant learning curve associated with the limited intraoperative visualisation (Hissink, Bruins et al. 2010). Cannulation is difficult with only real-time ultrasound information. A possible addition to the system is prereoperative image overlay for better orientation and for pre-planning the procedure.

For RF ablation, Covidien (Dublin, Ireland) patented the Venefit procedure, which seals varicose veins using an in-house developed catheter-energy generator-stylist triplet. Zilinzi et al (Zilinzi, Salles-Cunha et al. 2005) reported the use of one of their earlier RF ablation technologies in treating great saphenous vein incompetence in what was one of the first minimally invasive procedures to treat chronic venous insufficiency.

A randomised controlled trial has been conducted to compare outcome in laser and RF ablation using the two systems described above (Gale, Lee et al. 2010). They concluded that endovascular laser use caused more bruising, but yielded better long-term results than RF ablation. Currently, there is a comparative clinical study running until 2028 to further investigate the difference in short and long-term effects of laser vs. RF ablation of varicose veins (Clinical Trials 2017).

More recently, endovenous foam sclerotherapy was developed for minimally invasive treatment of varicose veins. A sclerosant solution is injected into the veins in order to cause clots and block the damaged veins. These unfunctioning veins will be resorbed in the body with time. The injection is performed under ultrasound guidance. This being a novel therapy, there has been little follow-up on the effects of foam injection. However, several complications (Circulation Foundation 2017) are expected: thrombophlebitis due to hardening of the foam in the superficial veins, thrombosis in the bigger veins, and stroke from excess foam (Bundy 2014). The NIHR is currently funding a clinical trial to further compare the different endovenous therapies for chronic vein insufficiency (Ellis and Lavine 2014).

Table 2: EMcision devices for endovascular ablation of the hepatic vascular system

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habib VesOpen Catheter</td>
<td>Endovascular RF catheter for vascular remodelling and dilatation of vascular stenosis Interventional radiologist inserts catheter for benign and malignant cases of vascular stenosis and occlusion. Dr Madhava Pai (Department of Surgery, Hammersmith Hospital, Imperial College London, UK) reported its use for treating hepaticcellular carcinoma with portal vein thrombus (PVT).</td>
</tr>
<tr>
<td>Habib VesCoag</td>
<td>Precise vascular occlusion, RF endovascular ablation for primary and secondary liver cancers, thus cutting out the blood supply to the tumour. It also stops local endoluminal or endovascular haemorrhage and can be used as a chemical delivery system, e.g. for arteriovenous fistule or varicocele.</td>
</tr>
<tr>
<td>Habib EndoHPB</td>
<td>Endoscopic bipolar RF probe for tissue ablation in the gastro-intestinal tract, for tumour ablation in the bile duct and head of the pancreas Preparation of tissue for stent insertion in order to delay clotting on the metal lace.</td>
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</tr>
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</table>
2. Devices for Endovascular Interventions

2.1. Imaging

While strictly speaking not a medical device, the imaging used in guidance and deployment of endovascular devices does play a major role in their design and effectiveness in vivo. We cover below the current clinically available imaging modalities as well as the state-of-the-art modalities, methods and new sensing technologies that are relevant to endovascular devices.

2.1.1. Preoperative Imaging

Preoperative imaging for endovascular planning typically involves MRI or contrast-enhanced CT in the form of a CT angiogram. Segmentation of the vessels allows for a complete 3D understanding of the shape and underlying complexity of the patient-specific anatomy. The use of 3D printing for planning and visualisation for particularly complex cases has also received attention. While the cost of 3D printing is steadily reducing, the recent increased attention given to virtual reality may see this technology replaced.

Haemodynamic quantification is possible using imaging methods such as phase-contrast MRI or Doppler ultrasound. However, when such methods are unavailable, the use of computational fluid dynamics to perform simulations within the 3D reconstruction has shown promise for the prediction of the impact of intervention on haemodynamics.

2.1.2. Intraoperative Imaging

The majority of endovascular procedures are guided via X-ray fluoroscopy with the use of iodine-based contrast agent to highlight vessel locations. For intraoperative 3D reconstruction, the same machine can provide cone-beam CT scans. While this imaging modality is affordable, the radiation dosage to the patient and the practitioner is significant. The contrast agent used is also nephrotoxic. Reduction of the X-ray exposure and the use of contrast agent is therefore important.

There has been much research into the use of MRI for guiding endovascular procedures (Saeed, Hetts et al. 2012). By integrating micro-coils into medical devices, their 3D position can be shown with respect to the anatomy. MRI is a safe imaging modality although it is currently loud, expensive, and requires special, MR compatible tools. However, MRI is a versatile technique, providing not only anatomical information but also functional data including quantitative measures such as shear stress, elasticity, perfusion and velocity. The incorporation of this information would aid in intervention decision making and device placement in vivo. For intracardiac use, imaging to determine tissue temperature or ablation depth would aid in treatment of arrhythmias with MRI. Similarly, for thermal ablation, functional imaging could assess the effectiveness of energy delivery.

Ultrasound imaging has been used to guide mitral valve repair and transcatheter aortic valve replacement (Bundy 2014) but there is scope for more effective use of the imaging technology. It has been shown that ultrasound can be used for targeting instruments and anatomy with sufficient accuracy and with this, safety of the procedure has been improved. Ultrasound imaging augmented with preoperative images can replace X-ray fluoroscopy and improve guidance in valve replacement procedures (Li, Rajchl et al. 2015).

2.1.3. Intravascular Imaging

For intravascular imaging, current techniques include ultrasound and Optical Coherence Tomography (OCT). Intravascular Ultrasound (IVUS) is a radial ultrasound transducer at the tip of a catheter and is already in clinical use for classification of arterial tissues. OCT is another biomedical tissue-imaging technique that provides high-resolution optical images of the vessel but only allows for limited imaging depth. While IVUS offers greater imaging depth than OCT, both imaging modalities are still less commonly available in UK hospitals compared to those in North America.

A forward facing intracardiac ultrasound probe is currently being developed by VytronUS, Inc (Sunnyvale, CA, USA): this probe is based on low-intensity collimated ultrasound and the system allows both 3D reconstruction of the endocardial walls and ablation of tissue, both through blood and without tissue contact. Pre-clinical studies have demonstrated the safety and efficacy of the system when performing ablation to isolate the pulmonary veins (Koruth, Schneider et al. 2015). An increased interest in photoacoustic imaging methods has also raised the possibility of incorporating this imaging modality onto intravascular catheters and guidewires.

2.1.4. Sensing

Apart from imaging, the 3D position and orientation of devices in vivo can be achieved through electromagnetic (EM) tracking and navigation. It is anticipated that this technology, already in use in cardiac electrophysiology for the 3D position tracking of the distal end of mapping and ablation catheters, will be gaining more applications in endovascular interventions (Manstad-Hulaas, Tangen et al. 2012). Other tracking technologies are currently incorporated into existing commercial systems, particularly for cardiac catheter ablation. These include the Biosense-Webster CARTO system and Boston Scientific Rhythmia system, both based on magnetic fields, and the st Jude EnSite system, based on impedance mapping.

Companies such as Sensuron (Sensuron 2016) have also started looking into the provision of fibre-optic based shape sensors that can be incorporated into guidewires and catheters. Whilst EM sensors can only provide the 3D position of a discrete set of points, fibre-optics sensors have the potential to determine the entire 3D shape of medical devices in vivo. New research has looked at the use of shape sensing for improved navigation for endovascular procedures (Mandali, Parent et al. 2016).

2.1.5. Clinical Need

More effective use of the current available imaging modalities in endovascular guidance would contribute to shorter procedural time and more effective procedures. This would aid in the reduction of radiation without requiring an outlay of capital for new imaging equipment. However, the future of endovascular interventions would be in newer, safer, faster imaging modalities but these are still at the development stage. There is promise in the use of other similar technologies, such as electromagnetic tracking, which is already in use in cardiac electrophysiology mapping and in percutaneous procedures.

Better use of the latest imaging modalities in endovascular guidance would contribute to shorter procedural time and more effective procedures.
2.2. Implants

Drug Eluting Stents
The first balloon angioplasty for the treatment of coronary heart disease was performed in 1977, while the first coronary stent implantation was in 1984. Since then, percutaneous, catheter-based interventions for coronary heart disease have evolved and significant advances have been made (Katz, Harchandani et al. 2015). However, the use of angioplasty and bare metal stents tended to result in restenosis, and this eventually led to the development of drug eluting stents which could locally deliver antiproliferative drugs to reduce neointimal hyperplasia, the primary cause of restenosis.

The use of drug eluting stents over bare metal stents in the treatment of extracranial vertebral artery disease has been investigated, with results showing that the use of drug eluting stents reduces restenosis, recurrent symptoms and target vessel revascularisation (Tank, Ghosh et al. 2015). However, there is some evidence to suggest that the use of some drug eluting stents is linked to a high incidence of thrombosis (Palmerini, Biondi-Zoccai et al. 2012).

Bioabsorbable Stents
While drug eluting stents are now mainstream in the treatment of coronary artery disease, they still carry some risks, including thrombosis, local inflammatory reaction, and restriction of vasomotion (Brie, Penson et al. 2016). Bioabsorbable stents, such as the ABSORB BVS (Abbott Vascular, Santa Clara, USA), the first fully bioresorbable vascular scaffold, have shown to provide both vessel support and drug delivery without the need for the traditional metal structures. However, further studies are still required to show results comparing bioabsorbable stents to drug eluting stents or bare metal stents and these need to focus on the long term, after full absorption (Wayangankar and Ellis 2015). Limitations to current bioabsorbable stents include their bulk, the risk of stent fracture, and the challenges of visibility under X-ray guidance.

Stent Grafts
Stent grafts are tubes of fabric reinforced with metal stents and are widely used for the endovascular treatment of aneurysms, typically deployed via catheters. The main challenges are their use in the treatment of aneurysms located near branching vessels (Crawford, Sanford et al. 2016). The use of fenestrated stent grafts in FEVAR (fenestrated endovascular aneurysm repair) have been shown to be effective in the short and median term (Georgiadis, van Herwaarden et al. 2016), with most clinical issues similar to those experienced in EVAR (endovascular aneurysm repair). The use of in-situ fenestrations in stent grafts (Malina and Sonesson 2015) or physician modified stent grafts may help catheter-based treatment of more complex aneurysms. The main limitations are the time and costs required to manufacture patient-specific fenestrated stent grafts as they are currently all handmade. The ability to automate some or all of the planning and manufacturing steps will help reduce costs and ensure that patients are able to be treated as soon as possible.

