Health Policy Advisory Committee on Technology

Technology Brief

Endovascular arteriovenous fistula creation systems

March 2017
Summary of findings

Two case series studies were eligible for inclusion in this Technology Brief. Each reported on a different endovascular device for creating arteriovenous fistulae (AVF) in patients requiring haemodialysis. The devices were the everlinQ™ endoAVF System (TVA Medical, Inc.) and the Ellipsys® Endovascular Access System (Avenu Medical, Inc.).

Endovascular AVF systems are of interest as they could potentially eliminate the need for an open surgical procedure to create a haemodialysis access site. They may also improve patient satisfaction and reduce the risk of vessel trauma, infection and hospitalisation associated with surgical AVF creation.

Initial results indicate high rates of technical and clinical success. The technical success rate, or the successful creation of a patent AVF, ranged from 97 to 100 per cent. Clinical success, or maturation of the fistula and its successful use for haemodialysis access, ranged from 70 to 100 per cent up to 6 months’ follow-up. The majority of device- or procedure-related adverse events reported were considered minor. The most common complications included pseudoaneurysm (one of which was considered serious), haematoma and thrombosis. Comparative evidence is needed to assess how the rates and types of complications after endovascular AVF creation compare with those of the gold standard.

The current evidence base is poor; therefore limited conclusions can be made regarding the efficacy of the everlinQ and Ellipsys devices. In particular, it is important to consider the industry involvement in the execution and reporting of the two included trials when interpreting their findings. Larger, multicentre case series studies have recently been completed and their results are likely to be published in the near future. Ideally, randomised controlled trials comparing endovascular AVF creation with the gold standard are needed.

HealthPACT Advice

Endovascular devices for creating arteriovenous fistulae such as the everlinQ™ endoAVF System and the Ellipsys® Vascular Access System have been proposed as means of reducing the risk of infection and hospitalisation associated with surgical AVF creation. Although both of these devices do not have FDA approval, they do; however, have CE Marking, which has implications for the Australian TGA approval mechanisms.

The available published evidence on these endovascular devices reported conflicting results to those described by clinicians involved in clinical trials currently underway in Australia. These trials suggest that endovascular devices such as the everlinQ™ and Ellipsys® are suitable for only a select, limited group of patients.

HealthPACT does not support public investment in endovascular devices such as the everlinQ™ and Ellipsys® for the creation of arteriovenous fistulae in clinical practice at this time, except under the auspices of an evaluation trial conducted in a clinical setting.
Endovascular arteriovenous fistula creation systems: March 2017

Technology, Company and Licensing

Register ID WP253
Technology name Endovascular arteriovenous fistula creation systems
Patient indication Patients with chronic kidney disease requiring haemodialysis

Description of the technology

Each kidney contains approximately one million nephrons which are made up of a glomerulus (filter) attached to a tubule. Blood enters the kidneys through the renal arteries and passes through the nephrons, which filter out fluid, excess minerals and waste products. Most of this fluid is returned to the blood and the waste is concentrated in the remaining fluid as urine. Urine then flows out of the kidneys through the ureter into the bladder where it is removed from the body. The filtered blood re-enters circulation via the renal veins. The kidneys filter approximately one litre of blood each minute.

Kidney function is often measured by the level of creatinine (waste product) in the blood, which is an indicator of filtration rate. The higher the filtration rate the better the kidneys are working. A glomerular filtration rate of 100 mL/minute/1.73m² is considered normal (100% kidney function). Chronic kidney disease (CKD) is the condition caused by the progressive loss of kidney function over months or years. People with end-stage kidney failure (< 10% kidney function) require dialysis, which removes waste, excess chemicals and fluid from the blood.

Figure 1: Kidneys

Kidney function is often measured by the level of creatinine (waste product) in the blood, which is an indicator of filtration rate. The higher the filtration rate the better the kidneys are working. A glomerular filtration rate of 100 mL/minute/1.73m² is considered normal (100% kidney function). Chronic kidney disease (CKD) is the condition caused by the progressive loss of kidney function over months or years. People with end-stage kidney failure (< 10% kidney function) require dialysis, which removes waste, excess chemicals and fluid from the blood.
Haemodialysis involves the use of an artificial kidney (haemodialyser). Blood is taken from the body through a blood vessel, usually in the arm. Two needles attached to soft tubing are inserted into the blood vessel; one to remove the blood to be filtered and another to return the filtered blood. There are three types of vascular access that can be used for dialysis: a fistula, a graft and a catheter. This Technology Brief is concerned with fistulae for haemodialysis access.