Flow Diverters
Intracranial aneurysms may be treated via the insertion of flow diverters, allowing, as their name suggests, the diversion of flow and endoluminal vessel reconstruction (Rosenwasser, Chalouhi et al. 2014). The use of devices such as the Pipeline\textsuperscript{TM} Embolization Device (PED) (Covidien, Irvine, CA, USA) has been shown to be more cost effective and time efficient, with higher occlusion rates within large, unruptured aneurysms. Like most other implantable devices, however, longer follow up studies are required to determine the rate of complete occlusion within patients (Briganti, Leone et al. 2015).

2.2.2. Monitoring Devices
Monitoring devices such as the CardioMEMs, the first and only FDA-approved heart failure (HF) monitor, have been shown to improve quality-of-life in patients and reduce hospital admissions. CardioMEMS (St Jude Medical, St. Paul, MN, USA) is a permanent implant delivered via catheter to the pulmonary artery, where arterial blood pressure is measured. The CHAMPION randomised control trial showed that the use of the CardioMEMS device was linked to a reduction of hospital readmissions in NYHA class III heart failure patients (Abraham, Adamson et al. 2011).

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CASE STUDY: From Concept to Clinical Translation - Endovascular delivery of permanent PA pressure sensor – Dr Chris McLeod, Imperial College

We have been developing a permanent implantable pulmonary artery (PA) pressure sensor and is currently working at clinical translation of the device. This was developed with funding from the Wellcome Trust and the Department of Health under the Health Innovation Challenge Fund.

Hypothesis
1. Heart Failure (HF) is a progressive disease whose progression can be retarded by avoiding destabilisation episodes and re-hospitalisation.
2. HF is composed of multiple pathologies for which different treatments are required. The pathologies result in detectable biochemical and physical signals and in clinical symptoms.
3. Of the physical signals, monitoring filling pressure will give the earliest warning of potential destabilisation (Adamson 2009).
4. Device-less telemonitoring of self-reported symptoms has been shown to provide PAP data from patients during the full range of daily activities. This will generate a more complete picture of patients’ natural responses to rest, exercise and sleep. The sensor is excited, and read, wirelessly at a high radio frequency (RF).
5. Pulmonary Artery Pressure (PAP) is safer than Left Atrial Pressure (LAP) in the first instance – until thromboembolism has been excluded from the risks.
6. Continuous, ambulatory monitoring offers the full picture – resting levels, responses to exercise, variability on circadian, sleep, autonomic, respiratory cycle timescales.
7. Titration of pharmaceutical therapy based on objective PAP data will enable better control of PAP while minimising pharma side-effects.

Data Supporting the Hypothesis
The CHAMPION trial using CardioMems’ permanently-implanted PAP sensor has shown a very significant decrease (38%) in its primary endpoint – reduction in re-hospitalisation. The data was one daily PAP trace of about 20 seconds recorded while the patient lay supine on a bed over the recording equipment.

Development Roadmap
A new technology, derived from one implementation of a real-time automotive tyre pressure monitoring system, can be used with a portable, wireless monitoring system to provide PAP data from patients during the full range of daily activities. This will generate a more complete picture of patients’ natural responses to rest, exercise and sleep. The sensor is excited, and read, wirelessly at a high radio frequency (RF).

HF is categorised into preserved-ejection-fraction (HEFPEF) and reduced-ejection-fraction (HEFREF), largely coinciding with diastolic HF and systolic HF respectively. PAP during exercise has been shown to be a very potent prognostic indicator for HEFPEF patients (Dorfs, Zeh et al. 2014).

A new RF PAP sensor should be implanted by endovascular access. The patient will wear a reader which will supply power to the sensor and read its signal. The reader will store the data and be able to stream it in real-time to a remote server.

Funding
An initial fund of about £100k was raised in 2007 from Imperial College and Imperial Innovation to employ a post-doctoral research assistant for one year to manufacture test samples of a sensor working at physiological pressures.

The data generated enabled a successful grant application to the Wellcome Trust technology transfer section for a 3-year development programme (2008-2011) including an appropriately-sized sensor and a reader. The results enabled a successful larger grant application to the Health Innovation Challenge Fund for working sensors and retaining stent for the PA, a delivery and deployment catheter and a portable reader suitable for patient use. The programme (2011-2015) included the technical developments necessary for a repeatable production process for all the components, a pre-clinical trial in an animal model, application to the Medicines and Healthcare products Regulatory Agency (MHRA), ethics committee(s) and research regulatory committee(s) for a Phase 1 (first-in-man, safety) study, and the completion of this study.

Initially, the scope of the clinical trial could not be predicted and the funders have subsequently generously added an extension to cover the time and cost of the trial.

Collaborations and Sub-contracts
While the fundamental system design and the detailed design of the components has been carried out within Imperial College, all the manufacturing has been subcontracted to companies already proficient within their specialist areas. For some companies this has been their first medical device development.

We have, within the College team, Professor Sir Magdi Yacoub as Clinical Lead and Dr Iqbal Malik, head of the catheterisation lab at the Hammersmith Hospital, as a very experienced interventionist. Those two have advised all clinical aspects of sensor position – allowing for the limited penetration of RF into and out of the body – and its anchoring within the PA. They have also set specifications for the delivery catheter (femoral vein to PA) and control during deployment. They have participated in the early animal trials and specified any modifications necessary for improving the system.

Current Position
We have successfully deployed devices in the PA of 80kg swine and measured PAP acutely. The designs of the components have been altered slightly and frozen. Production-equivalent devices are now being made for testing in chronic animal recordings.

Next Steps
The data from the chronic animal studies will be presented along with the design files in an application to the MHRA for a Phase 1 clinical trial. The same data and files will be prepared for eventual submission, along with the results from the clinical trial, to a Notified Body when we apply for a CE mark for the system. By this time a commercial entity will be needed to hold the CE mark.

If these steps are all successful, a Phase 2 (efficacy) trial should follow. This will necessarily be a much more expensive undertaking than the Phase 1 trial and will need significant commercial funding.

Conclusion
Although there is no conclusion yet, we hope that the above description will illustrate some of the processes in translating an idea into an endovascular device and the timescale required if the system is complex.
2.2.3. Valve Replacements

The four main valves of the heart are the two atrioventricular valves: the mitral valve and the tricuspid valve, and the two semilunar valves: the aortic valve and the pulmonary valve. Transcatheter valve technology today has enabled the replacement of these valves via minimally invasive means (Figulla, Webb et al. 2016). The first transcatheter heart valve implantation was performed in the pulmonary position in 2000 and in the aortic position in 2002 (Testa, Latib et al. 2016); since then, thousands of patients have been treated in this way. Another minimally invasive alternative to surgical approaches is to perform valve replacement transapically. Percutaneous pulmonary valve implantation is a less invasive means of treating right ventricular to pulmonary artery stenosis or pulmonary regurgitation (Ansari, Cardoso et al. 2015). Patients with adult congenital disease are most likely to benefit as they require repeated surgical intervention due to right ventricle outflow tract dysfunction.

Transcatheter Aortic Valve Implantation (TAVI) or Transcatheter Aortic Valve Replacement (TAVR) is now an established method for patients with aortic stenosis, who are unable to tolerate the conventional surgical aortic valve replacement. Since the first case in 2002, over 200,000 procedures have been performed worldwide (Vahl, Kodali et al. 2016). Important issues to be considered in the future for TAVI include device durability and expansion of clinical indications; concerns about the former are the main reason why TAVI has not been expanded to lower-risk patients. Recent trials (PARTNER-1, CoreValve, and NOTION) comparing TAVR to surgical aortic valve replacement (SAVR) have shown the benefits of TAVR for high-risk patients but further trials are required for lower-risk patients (Caruval, Villalbanca-Spinetto et al. 2016). The field is rapidly evolving and it is likely that these large trials will help define future directions. The use of TAVI or other catheter based procedures for patients with aortic regurgitation, however, is still not established due to the presence of valvular calcification and distortion of aortic root anatomy (Bonow, Leon et al. 2016).

Unlike the aortic valve, transcatheter mitral valve implantation is a less commonly performed procedure (Testa, Latib et al. 2016). The procedure is more difficult than TAVI, with less direct valve delivery, heterogeneity of mitral valve disease and the need for better imaging and navigation during the procedure (Nishimura, Vahanian et al. 2016). While a number of devices already exist, there is a lack of studies showing clinical proof of safety and efficacy. Thus far, there is a strong association between severe tricuspid regurgitation (TR) and mortality. For effective treatment of the former, new devices for transcatheter treatment have become available (Rodet-Cabau, Hahn et al. 2016). However, this area is generally understood to be the least represented in terms of clinical device availability with major challenges due to large tricuspid valve annulus dimensions, a lack of valve calcification, close proximity to the right coronary artery, and fragility of the tricuspid valve annulus tissue. Appropriate prospective trials are required to determine the effectiveness of transcatheter approaches over traditional surgical methods.

In the future, new technologies such as tissue engineered valves and issues with device durability are expected to see an increase in use of these minimally invasive procedures.

2.2.4. Electrodes

Recently, it has been shown that it is possible to record brain activity from within a vein using a passive stent-electrode recording array (Oxley, Opie et al. 2016). Traditionally, high-fidelity intracranial electrode arrays require direct implantation into the brain and this endovascular approach, thus making this approach safer. Current limitations are the durability of the delivery wire but the approach is very promising for reliable chronic neural recordings.

Table 3: A summary of commercially available transcatheter valve devices.
CASE STUDY: The UK TAVI Trial

UK TAVI Registry


Purpose
The UK TAVI registry was primarily organised as a support platform for introducing the TAVI procedure in the UK. The focus was on collecting and analysing high quality data from these procedures via the Central Cardiac Audit Database (CCAD). The data was encrypted before it was collected centrally in the CCAD.

Collaborations
The UK TAVI registry is the result of collaborative work between professional societies, i.e., the British Cardiovascular Intervention Society (BCIS) and the Society for Cardiothoracic Surgery (SCTS), the Department of Health and specialist commissioners, and health technology assessment organisations and regulators, i.e., the National Institute for Health and Care Excellence (NICE).

Data
The dataset comprised information from cases before 31 December 2009. This amounts to 872 patients from 26 centres. There were 67 subjects from 2007, 272 from 2008, and 533 from 2009. Out of the 872 cases, 10 were unsuccessful valve implants.

Analysis
The documented valves were of two types: 460 CoreValve (Medtronic, Minneapolis, MN, USA) and 402 SAPIEN (Edwards, Irvine, CA, USA). The analysis on the registry showed that the two types were preferred in conjunction with different access and implantation techniques. The statistical analysis also covered the mortality and morbidity outcome depending on the vascular access. Finally, the results of a 2-year follow-up were published. The survival rate was higher for patients whose valves were implanted transfemorally compared to other methods (statistical significance value of the test p = 0.017). The two curves are shown in the second figure. The study also included an analysis of the learning curve, as the trial was conducted in order to support the uptake of TAVI in the clinical praxis. The 2-year survival rate in the first 20 cases was compared to the survival rate in the rest, with the outcome of the subsequent cases being only marginally better than that of the first ones.

In a more recent analysis of the same dataset, at a 6-year follow-up of the same cohort, it was observed that the clinical profiles of TAVI patients did not change, but they were discharged sooner after the procedure than in the early years. Moreover, their long-term outcomes improved over the 6 years of TAVI experience. The study also helped in defining risk and outcome predictors: periprocedural stroke, nonfemoral access, and postprocedural aortic regurgitation (Leyon, Littlehales et al. 2014).

Another study based on the dataset in the UK TAVI registry investigated the dependency of procedure outcome on the access route (transfemoral, transapical, or subclavian) and the valve type (SAPIEN vs. CoreValve). It was discovered that the transapical heart puncture and valve implantation correlated with higher mortality than in a transfemoral access and delivery (Li, Rajchl et al. 2015).

Conclusion
The UK TAVI registry was a successful UK-wide data collection project, with subsequent analysis of several key indicators, including mortality and morbidity as function of endovascular access method, but also including steepness of the procedure learning curve. Keeping in mind that the analysis was performed in the early days of TAVI (2007–2009), the in-hospital mortality of 6.2% and the 1-year mortality of 19.7% were deemed as encouraging results, which actually improved to the current day.

UK TAVI trial

http://www.nets.nihr.ac.uk/projects/hta/095563

Start date: February 2013

Collaborations: interventional cardiologists, cardiac surgeons, patient representatives, experts in research design, clinical trials, medical statistics, health economics, cardiac imaging, geriatric medicine. Additionally, institutions are also involved in the trial: Department of Health Heart Team, the National Specialised Commissioning groups, NICE, and the national societies for interventional cardiology and cardiac surgery.

Purpose
1. Assessment of clinical effectiveness and cost utility of TAVI vs. open surgical repair of aortic valve, as well as development of morbidity and mortality predictors to guide the patient-specific decision between the two procedures. Only immediate effectiveness of TAVI has been documented so far; the trial will investigate the long-term outcomes (5-year follow-up) and compare them to the well-established conventional procedure. http://www.nets.nihr.ac.uk/_data/assets/pdf_file/0007/113947/PRO-09-55-63.pdf

2. Mortality at 30 days, 1, 2, 3, 4, and 5 years

Even with a very low mortality rate of 5.8% in surgical aortic valve replacement, one third of the elderly patients are still considered at high risk for this procedure (Lopera, Suri et al. 2013). Ten years after this publication, the UK TAVI Trial defined its one of its objectives to assess TAVI effectiveness, develop performance indicators, and make recommendations for the treatment of the high-risk patients with transcatheter procedures.

Hypothesis
TAVI is non-inferior to surgical repair at one year and each year up to 5 years.

Data
808 patients with aortic stenosis and at medium or high risk for open surgery for which procedure-related outcomes such as stroke, symptom relief, quality of life, occurrence of aortic regurgitation, and valve-durability during follow-up are known.

Any CE-marked device and any approach in clinical use are allowed for this study. There are 3 valves meeting the European standards: Medtronic self-expanding CoreValve, Edwards balloon-expandable SAPIEN and SAPIEN XT.

Dissemination
1. Based on the results of this study, the NHS will enforce a policy for the uptake of TAVI as routine clinical practice and as potential individually tailored treatment for patients with aortic stenosis.

2. There will be an economic analysis attached to the study and this will include device, staff, consumables, complications, and hospital stay costs and will also compare these figures for transarterial and transapical procedures.
2.3. Robotics

Current endovascular approaches are limited by excessive exposure to radiation, a lack of 3D mapping, as well as lost haptic feedbacks. In the last two decades, there is a growing interest in robotic steerable catheter technology which brought benefits such as improved precision and stability, reduced radiation doses, improved comfort and access to difficult and tortuous anatomy (Di Biase, Wang et al. 2009). However, these commercial platforms tend to alter the natural bedside manipulation skills of the operator, hence manually acquired experience and dexterity are not well utilised. Improved 3D navigation, integrated force feedback and improved ergonomics are unmet clinical needs in the development of robotic endovascular intervention.

2.3.1. Current Commercial Robotic Platforms

Robotic Systems for Electrophysiology Therapies

Sensei X2 by Hansen Medical (Mountain View, CA, USA, now part of Auris Medical) and Niobe magnetic navigation system (St. Jude Medical, MN, USA) are two major commercial robotic platforms for cardiac electrophysiology (EP) therapies. The Sensei X2 system has been successfully used in cardiac mapping and ablation (Saliba, Reddy et al. 2008, Di Biase, Wang et al. 2009). It can be used with the Artisan® or the narrower Magellan steerable catheters. These robotic catheters consist of an inner (leader) catheter within an outer sheath and the deflection of each component is controlled via tendon-driven actuation. Both systems are arranged in a master-slave setup, with which the operator uses either a 3D joystick or navigation buttons on the remote workstation. The Cohesion visualization module in Sensei X2 allows the integration of a commercial 3D electro-anatomical mapping system (EnSite, St. Jude Medical, MN, USA). It can also incorporate a distal tip force measurement system (IntelliSense), which provides visualization of the forces and tactile feedback.

The Niobe system, on the other hand, uses two permanent magnets to generate a magnetic field for controlling the tip deflection of the catheters. The deflection angle and direction are controlled by changing the orientation of the outer magnets using a mouse and/or a joystick at the workstation, while a distal motor drives the translational movement of the catheters. This system has been successfully used for mapping and ablation, as well as treatment of coronary and peripheral arterial disease (Ernst, Ouyang et al. 2004, Di Biase, Fahmy et al. 2007). 3D mapping and navigation are provided by the 3D electroanatomical CARTO mapping system (Biosense Webster, Brussels, Belgium). Magnetic navigation brings benefits such as lower stiffness of the magnetic catheters compared to the tendon driven instruments, with reduced risk of tissue perforation and damage. Recently, the ViDrive of the Niobe system was cleared by FDA, which allows Niobe to control third party diagnostic catheters and ablation devices.

Other magnetically steered robotic catheter systems for EP application include the CGCI (Catheter Guidance Control and Imaging) by Magnetecs Inc. (CA, USA) and the Aeon Phocus by Aeon Scientific (Zurich, Switzerland). The CGCI system uses eight electromagnets to enhance the field strength and contract forces between the catheter and the tissue. Moreover, Amigo (Catheter Robotics Inc. NJ, USA) is a mechanically driven remote system which allows manipulation of standard commercial mapping catheters in 3 degrees-of-freedom to control respectively insertion, retraction and deflection of the catheter tip. It is equipped with an intuitive remote controller that replicates the natural skills of manipulating standard EP catheter.

Robotic Systems for Endovascular Interventions

The development of steerable robotic catheter technology also facilitates its clinical application in more general vascular surgeries. The Magellan system by Hansen Medical, for example, works with standard 2D fluoroscopy images and force sensing is not incorporated. The Magellan system is equipped with narrower steerable catheters compared to the Sensei system, it also consists of a guidewire driving system that allows the synchronization control of its robotic catheter and a conventional guidewire, which is useful for accessing narrow anatomy. The Magellan robotic eKit was FDA approved, allowing manipulating third party micro-catheters through its robotic catheter. This facilitates access to more tortuous vessels.

The CorPath GRX System (Corindus Vascular Robotics, MA, USA) is another robotic system to mechanically drive standard instruments specifically in percutaneous coronary interventions. The bedside robotic driver allows retraction/insertion and rotation of guidewire and stent/balloon catheter separately. The operator can...
also manipulate the instruments outside the operation room to avoid radiation exposure. The system has been approved by FDA after clinical practices since 2011 (Granada, Delgado et al. 2011). A trend for these commercial systems for general endovascular intervention is to integrate third party standard catheters. Researchers have also proposed linear drive system to allow haptic feedback (Fu, Guo et al. 2013). Another group incorporates force sensors into the friction sensing and haptic feedbacks are also lost in current systems since miniaturising the force sensors for these catheters is challenging.

### Table 4. Current commercial robotic platforms for endovascular procedures

<table>
<thead>
<tr>
<th>Robotic Platforms</th>
<th>Application</th>
<th>Vascular (V)</th>
<th>Steerable Catheter</th>
<th>Feedback</th>
<th>Intuitive joystick/touch interface</th>
<th>3D navigation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensei X2</td>
<td>EP</td>
<td>Yes</td>
<td>Yes</td>
<td>Training Required</td>
<td>Yes</td>
<td>Steerable catheter actuated by pull-wire; remotely controlled by buttons and a joystick.</td>
<td></td>
</tr>
<tr>
<td>Magellan</td>
<td>V</td>
<td>Yes</td>
<td>No</td>
<td>Training Required</td>
<td>No</td>
<td>Steerable catheter actuated by pull-wire; remotely controlled by buttons and a joystick: Allows manipulation of third party micro catheters in the intervention.</td>
<td></td>
</tr>
<tr>
<td>Niobe</td>
<td>EP</td>
<td>Yes</td>
<td>No</td>
<td>Training Required</td>
<td>Yes</td>
<td>Steerable catheter actuated by permanent magnetic; joystick/mouse controller; Third party diagnostic/interventional catheters</td>
<td></td>
</tr>
<tr>
<td>Amigo</td>
<td>EP</td>
<td>Yes</td>
<td>No</td>
<td>Easy</td>
<td>No</td>
<td>Conventional steerable catheter; Hand-held ergonomic controller replicated natural skills</td>
<td></td>
</tr>
<tr>
<td>CorPath 200</td>
<td>V</td>
<td>No</td>
<td>No</td>
<td>Training Required</td>
<td>No</td>
<td>Conventional catheters and guidewire only for percutaneous coronary intervention procedure; joystick controller</td>
<td></td>
</tr>
<tr>
<td>CGCI</td>
<td>EP</td>
<td>Yes</td>
<td>No</td>
<td>Training Required</td>
<td>Yes</td>
<td>Magnetic steerable catheter, joystick controller</td>
<td></td>
</tr>
<tr>
<td>Aeon Phocus</td>
<td>EP</td>
<td>Yes</td>
<td>No</td>
<td>Training Required</td>
<td>Yes</td>
<td>Magnetic steerable catheter, joystick controller</td>
<td></td>
</tr>
<tr>
<td>Robocath R-one</td>
<td>V</td>
<td>No</td>
<td>NA</td>
<td>Training Required</td>
<td>NA</td>
<td>Conventional catheters and guidewires; joystick controller</td>
<td></td>
</tr>
</tbody>
</table>