A fistula is an abnormal connection between two structures inside the body. An arteriovenous fistula (AVF) can be formed surgically by connecting an artery and a vein to create an enlarged blood vessel. AVFs make needle insertion for dialysis easier and create faster blood flow. When a dialysis needle is inserted into a regular vein repeatedly it causes scarring and potential destruction of the vein. Traditionally, AVFs are created surgically and take up to two months to ‘mature’ before they are ready for use. Not all patients are eligible for AVF creation, and although the use of AVF for haemodialysis is considered the best option, it is also problematic. Surgically created AVFs fail up to 60 per cent of the time (especially in patients with small vessels and multiple comorbidities), require multiple interventions to maintain functionality and can take several months to become viable.

More recently, endovascular devices for AVF creation have been investigated. Two such devices are the everlinQ™ endoAVF System (Figure 2) and the Ellipsys® Vascular Access System (Figure 3). Table 1 provides an overview of how each device is used.

Table 1 Procedure used to create AVFs using the everlinQ and Ellipsys endovascular access systems

<table>
<thead>
<tr>
<th>everlinQ endoAVF System</th>
<th>Ellipsys Vascular Access System</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Two guidewires are inserted into an artery and a vein in the arm under fluoroscopic guidance.</td>
<td>1. A guidewire is passed through the perforating vein in the arm and into the nearby radial artery.</td>
</tr>
<tr>
<td>2. Two everlinQ magnetic catheters are inserted into the artery and the vein.</td>
<td>2. The needle is withdrawn and a sheath is placed over the wire into the artery. The Ellipsys catheter is positioned so that it spans the walls of the artery and the vein.</td>
</tr>
<tr>
<td>3. The magnetic catheters are drawn to one another, bringing the artery and vein into contact.</td>
<td>3. The catheter halves are then closed and activated, and a fistula is created using low-power electric current.</td>
</tr>
<tr>
<td>4. A radiofrequency electrode on the venous catheter is energised for 2 seconds, making a hole in the vessel walls and creating a channel between the artery and vein.</td>
<td>4. The sheath is removed and the puncture wound is closed.</td>
</tr>
<tr>
<td>5. The vein is then blocked with a coil to force blood flow to the superficial veins.</td>
<td></td>
</tr>
<tr>
<td>6. Both catheters are removed and the puncture wound is closed.</td>
<td></td>
</tr>
</tbody>
</table>

**Company or developer**

everlinQ endoAVF System, TVA Medical, Inc., Texas, United States of America.

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**Reason for assessment**

The lives of more than two million people worldwide rely on haemodialysis. Endovascular AVF systems offer a minimally invasive, catheter-based approach to AVF creation for patients requiring haemodialysis. The use of such devices may eliminate the need for an open surgical procedure, reduce vessel trauma, improve patient satisfaction and reduce the risk of infection and hospitalisation associated with AVF creation.

**Stage of development in Australia**

- Yet to emerge
- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
Licensing, reimbursement and other approval

The everlinQ system does not have Therapeutic Goods Administration (TGA) approval. The system is not available for sale in the United States and is pending clearance from the United States Food and Drug Administration (FDA). It has been issued European CE Mark (in September 2014) and a Medical Device License from Health Canada for the creation of an AVF in patients with chronic kidney disease who require haemodialysis.\(^8,9\)

The Ellipsys system does not have TGA approval. The system was issued European CE Mark approval for commercial sale in June 2016.\(^10\) The manufacturer intends to apply for FDA market authorisation at the end of 2016.\(^10\)

Australian Therapeutic Goods Administration approval

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARTG number (s)</td>
</tr>
</tbody>
</table>

Technology type    Device; Procedure
Technology use    Therapeutic

Patient Indication and Setting

Disease description and associated mortality and morbidity

CKD is defined as the occurrence of kidney damage and/or reduced kidney function that lasts three months or more.\(^11\) CKD tends to be asymptomatic until up to 90 per cent of kidney function is lost. The first signs of CKD may include, but are not limited to, high blood pressure (hypertension), severe itching, increased night-time urination, restless legs, blood in the urine, difficult or laboured breathing, lethargy, nausea/vomiting, malaise and anorexia.\(^11\)