### 2.3.2. Research Platforms and Future Directions

#### 2.3.2.1. Research Platforms in Robotic Catherization

In parallel to commercial developments, there are also many research platforms that are being developed in academic research institutions. Most groups focus on building compact and light systems while integrating force feedbacks. The System for Endovascular Teleoperated Access (SETA) is a robotic catheterization platform that can manipulate the catheter and the guidewire simultaneously (Srinathweeravalli, Kesavadas et al. 2010). It is constructed by friction drive wheels and a translatable pulley stage that allows translational and rotational movements of the instruments. Force-torque sensors are embedded at the wrist of the robot for proximal force sensing and force feedback to the user is through the master interface. Another characteristic friction drive wheel-based system is the dual-finger robotic hand (DRH) for Percutaneous Coronary Intervention (PCI) (Blair, Xie et al. 2013). It has an active wheel driver paired with an idle driver. The rollers can insert and retract a conventional catheter or guidewire, while twisting the elongated instruments can be achieved by moving the rollers up and down. It is a bioinspired design that replicates the motions of the forefinger and the thumb when naturally manipulating the catheter. Researchers have also proposed linear stepping and clutch-based design for inserting and rotating the catheter (Arai, Fujimura et al. 2002, Guo, Wang et al. 2013). Instead of using roller-based driving mechanisms, the catheter was actuated by rotation and linear translation of the stage, with a secondary stage controlling the tip deflections (Marcelli, Cercenelli et al. 2008, Fu, Gao et al. 2011, Tavallaei, Gelman et al. 2015). A steerable catheter with Shape Memory Alloy (SMA) actuation has also been presented, with the advantage of producing large and plastic tip bending (Jayender and Patel 2008). Recent developments of those platforms focused on integrating more commercial endovascular instruments, such as allowing manipulation of conventional catheters and guidewires, as well as Y-connectors for contrast agent injection (Cha, Yoon et al. 2016).

In endovascular procedures, there is a general loss of haptic feedback during manipulation. Carefully managed force control can lower the risk of complications in intracardiac procedures and endovascular interventions. Many research platforms embedded distal force sensors at the tip of the catheter that allows force feedback through their haptic interfaces such as Phantom Omni (Sensable Technologies) and Novint Falcon (Novint Technologies) (Guo, Kondo et al. 2007, Wang, Zhang et al. 2010), as well as customised haptic device that utilises natural skills of the operator in catheter manipulation (Payne, Rafii-Tari et al. 2012). Other platforms for catheter manipulation provide force feedback to the operator according to proximal force measurements at the slave side, through a gimbal-based master joystick or an ergonomic catheter handle which replicates conventional manipulations (Park, Choi et al. 2015). Another group incorporates force sensors into the friction drive system to allow haptic feedback (Fu, Gao et al. 2011). Shape based analysis of the catheter can also provide tip contact force and direction estimation through real-time images (Back, Manwell et al. 2015). Kesner and Howe also proposed a new control method based on visual servoing that uses intraoperative US images of the beating heart to regulate the catheter tip forces and compensate fast tissue movements (Kesner and Howe 2011).

There are also extensive interests in computer-assisted navigation. These systems typically use electromagnetic sensors at the tip of the steerable catheter to provide semi-autonomous navigation (Ganj, Janabi-Sharifi et al. 2009). Other approaches also incorporate virtual fixtures to construct a virtual environment to regulate catheter motions. These include using real-time 2D images to track distance between the catheter tip and the vessel centreline, hence providing haptic feedback to prevent collision and endothelial damage (Park, Choi et al. 2011, Ghembaza and Amirat 2004). For improved ergonomics, Thakur et al. (Thakur, Bax et al. 2009) proposed a design of recording translational and rotation motions when operator is manipulating a “master” catheter, and then replicates those motions on a “slave” catheter. Customised joysticks with force feedbacks were also proposed by various group (Tanimoto, Arai et al. 2006, Guo, Guo et al. 2015). Another design is to integrate handle of a conventional steerable catheter on the master manipulator for controlling the tip deflection (Tavallaei, Gelman et al. 2015). To reduce the cognitive load of the operator during manipulation, methods based on learning from demonstration for human-robot shared-control have been proposed (Rafi-Tari, Liu et al. 2013).
Future Research Challenges

Currently, navigation of endovascular intervention still relies heavily on 2D X-ray images and static digital subtraction angiography (DSA). 3D anatomy and depth information are lost so operators need to register the live 2D images based on the memory of 3D anatomy. MRI-guided intervention is an emerging topic that can potentially provide dynamic 3D images in endovascular intervention. However, the development of fully MRI compatible robots remains challenging.

Incorporating miniaturised force and motions sensors into small instruments such as catheters and guidewires is practically difficult. One of the solutions for force sensing is to embed sensors at the proximal site, but the friction between elongated instruments and the sheath may attenuate the forces from the distal site. Vision-based forces sensing through catheter shape analysis has been introduced, but problems such as limited image quality and lateral force measurements in tortuous anatomy remain to be solved. Most instrument tracking methods can only track the tip positions of the instruments. However, tracking the body of the instruments is also important for peripheral endovascular interventions. Robust tracking of both catheters and guidewires under X-ray imaging can be achieved, especially with the continuing improvement of fluoroscopic imaging devices.

As mentioned earlier, most robotic catheterization platforms did not consider the natural manipulation skills of the instruments, and high costs of proprietary instruments limit the wide application of those platforms. Future directions include designing ergonomic master interface that simplifies training, preferably using low-cost conventional instruments while enhancing the stability and precision of catheterization.

Figure 10. The compact telerobotic catheter navigation system proposed by (Tavallaei, Gelman et al. 2015) (©2015 with permission from John Wiley and Sons)

<table>
<thead>
<tr>
<th>Research Robotic Platforms</th>
<th>Application: EP or Vascular (V)</th>
<th>Steerable Catheter</th>
<th>Force feedback</th>
<th>Intuitive Human / Robot Interface</th>
<th>3D Navigation</th>
<th>MRI Compatible</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srimathveeravalli et al.</td>
<td>V</td>
<td>No</td>
<td>Yes</td>
<td>Training Required</td>
<td>No</td>
<td>No</td>
<td>Friction drive mechanism, both standard guidewire and catheter manipulation</td>
</tr>
<tr>
<td>Guo et al.</td>
<td>V</td>
<td>No</td>
<td>Yes</td>
<td>Easy</td>
<td>No</td>
<td>No</td>
<td>Ergonomic master interface, Linear Stepping driving, Standard catheter</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>V</td>
<td>No</td>
<td>Yes</td>
<td>Training Required</td>
<td>Yes</td>
<td>No</td>
<td>Standard catheter, haptic interface</td>
</tr>
<tr>
<td>Jayender et al.</td>
<td>V</td>
<td>Yes</td>
<td>Yes</td>
<td>Training Required</td>
<td>No</td>
<td>No</td>
<td>SMA actuated catheter</td>
</tr>
<tr>
<td>Fu et al.</td>
<td>V</td>
<td>Yes</td>
<td>Yes</td>
<td>Training Required</td>
<td>Yes</td>
<td>No</td>
<td>Steerable pull-wire catheter with EM sensors, haptic controller</td>
</tr>
<tr>
<td>Thakur et al.</td>
<td>V</td>
<td>No</td>
<td>No</td>
<td>Easy</td>
<td>No</td>
<td>No</td>
<td>Standard catheter, master replicating natural motion</td>
</tr>
<tr>
<td>Tanimoto et al.</td>
<td>V</td>
<td>No</td>
<td>Yes</td>
<td>Easy</td>
<td>No</td>
<td>No</td>
<td>Standard catheter, master replicating natural motion</td>
</tr>
<tr>
<td>Payne et al.</td>
<td>V</td>
<td>No</td>
<td>Yes</td>
<td>Easy</td>
<td>No</td>
<td>No</td>
<td>Standard catheter, master replicating natural motion</td>
</tr>
<tr>
<td>Tavallaei et al.</td>
<td>V</td>
<td>Yes</td>
<td>No</td>
<td>Easy</td>
<td>No</td>
<td>Yes</td>
<td>Standard catheter, master replicating natural motion and catheter handle</td>
</tr>
<tr>
<td>Bian et al.</td>
<td>V</td>
<td>No</td>
<td>No</td>
<td>Easy</td>
<td>No</td>
<td>No</td>
<td>Standard catheter, master replicating natural motion</td>
</tr>
<tr>
<td>Cercenelli et al.</td>
<td>EP</td>
<td>Yes</td>
<td>No</td>
<td>Training required</td>
<td>No</td>
<td>No</td>
<td>Standard steerable EP catheter, joystick controller</td>
</tr>
<tr>
<td>Park et al.</td>
<td>EP</td>
<td>Yes</td>
<td>Yes</td>
<td>Easy</td>
<td>No</td>
<td>No</td>
<td>Standard steerable EP catheter, controller replicating catheter handle</td>
</tr>
<tr>
<td>Ganji et al.</td>
<td>EP</td>
<td>Yes</td>
<td>Yes</td>
<td>Training required</td>
<td>No</td>
<td>No</td>
<td>Standard steerable EP catheter with EM sensor, haptic controller</td>
</tr>
</tbody>
</table>

Table 5. Current research robotic platform for endovascular procedures
2.4. Delivery of Therapies

2.4.1. Endovascular Catheterisation

<table>
<thead>
<tr>
<th>Imager II Angiographic Catheter</th>
<th>Pulmonary arteriovenous embolization (Jones, Rai et al. 2015), catheterisation of intercostal and lumbar arteries (Koruth, Schneider et al. 2015), renal artery pseudoaneurysm treatment (Krajina and Chrobok 2014)</th>
</tr>
</thead>
</table>


Table 7. Boston Scientific (Marlborough, MA, USA) thrombectomy systems

<table>
<thead>
<tr>
<th>Vessel section</th>
<th>Strategy</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortoiliac artery</td>
<td>Self-expandable stent, e.g. Xpert Pro, Absolute Pro and Absolute Pro LL</td>
<td>Common femoral artery</td>
</tr>
<tr>
<td>Mitral Valve</td>
<td>Balloon-expandable stent, e.g. Omnilink Elite Peripheral Stent System (Abbott Vascular, Santa Clara, CA, USA)</td>
<td>MiraClip</td>
</tr>
<tr>
<td>Covered stent</td>
<td>Upper brachial/radial extremity</td>
<td></td>
</tr>
<tr>
<td>Common femoral artery</td>
<td>Angioplasty</td>
<td>Common femoral artery</td>
</tr>
<tr>
<td>Femoropopliteal artery</td>
<td>Atherectomy</td>
<td>Common femoral artery</td>
</tr>
<tr>
<td>Self-expandable stent</td>
<td>Common femoral artery</td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Endovascular strategies for treating critical limb ischemia (Golzarian, Sapoval et al. 2010)

Peripheral Artery Disease and Critical Limb Ischemia

As in many other revascularisation applications, the endovascular approach has become the first choice for patients suffering from peripheral artery disease, with surgical bypass only as a backup option (Mandal, Parent et al. 2016). These include:

- Percutaneous transluminal angioplasty, with possible stent implantation in order to keep the vessel dilated. The balloons come in different lengths, facilitating quick therapy even for long lesions (Golzarian, Sapoval et al. 2010),
- Subintimal angioplasty, for which a guidewire creates access by piercing the vessel lining to bypass the occlusion and then enter back the true lumen. This procedure is performed for total occlusions of the vessels and can avoid blockages even longer than 15 cm. One example of these devices enhanced with visualising technology is the Pioneer Plus catheter (Volcano, San Diego, CA, USA) which incorporates IVUS for cross-sectional imaging of the artery.
- Simple nitinol, covered, drug-eluting, and bioabsorbable stents.
- Cryoplasty, during which the vessel walls are frozen in the vessel’s expanded state.
- Excimer laser-assisted angioplasty.
- Excisional atherectomy.
- Cutting balloon angioplasty.
- Several state-of-the-art endovascular atherectomy devices are presented in Table 8. Many of them have slightly adapted versions for coronary vessel plaque removal, a very similar procedure to the endovascular therapy for peripheral artery disease. Untreated peripheral artery disease and advanced thickening of the vessel wall lining can lead to critical limb ischemia, which shows as rest pain, ulcers, and even gangrene. The constriction is caused by atherosclerotic plaque and the therapy is therefore similar to the management of coronary vessel atherectomy and angioplasty. The purpose of atherectomy in this case is (complete) leg salvage by revascularisation (Golzarian, Sapoval et al. 2010). The authors gave a summary of the endovascular strategies and possible access sites depending on the constricted section of the vessel. This is shown in Table 8.

Chronic Total Occlusion (CTO)

About 20-40% of the critical limb ischemia and peripheral arterial disease patients suffer from additional chronic total occlusions which obstruct the advancement of catheters in the vessels during endovascular procedures (Maiti, Bir et al. 2016). While angioplasty and stenting are viable options for these patients, a new technology combining forward imaging and atherectomy has emerged. Examples of this are the Ocelot, Ocelot PIXL, and Ocelot MVIRX catheters (Avinger, Redwood City, CA, USA), which incorporate optical coherence tomography for real-time cross-sectional visualisation of the vessel wall and a spiral tip for protruding through the occlusion. While there is a significant overlap in the technologies used for critical limb ischemia and peripheral arterial disease, chronic total occlusion also requires refined devices that can protrude through the blockage, a step prior to either angioplasty or atherectomy. Alongside the Ocelot catheters stand the Crosser CTO Recanalization Catheter (Bard, Tempe, AZ, USA) and the FRONTRUNNER XP CTO Catheter (Cardis, Bridgewater, NJ, USA). While the FRONTRUNNER deploys a simple pair of hinged jaws to...
Rotaablation and Atherectomy
Mechanically similar to thrombectomy but used for a different application is the so-called rotaablation on rotational atherectomy. While it does not involve energy delivery per se, as in the case of RF or laser ablation, it does cause destruction of unwanted tissue. Rotaablation is actually a mechanical removal of arterial calcium and cholesterol plaque with a drilling catheter inserted via the endovascular route. The most affected vessels are coronary arteries and veins, but the technique is also used for treating peripheral arterial disease (Akkus, Abdulbaki et al. 2015). Atherectomy, as the more general term for this procedure, involves shaving or vaporising plaque. (Akkus, Abdulbaki et al. 2015) gave a review of the available and approved atherectomy technologies in 2015, which are summarised in Table 10.

Table 10. Atherectomy devices in clinical use

<table>
<thead>
<tr>
<th>Method</th>
<th>Devices</th>
<th>Application</th>
<th>Device description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotablator</td>
<td>SilverHawk and TurboHawk (ev3, Plymouth, MN, USA)</td>
<td>Peripheral arterial disease</td>
<td>Angulated tip for carving plaque as the device advances. The angle is adjustable. Disadvantage: distal embolization 7.3% (Akkus, Abdulbaki et al. 2015) calls for additional embolic protection device. <a href="http://www.ev3.net/peripheral/plaque-excision">http://www.ev3.net/peripheral/plaque-excision</a></td>
</tr>
<tr>
<td>CVS-300 Eximer Laser and Turbo-Power/ Elite/Tandem (Spectranetics, Colorado Springs, CO, USA)</td>
<td>Chronic total occlusion</td>
<td>Coronary and peripheral arterial disease Fibre-optic catheters to vaporise the plaque. High revascularisation rate with small distal embolization risk, comparable to angioplasty. <a href="http://www.spectranetics.com/solutions/">http://www.spectranetics.com/solutions/</a> The technology can also be used in chronic total occlusion, where it has the advantage that no guidewire is needed to pass through the blockage before the therapy can be delivered (Lusmed, Davies et al. 2009).</td>
<td></td>
</tr>
</tbody>
</table>

Some of the diagnostic catheters used in conjunction with the CTO recanalization systems are enumerated in Table 9. The chosen examples are manufactured by Cordis (http://emea.cordis.com/emea/endovascular/lower-extremity-solutions/access/diagnostic-catheters.html).

Table 9. Examples of Cordis (Bridgewater, NJ, USA) diagnostic catheters used with CTO recanalization systems.

<table>
<thead>
<tr>
<th>Device</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPO AQUA Catheter</td>
<td><a href="http://emea.cordis.com/emea/endovascular/lower-extremity-solutions/access/diagnostic-catheters/tempo-aqua-hydrophilic-coated-angiographic-catheter.html">http://emea.cordis.com/emea/endovascular/lower-extremity-solutions/access/diagnostic-catheters/tempo-aqua-hydrophilic-coated-angiographic-catheter.html</a> Hydrophilic coating for easy navigation in the vessel wall, between the lining and the true lumen, tactile and torque control due to braided shaft. However, the distal tip is non-braided and boasts increase flexibility. This prevents damage by piercing the vessel wall. Tungsten-filled tip for tracking less use of contrast agent.</td>
</tr>
<tr>
<td>SUPERTORQUE Angiographic Catheter</td>
<td><a href="http://emea.cordis.com/emea/endovascular/lower-extremity-solutions/access/diagnostic-catheters/supertorque-angiographic-catheter.html">http://emea.cordis.com/emea/endovascular/lower-extremity-solutions/access/diagnostic-catheters/supertorque-angiographic-catheter.html</a> Braided polyurethane body Able to withstand high flow rates</td>
</tr>
</tbody>
</table>

Cut through the occlusion, the CTO is actuated with AC current which brings piezoelectric crystals in the catheter tip to high-frequency mechanical vibrations, thus breaking through the blockage. The catheters usually require additional diagnostic catheters. This is a safety measure which stemmed from early experience and failure with the non-surgical treatment of chronic total occlusions in both peripheral and coronary vessels (Rosenwasser, Chalouhi et al. 2014, Mohar and Levandovski 2015).

Rotaablation and Atherectomy
Mechanically similar to thrombectomy but used for a different application is the so-called rotaablation on rotational atherectomy. While it does not involve energy delivery per se, as in the case of RF or laser ablation, it does cause destruction of unwanted tissue. Rotaablation is actually a mechanical removal of arterial calcium and cholesterol plaque with a drilling catheter inserted via the endovascular route. The most affected vessels are coronary arteries and veins, but the technique is also used for treating peripheral arterial disease (Akkus, Abdulbaki et al. 2015). Atherectomy, as the more general term for this procedure, involves shaving or vaporising plaque. (Akkus, Abdulbaki et al. 2015) gave a review of the available and approved atherectomy technologies in 2015, which are summarised in Table 10.
Balloon Angioplasty
This is a non-corrosive alternative to atherectomy. It does not involve carving, cutting, or ablating through plaque, but rather widening the vessel with a water-inflated balloon. In order to keep the vessel expanded, a metallic stent is sometimes implanted. According to (Mauffrey, Cuellar III et al. 2014, Maiti, Bir et al. 2016), the 5-year limb salvage rate can be as high as 89%. While atherectomy remains a niche therapy, possibly due to its less investigated safety, balloon angioplasty and stenting are the methods of choice for most patients with peripheral artery disease (Marcus, Payne et al. 2016).

While some of the angioplasty and atherectomy devices for peripheral artery disease have been discussed in the previous section, we will now give examples of balloon angioplasty systems for coronary occlusion, without excluding their adaptability and application to the peripheral vessels. Some available designs for peripheral artery disease are included.

Table 11. Examples of balloon angioplasty systems currently available

| ATLAS GOLD PTA Dilatation Catheters | BARD Peripheral Vascular (Tempe, AZ, USA) | http://www.bardpv.com/?portfolio=atlasgold | BARD Peripheral Vascular claim this catheter to be the most non-compliant large diameter balloon on the market. better fit of the balloon in the vessel, thus minimising the lumen straightening which occurs if a too long balloon is used. large diameter vessels. |

Despite being a better option than surgery, angioplasty can have certain risks. These include embolization, where the displaced plaque enters the blood stream, vessel rupture due to over-inflating of the balloon, access site inflammation, and radiation exposure. While there used to be concern over re-stenosis and reversibility of angioplasty in its early years (Gralnek 2014), it seems that more consistent studies have overruled this assumption.

An alternative to the common inflating balloon angioplasty is the cutting balloon angioplasty. While this is a more invasive procedure, it mediates the risk of re-stenosis and vessel expansion (Marcus, Payne et al. 2016). It is also suggested that this is a technology superior to atherectomy and rotablation thanks to the soft balloon which supports the microblades and thus allows for a more controlled remodelling of the lumen. It was concluded from pre- and postoperative imaging that cutting balloon angioplasty achieved its success by acting on the plaque itself and not on the vessel wall, as with inflating balloon angioplasty (Maiti, Bir et al. 2016). Two manufacturers currently offer cutting balloon catheters: Boston Scientific (Marlborough, MA, USA) with their Flextome Cutting Balloon Dilatation Device (Scientific 2017) and the Spectranetics (Colorado Springs, CO, USA) AngioSculpt PTA Scoring Balloon Catheter (Spectranetics 2017).

In addition to angioplasty for revascularisation of limbs and heart, new devices have emerged for other non-traditional uses. The technology in inflating or cutting balloon angioplasty has been used for revascularisation and re-opening of other vessels, such as the ones involved in dialysis. Boston Scientific has been commercialising one of these devices, the Peripheral Cutting Balloon, a Microsurgical Dilatation Device for Haemodialysis Access Management (Boston Scientific 2017), but BARD Peripheral Vascular (Tempe, AZ, USA) have a whole range of endovascular drug delivery products.

Despite positive experience with cutting balloon angioplasty, there used to be some concern about the size of the bladed balloons and the devices causing pressure and vessel perforations (Mauffrey, Cuellar III et al. 2014). While these might have been issues in the early days of this technology, newer generation cutting balloons, such as the ones previously listed, have systems for controlling inside pressure and balloon inflation sizes and thus avoiding injuries.
2.4.2. Delivery of Cardiac Devices

**TAVI**

The key to a successful TAVI procedure is accurate placement of the replacement valve. This in turn can be achieved with precise tracking of the end effector, whether it is an instrument that grasps and saws a chord onto a mitral valve leaflet, an expandable stent for valve replacement, or an ablation catheter.

In mitral valve replacement, a difference was noted between the navigation and the positioning phase. Navigating safely to the target is clearly important. If the navigation takes too long or is impaired, the procedure itself on the target cannot take place. The technology for each of the submillimetre range, the guidance, i.e., preoperative and intraoperative image registration, for the navigation step itself does not need to be this accurate. As a matter of fact, since online registration is a computationally expensive process, the continuous update of a very accurate registration algorithm could cause longer navigation times.

The challenges enumerated in this section are shared by all major procedures: TAVI, AAA or other stent placement interventions. These include migration, kinking or failure of stents. One of the main reasons of the intraprocedural damage is the lack of personalised implants, i.e., of patient-specific grafts, but more importantly of implants suitable for each part of the anatomy. The kinking of stents during implantation has already been addressed by medical companies in their newest products. Bolton Medical (change to Sunrise, FL, USA) has introduced a braided layer in the outer sheath of their delivery system in order to prevent the destruction of the stent-graft during insertion (Bolton Medical 2017).

### 2.4.3. Energy Delivery

It is estimated that a new range of endovascular platforms will emerge in the near future, enabling the delivery of drugs in situ in order to accelerate arterial wall healing. The safety of ablation catheters need to be proven in order to be accepted as means of energy delivery. The reasons are the dangers of energy delivery itself, but also of contact with dynamic soft tissue under minimal visualisation. The intra procedural guidance is provided by limited fluoroscopy sequences, low-resolution ultrasound, and sometimes by more expensive electroanatomical mapping systems and auxiliary electromagnetic sensors attached at the tip of the catheter. The state-of-the-art tools all try to address these navigation and safety issues. For cardiac ablation, the purpose is transmural scar to block abnormal conduction; in chronic vein insufficiency, this is complete vessel sealing, while for cancer treatment it is full destruction of tumour.

The American Foundation for Women’s Health and StopAfib provided a review of the types of (StopAfib 2017) catheter in use for cardiac ablation. They are summarised in Table 12.

In the application of cardiac ablation, a considerable amount of work has been done to correlate tissue parameters for monitoring the effect of each energy impulse. The question concerns both aspects of the energy delivery – efficiency (was it enough to change the substrate?) and safety (was it enough not to create damage to neighbouring tissue?). This can potentially open new research in the field of online tissue characterisation, but so far there has been only limited progress on enabling real-time intraoperative use of this method.

One of the means employed so far is the measurement of contact force, which is correlated to the result of the ablation. While its amplitude or direction relative to the cardiac wall are not visualised per se intraoperatively, state-of-the-art electroanatomical mapping systems such as CARTO (Biosense Webster, Diamond Bar, CA, USA) or RHYTHMIA (Boston Scientific, Marlborough, MA, USA) display the raw information from the catheter tip. Table 12 shows some example catheters for therapeutics, ultrasound, ablation and intraoperative electroanatomical guidance.

It has been suggested that a viable alternative to the real lesion depth measurement is the combined monitoring of tissue temperature, catheter tip contact force and cooling. For tachycardia interruption procedures or pulmonary vein isolation, intraoperative imaging showing the continuity of the lesion line should be added.

Concrete evidence of improving outcomes is the major hurdle for translating new technologies to clinical use. To demonstrate the effectiveness of new technologies, extensive clinical studies need to be conducted with due consideration of efficacy, cost-effectiveness and user acceptance.

---

<table>
<thead>
<tr>
<th>Catheter type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic catheter</td>
<td>NAVISTAR DS Multiple electrode catheter with deflectable tip.</td>
</tr>
<tr>
<td>Ultrasound catheter</td>
<td>SOUNDSTAR Enhance lesion formation monitoring and safety in atrial fibrillation and ventricular tachycardia procedures by combining intracardiac echo and electroanatomical mapping for better anatomy visualisation.</td>
</tr>
<tr>
<td>Diagnostic catheter</td>
<td>Dynamic Tip Diagnostic Catheter Very steerable tip with a handle-controlled lock mechanism, placement in the coronary sinus.</td>
</tr>
<tr>
<td>Diagnostic catheter</td>
<td>LASSO Reference location information in atria. Deflectable catheter with electrode pairs equally spaced along the curvature.</td>
</tr>
<tr>
<td>Ablation catheter</td>
<td>Chilli II Cooled Ablation Catheter Patented Closed-loop Cooling System so that no fluid enters the bloodstream. This also reduces the risk of air emboli and cools the catheter regardless of tissue contact angle. Catheter cooling prevents coagulum formation and enables the use of higher RF power. 25,000 cases in the US.</td>
</tr>
<tr>
<td>Mapping catheter</td>
<td>Constellation Full Contact Mapping Catheter focal arrhythmia mapping in real time. whole electroanatomical map in one heartbeat from 64 electrodes. pacing capabilities. super-elastic alloy as material for a spline-shaped catheter. basket conforms to atrial anatomy</td>
</tr>
</tbody>
</table>

Table 12: Examples of catheters produced by Biosense Webster (Diamond Bar, CA, USA)
EvenCool Technology for better coolant delivery

The catheter has several electrodes with energy delivery capabilities. The catheters can work in bipolar mode, reducing thermal injuries to adjacent tissue. However, there is little clinical experience with these catheters.

RF catheters with contact force sensing

There is a force sensor integrated in the catheter tip to assess contact force and quality of lesion formation.

Balloon catheters

Laser and cryoablation balloon catheters, used most often for atrial fibrillation treatment by pulmonary vein isolation. The catheter is advanced into the left atrium and the balloon at the tip is inflated. The energy delivery from the balloon to the pulmonary vein ostia occurs at the same time and continuous along the whole contact perimeter.

Merchant et al (Merchant, Levy et al. 2016) completed a review on the usefulness of the myriad of available ablation catheters to conclude that the tools’ application is dependent on the patient-specific anatomy. They analysed the case of circular catheters in pulmonary vein isolation, showing that the one-size-fits-all circular catheter couldn’t be used in more than 10% of their patients.

More recently, visually guided laser balloons have been proposed to replace ablation catheters in pulmonary vein isolation (Dukkipati, Cuoco et al. 2015) (Figure 13). The aim of this technology is to create a continuous isolation line around the pulmonary veins, which is currently imperfect when created point-by-point with RF ablation catheters. First results from the study were that the two techniques are equivalent. However, the operators had not had previous experience with the visually guided laser balloon. This raises hopes for even better results in the future.

It was reported that patients remained free of atrial fibrillation in 90% of the cases compared to 20% using point-by-point RF ablation, according to follow-up at three months (Segal 2017).

Table 13. Catheter types used in cardiac ablation procedures (StopAfib 2017)

<table>
<thead>
<tr>
<th>Catheter type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single point RF catheters</td>
<td>Only the catheter tip can deliver energy and ablation can only be performed in a point-by-point fashion, keeping each ablation point close to the previous in order to produce a continuous lesion. The single-point technology allows only for unipolar energy delivery.</td>
</tr>
<tr>
<td>Multielectrode RF catheters</td>
<td>The catheter has several electrodes with energy delivery capabilities. The catheters can work in bipolar mode, reducing thermal injuries to adjacent tissue. However, there is little clinical experience with these catheters.</td>
</tr>
<tr>
<td>RF catheters with contact force sensing</td>
<td>There is a force sensor integrated in the catheter tip to assess contact force and quality of lesion formation.</td>
</tr>
<tr>
<td>Balloon catheters</td>
<td>Laser and cryoablation balloon catheters, used most often for atrial fibrillation treatment by pulmonary vein isolation. The catheter is advanced into the left atrium and the balloon at the tip is inflated. The energy delivery from the balloon to the pulmonary vein ostia occurs at the same time and continuous along the whole contact perimeter.</td>
</tr>
</tbody>
</table>

Table 14. The Medtronic (Minneapolis, MN, USA) Cardiac CryoAblation system, for atrial fibrillation treatment, i.e., pulmonary vein isolation

<table>
<thead>
<tr>
<th>Ablation catheter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi-directional steering</td>
<td>Variable curve-sizes with one catheter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cryoablation catheter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freezor Cardiac CryoAblation Catheter</td>
<td>Focal ablation of reentrant tachycardias occurring at the atrioventricular node. Mapping mode also available with the same catheter in order to test the potential ablation site. The reversibility of short-term cryoablation is used here to allow the recovery of the AV node in case of accidental ablation (<a href="http://www.epidigest.com/articles/Mechanisms-and-Application-Cardiac-Cryoablation">http://www.epidigest.com/articles/Mechanisms-and-Application-Cardiac-Cryoablation</a>). This would not be possible in the other thermal procedures, where the heat effect is irreversible.</td>
</tr>
</tbody>
</table>

Figure 12: Left: visually guided laser balloon. The white spot is the aiming and ablation spot. Right: endoscopic view from the balloon in the left superior pulmonary vein: The arrow points out the ablation spot (Dukkipati, Cuoco et al. 2015).

Figure 13. The aim of this technology is to create a continuous isolation line around the pulmonary veins, which is currently imperfect when created point-by-point with RF ablation catheters. First results from the study were that the two techniques are equivalent. However, the operators had not had previous experience with the visually guided laser balloon. This raises hopes for even better results in the future.

Table 15 illustrates some of the example ablation devices for other arrhythmias, including RF and cryoablation catheters, diagnostic catheters, and sheaths used for insertion and stabilisation of these catheters (http://www.medtronic.com/us-en/healthcare-professionals/products/cardiac-rhythm/ablation-arrhythmias.html).
2.4.4. Chemicals Delivery

Apart from vessel expansion, another application of inflating balloons, which actually required an extension and additional development, is drug delivery. While the inflation or cutting produces a physical effect on the vessel at macro-scale, modern technology addresses and targets tissue at smaller scale, by chemical treatment, cell, or gene infusion. Boston Scientific and BART Peripheral Vascular (Tempe, AZ, USA) already produce balloons catheter for targeted drug delivery (Table 16).

Endovascular drug therapy by coated inflating balloon provides only short-term delivery, which may not be sufficient to treat the target region. A longer-term alternative, although not suitable for any anatomy, are drug-eluting stents. These are easiest ways for implanting in large enough vessels, which are less prone to bending or kinking. Abbott Vascular (Santa Clara, CA, USA) has a range of drug-eluting stents as listed in Table 17. While most of them are for coronary disease, there are also solutions for peripheral use available.

In a review of endovascular intervention for various types of peripheral artery disease, Thukkani and Kinlay (Marcus, Payne et al. 2016) concluded that total occlusions, critical limb ischemia and other peripheral artery lesions can be treated more successfully with drug-eluting stents, even in high-risk patients, such as those suffering from diabetes mellitus. Comparing results at 6 months in patients with bare-metal stents, it was discovered that the drug-eluting devices reduced the restenosis rate from 55% to 4% (Molvar and Lewandowski 2015). These figures were similar in peripheral and coronary artery disease.

The closely related drug-coated balloons, while having the disadvantage of temporary treatment and vessel occlusion, can potentially extend the range of anatomy for which drug-eluting technologies can work. While stents are prone to thrombosis and fracture, the balloon can advance higher, beyond the knee which currently limits the height of stent implantation (Marcus, Payne et al. 2016).

2.4.5. Endovascular Gene and Cell Therapy

One of the most recent research directions is therapy at small scale, i.e., cell and gene therapy. There is a myriad of publication on possible applications and preliminary results. Some of the endovascular approaches emerged in recent years are highlighted here.

Early work was conducted by (Sensuron 2016) and studied the enhancement of gene delivery to the arterial wall by ultrasound impulses. The clinical background was given by the high restenosis rate after angioplasty. Gene therapy was believed to be able to heal the vessel wall before restenosis initiated. The impact of the study was a spur for future work into making gene therapy more efficient.

Gene therapy and cell transplantation were also thought to be an alternative for patients who cannot be considered for standard revascularisation procedures in peripheral arterial disease (Crawford, Sanford et al. 2016). The authors reviewed some of the delivery catheters, most of them modified balloons similar to the ones for chemicals delivery. They classified them into passive diffusion catheters, pressure-driven balloon catheters, and mechanically-assisted injection catheters. Furthermore, they described angiogenesis, i.e., artificial growth of endothelial cells for vessel wall lining, which are to be implanted endovascularly after development.

Similarly to the peripheral arterial disease, gene therapy found application in endovascular treatment of intracranial aneurysms (Georgiadis, van Hennwaarden et al. 2016). The purpose was the development of natural occlusion of aneurysms, in order to avoid surgical clipping or mitigate incomplete coil embolisation.

One more promising application in recent years was gene therapy for the brain-affecting Hurler disease (Briganti, Leone et al. 2015). The genes would be delivered endovascularly or intraventricularly, much like in intra-arterial chemotherapy for brain tumours. While the delivery route did not seem to pose a problem, the issue was the consensus about which genes would be the most effective.

### Table 16. Balloon catheters for targeted drug delivery

| BART Peripheral Vascular (Tempe, AZ, USA) | LUTONIX 035 Drug Coated Balloon PTA Catheter | http://www.bardpv.com/?portfolio=lutonix-035 |


Table 17. Abbott Vascular (Santa Clara, CA, USA) drug eluting stents
Concrete evidence of improving outcomes is the major hurdle for translating new technologies to clinical use. A recent study has examined the regulatory clearance and/or approval of new medical devices (Marcus et al. 2015). While not solely focused on endovascular devices, their cross-sectional study showed in decreasing order of likelihood for a device to obtain regulatory approval if it was 1) developed by industry alone, 2) developed jointly by industry and academia, and 3) developed by academia alone. However, the results were not statistically significant and there was no clear explanation as to why this was the case. The authors suggest that industrial interests are the main drivers for regulatory approval for specific devices. It may highlight the need for greater collaboration between academia and industry to ensure the clinical applicability and translation of medical devices developed. This has also led to the observation that most medical device innovations are currently driven by industry.

During the development of new medical devices, effective communication between the technical and clinical parties is essential. The key is not for engineers but what is required at each stage of the operation. While clinicians may initially have certain ideas about what the device should look like and what it should do, technical barriers can prevent an exact implementation. Continuous clinical input and feedback is essential during this developmental process. Another major challenge is the testing of new devices in patients. In addition to stringent regulatory requirements for in vivo testing, it can be difficult to find clinicians who are supportive of testing new technologies in patients particularly for engineering prototypes; this may be circumvented by including clinicians from the very beginning of product development. While testing may start on phantoms or animals, patient evidence is critical for any device to achieve clinical uptake.

To demonstrate the effectiveness of new technologies, extensive research and clinical studies have to be conducted with due consideration of ethics, data privacy, ergonomics and user acceptance. More importantly, they also need to consider cost-effectiveness and evidence of improving outcomes and competition by different solutions. Typical clinical studies may take years to perform and the outcome of improvement may not always be clear. As such, the cost of studies often discourages many commercial companies from investing in healthcare technologies, but to focus only on fast growing consumer markets. Coupled with the complex procurement processes, adopting new technologies in clinical practice is often challenging. There are however a number of organisations in the UK that provide support to companies developing medical technologies and conducting healthcare research that can provide support across this pathway.

**Translational Support from NIHR** - The access to larger patient cohorts is a clear benefit of multi-centre collaborations for clinical trials and for assessing the efficacy of new devices for endovascular interventions. The NIHR has thus far established a number of Healthcare Technology Co-operatives (HTCs) with different clinical focuses (https://www.nihr.ac.uk). These centres of expertise work closely with industry and act as a catalyst for NHS ‘pull’ for the development of new medical device concepts, healthcare technologies and technology-dependent interventions. A primary focus is on clinical areas of high morbidity and have high potential to improve treatments and quality of life for NHS patients, as well as the effectiveness of healthcare services that support them. The HTCs work closely with patient groups, charities, industry and academics. Closely related to endovascular intervention is the NIHR Cardiovascular HTC (http://www.guyssandthomascob.nihr.ac.uk/nihr-htc3), which is tasked to identity, encourage and facilitate the development of new medical devices and technology driven solutions that will improve the diagnostic, treatment and well-being of patients with cardiovascular disease. To coincide with the publication of the Life Science Industrial Strategy of the UK government, NIHR has recently announced 11 Medtech and In Vitro Diagnostic Co-operatives (MICs, https://www.nihr.ac.uk/funding-and-support/funding-to-provide-nihr-facilities/medtech-and-in-vitro-diagnostic-co-operatives.html). These NIHR MICs are to build expertise and capacity in the NHS to develop new medical technologies and provide evidence on commercially-supplied in vitro diagnostic test and to bring together patients, clinicians, researchers, commissioners and industry. These NIHR MICs will replace the existing NIHR HTCs as well as the NIHR Diagnostic Evidence Co-operatives by incorporating and retaining their remits.

**Adoption and NHS procurement** - The NHS in the UK is the “largest single healthcare delivery organisation in the world” (NHS National Innovation Centre 2012). Medical devices may be procured at national, regional and local levels, usually depending on the value, size and complexity requirements of a device and the NHS will consider the clinical and cost effectiveness of medical devices before they will be procured. From a medtech industry perspective, the NHS represents a major opportunity for medical devices, but in the same time a significant challenge in navigating the system's structures and requirements. The Accelerated Access Review, which aims to speed up access to innovative drugs, technologies and diagnostics for NHS patients included the publication of an innovation pathway covering the entire development lifecycle from product idea to adoption and uptake by the NHS, which is a useful aid for those navigating the pathway and includes details of a number of key organisations, including the NIHR, which can provide support along this pathway. It has been noted that less attention is often given to ‘how-to’ compared with ‘principles’ knowledge at the early stages of the product development process and that this has contributed to incomplete implementations or discontinuations after initial adoption (Kyratsis, Ahmad et al. 2012). Organisations such as Academic Health Science Networks (AHSNs) and the NIHR, can help to bridge the gap between developers and the NHS to enable due consideration of how product functionality aligns with clinical needs and care pathway considerations.

**Clinical evaluation and CE marking of medical devices** - In the case of devices to be placed on the market in Europe, manufacturers need to determine whether their product is a ‘medical device’ as defined by the Commission Directives ([https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en](https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en)). Products falling within the scope of these directives, will need to demonstrate compliance with the applicable essential requirements as part of the CE-marking process before they can be placed on the market. As part of the process of ‘clinical evaluation’ required by the Directives, that is the assessment of clinical data relating to the device to demonstrate its safety and performance, a specific clinical study or ‘clinical investigation’ may be required. Where this is the case, manufacturers must notify the relevant competent authority in advance. For studies taking
place in the UK, this will be the MHRA (https://www.gov.uk/guidance/notify-
mhra-about-a-clinical-investigation-for-
medical-devices-regulation-safety. For novel products particularly those that
that challenge the current regulatory framework, the MHRA Innovation Office,
provides a single point of access to free expert regulatory advice and guidance which
is available to all types and sizes of organisation. It is worth noting that what
clinical trials cannot answer either is what the true clinical durability of the tested
devices are; they are designed to test safety but provide no long-term clinical
proof of usefulness. With many vascular regions undergoing great movement or
high blood flow, the mechanical long-
term stability of the devices implanted are
unknown. By the time such knowledge is
available, it is likely that the devices
are supplanted by newer iterations.
A flood of devices prevents the
is already in place, it is likely this will grow
further. It is known that the devices
are supplanted by newer iterations.
Such a flood of devices prevents the
establishment of a standardised procedure
and corresponding standardised devices.
Approval and set-up of research in the
NHS in England, including both clinical
investigations for CE-marking purposes
as well as other clinical research studies of
deVICES, they will need to apply for
Health Research Authority (HRA) Approval
before they can begin. The HRA is one
of a number of organisations that work
together in the UK to regulate and
approve different aspects of health and
social care research. HRA Approval brings
together an assessment of governance and
legal compliance, with the independent
REC opinion provided through the UK
Health Departments’ Research Ethics
Service and replaces the need for local
checks of legal compliance and related
matters by each participating organisation in
England. Participating NHS
organisations now focus their resources on
assessing, arranging and confirming
their capacity and capability to deliver the
study. Through its Study Support Service, the
NIHR CRN can help researchers and the
life sciences industry to plan, set up and
deliver high quality research in the NHS
in England; this includes early feasibility
advice and help to identify appropriate
study sites as well as provide support
with performance oversight to support
successful delivery of the study to its
recruitment targets.

Data ownership and privacy - In the fast-
growing data driven wearables sector
there are important considerations for
developing the appropriate sharing of
information whilst ensuring personal
data is adequately protected. With
reform of the EU’s data protection
framework underway, including the
introduction of the new General Data
Protection Regulation (Regulation (EU)
2016/679) in 2016 which will apply from
May 2018, device manufacturers will
need to give due consideration to the
principles of data protection by design
and by default throughout the product
development lifecycle. In addition, the
recent publication of the proposal for a
Regulation on Privacy and Electronic
Communications, intended to update and
replace the existing Directive (2002/58/
EC), means that manufacturers need
to stay up-to-date with developments
in this area. Whilst some data sharing
between patients and healthcare workers
is already in place, it is likely this will grow
further. Therefore, there are important
considerations for the future on the
development of such data sharing, and
access to clear guidance and standards,
particularly for supporting small and
medium enterprises, will be key.

Environmental concerns – With increasing
awareness of the environmental impacts
from electronics and devices, new products
and devices have to adopt an eco-design
approach. From electronic components,
circuit design, package design, and
materials, to manufacturing processes,
transportation, recycling, and product
end-of-life, ‘green’ approaches can be
implemented across the whole product
cycle. There are life-cycle assessment
(LCA) tools, which support the design and
production of ‘green electronics’ (Griese,
Schischke et al. 2003, Mueller, Griese
et al. 2004, Stovels 2007) and further
advice on environmental management
systems is available from the Institute
of Environmental Management and
Assessment. Although very few regulations
apply for using only ‘green’ approaches,
especially RoHS Directive 2002/95/EC and
1907/2006) any changes to requirements
in this area could have significant
impacts on the cost of production and
manufacturing processes.

Following an open competition, leading NHS organisations have been awarded
funding to host NIHR Medtech and in vitro diagnostic Co-operatives (MICS).

- NIHR London In Vitro Diagnostics Co-operative (NIHR London IVD Co-operative)
- NIHR Leeds In Vitro Diagnostics Co-operative (NIHR Leeds IVD Co-operative)
- NIHR Newcastle In Vitro Diagnostics Co-operative (NIHR Newcastle IVD
Co-operative)
- NIHR Surgical MedTech Co-operative
- NIHR Brain Injury MedTech Co-operative
- NIHR Cardiovascular MedTech Co-operative
- NIHR Devices for Dignity MedTech Co-operative (NIHR D4D MedTech
Co-operative)
- NIHR Mental Health MedTech Co-operative (NIHR MindTech MedTech
Co-operative)
- NIHR Trauma Management MedTech Co-operative (NIHR Trauma MedTech
Co-operative)
- NIHR Children and Young People MedTech Co-operative (NIHR CYP MedTech
Co-operative)
- NIHR Community Healthcare MedTech and In Vitro Diagnostics Co-operative
(NIHR Community Healthcare MedTech and IVD Co-operative)

The NIHR MICS will build expertise and capacity in the NHS to develop new medical
technologies and provide evidence on commercially-supplied in vitro diagnostic
(IVD) tests. Funding is provided over five years for leading NHS organisations to
act as centres of expertise; bringing together patients, clinicians, researchers,
commissioners and industry.
Endovascular intervention is playing an increasingly important role clinically, not only for treating cardiovascular diseases, but also for oncological interventions. Innovative device design, integrated with sensing and therapeutic delivery would encourage further clinical uptake of the technologies. This report assesses the current state-of-the-art in endovascular devices and emerging technologies for addressing some of the unmet clinical needs.

With the range of new devices being developed, it is important to direct more funding to systematic clinical trials. There are few studies on the long-term durability of endovascularly implanted devices, partially due to the novelty of these devices. However, such long-term studies are required to prove clinical benefit to the patient. Funders of clinical research should help facilitate and encourage these studies.

It is also imperative that the development of medical devices, particularly within academia, involves clinicians who have direct experience in the use of these devices. There is a risk in academia for research to be performed without complete understanding of the unmet clinical needs. Future research projects should ensure that clinical collaborators are part of the team. Furthermore, improved reporting on patient outcomes are required to ensure that the current diagnosis and treatment policies in place are working. This includes improved monitoring of patients after treatment and the possible monitoring of patients in their own homes.

Recent advances in Robotics have demonstrated their role in the deployment of endovascular devices and the current commercially available systems have been shown to simplify catheter manoeuvrability with improved stability and safety. However, current systems are expensive, occupy a large footprint in theatre, and in many cases, significant training is required to teach clinicians a new system of catheter manipulation that is vastly different from manual catheterisation. New systems that are smaller, smarter and more affordable, while being more intuitive to use, are required.

The current state-of-the-art in intraoperative guidance is via X-ray fluoroscopy. As discussed previously, while this imaging modality provides real-time guidance, visualisation of soft tissues is limited and exposure to ionising radiation is a significant problem. Novel use of safer imaging methods, such as magnetic resonance imaging or ultrasound, and improved navigation technologies, such as the use of electromagnetic tracking in other endovascular applications apart from cardiology, are required to ensure the correct placement of devices, reducing complications, reoperation, and ionising radiation.

There are currently limited opportunities to treat diseases in the ascending aorta and aortic arch (thoracic region) due to the limitations in fenestrated stent grafts for this particularly complex region. Improvements to fenestrated stent grafts are required and these are likely to need personalisation of the devices on a patient specific level.

By creating lower profile devices, the proportion of patients suitable for EVAR is likely to increase. Lower profiles have already been achieved in stent grafts, for example, through newer modular designs, improved stent designs, and adoption of new stent metals and graft fabrics. Current research has shown that the most common source of peri- and post-procedural damage occurred because of the catheter shaft exerting pressure at undesired places in the vessel lumen, leading to complications such as trauma, haemorrhage, and arterial spasm. In this regard, it is necessary to research into new passive catheter design, including research into biomaterials for catheter shafts which cause less reaction. An alternative is the development of active catheter design, including sensors for better control, feedback, and guidance integrated with robotic navigation.

4. Recommendations and Conclusions

Endovascular intervention is playing an increasingly important role clinically, not only for treating cardiovascular diseases, but also for oncological interventions. Innovative device design, integrated with sensing and therapeutic delivery would encourage further clinical uptake of the technologies. This report assesses the current state-of-the-art in endovascular devices and emerging technologies for addressing some of the unmet clinical needs.

With the range of new devices being developed, it is important to direct more funding to systematic clinical trials. There are few studies on the long-term durability of endovascularly implanted devices, partially due to the novelty of these devices. However, such long-term studies are required to prove clinical benefit to the patient. Funders of clinical research should help facilitate and encourage these studies.

It is also imperative that the development of medical devices, particularly within academia, involves clinicians who have direct experience in the use of these devices. There is a risk in academia for research to be performed without complete understanding of the unmet clinical needs. Future research projects should ensure that clinical collaborators are part of the team. Furthermore, improved reporting on patient outcomes are required to ensure that the current diagnosis and treatment policies in place are working. This includes improved monitoring of patients after treatment and the possible monitoring of patients in their own homes.

Recent advances in Robotics have demonstrated their role in the deployment of endovascular devices and the current commercially available systems have been shown to simplify catheter manoeuvrability with improved stability and safety. However, current systems are expensive, occupy a large footprint in theatre, and in many cases, significant training is required to teach clinicians a new system of catheter manipulation that is vastly different from manual catheterisation. New systems that are smaller, smarter and more affordable, while being more intuitive to use, are required.

The current state-of-the-art in intraoperative guidance is via X-ray fluoroscopy. As discussed previously, while this imaging modality provides real-time guidance, visualisation of soft tissues is limited and exposure to ionising radiation is a significant problem. Novel use of safer imaging methods, such as magnetic resonance imaging or ultrasound, and improved navigation technologies, such as the use of electromagnetic tracking in other endovascular applications apart from cardiology, are required to ensure the correct placement of devices, reducing complications, reoperation, and ionising radiation.

There are currently limited opportunities to treat diseases in the ascending aorta and aortic arch (thoracic region) due to the limitations in fenestrated stent grafts for this particularly complex region. Improvements to fenestrated stent grafts are required and these are likely to need personalisation of the devices on a patient specific level.

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