Risk factors for developing CKD include diabetes, hypertension, established cardiovascular disease, a family history of CKD, previous acute kidney injury, obesity (body mass index ≥ 30 kg/m\(^2\)), smoking, and being over 60 years of age or of Aboriginal or Torres Strait Islander descent.\(^11\)

End-stage kidney disease is the final stage of CKD, when the kidneys can no longer support the body’s needs.\(^12\) This generally occurs when kidney function is below 10 per cent. Symptoms of end-stage kidney disease are similar to those of CKD with the addition of the following: headache, changes in skin pigment, nail changes, bone pain, problems concentrating, breath odour, easy bruising, nosebleeds, blood in the stool, excessive thirst, sleep problems and swelling of the hands and feet.\(^12\) People with end-stage kidney disease require dialysis or a kidney transplant to survive.
Number of patients
Approximately one in ten Australians aged over 18 years has biomedical signs of CKD, equating to 1.7 million people.\textsuperscript{11} Seventeen per cent of all hospitalisations in 2013-14 were due to CKD (principal diagnosis and/or additional diagnosis); 80 per cent of these hospitalisations were for regular dialysis. CKD was the underlying or associated cause of death in 15,900 (one in ten) deaths recorded in 2013. Hospitalisations and deaths due to CKD are three to five times higher among Aboriginal and Torres Strait Islander Australians, compared with non-indigenous Australians.\textsuperscript{13}

In New Zealand in 2013, there were a total of 1,099 hospital discharges for CKD and 204 deaths due to kidney failure.\textsuperscript{14}

Speciality Renal disease and urology
Technology setting Specialist hospital; General Hospital

Impact

Alternative and/or complementary technology
Endovascular AVF systems could partially replace surgical AVF creation, or offer an alternative to surgery. It is unlikely that endovascular technologies will replace surgery completely as there will remain a need for surgery for patients with complicated blood vessel access or multiple comorbidities.\textsuperscript{6}

Current technology
The current gold standard for AVF creation is surgery. Surgery usually takes place under local anaesthesia in hospital as a day-case or outpatient procedure.\textsuperscript{15} A small incision is made in the forearm to gain access to the blood vessels.\textsuperscript{15} Blood flow in these vessels is blocked throughout the procedure. Incisions are made in an artery and a vein and the two vessels are joined using silk sutures.\textsuperscript{15} Once joined, blood flow increases and the vein becomes thicker.\textsuperscript{15} Over a period of months, the connection between the artery and vein strengthens into a fistula that may then be used as a permanent vascular access point for haemodialysis.\textsuperscript{15}

Opportunity for disinvestment
Endovascular AVF systems may offer the opportunity for partial disinvestment in surgical AVF creation, noting that not all patients will be eligible for endovascular AVF creation (especially patients with small vessels and multiple comorbidities).
**Diffusion of technology in Australia**

The everlinQ system has been used in Australia and New Zealand as part of a clinical trial. This trial took place in nine centres across Australia (one in Queensland and one in Victoria), Canada (six centres) and New Zealand (one in Auckland).

**International utilisation**

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
</tr>
<tr>
<td>Australia</td>
<td>✓</td>
</tr>
<tr>
<td>Canada</td>
<td>✓</td>
</tr>
<tr>
<td>Germany</td>
<td>✓</td>
</tr>
<tr>
<td>Netherlands</td>
<td>✓</td>
</tr>
<tr>
<td>New Zealand</td>
<td>✓</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>✓</td>
</tr>
<tr>
<td>United States of America</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Cost infrastructure and economic consequences**

TVA Medical, Inc. and Avenu Medical, Inc. were contacted regarding the cost of the everlinQ device and the Ellipsys device; however, no responses have yet been received. Besides the cost of the device, use of endovascular AVF systems would be associated with initial staff training costs, although these are not likely to be substantial. The literature indicates that physicians with interventional endovascular experience are likely to become proficient with the procedure after approximately three cases. If the proposed benefits of endovascular AVF creation are realised, there will be cost savings with regards to lower rates of infection and hospitalisation.

The Medicare Benefits Schedule (MBS) item numbers currently used for surgical arteriovenous access creation are 34512 and 34509 (Personal communication, Royal Adelaide Hospital). Details of these item numbers are in Table 2. Costing for endovascular AVF creation would need to include a procedure fee and radiology fee.

**Table 2** MBS item numbers for surgical arteriovenous access creation

<table>
<thead>
<tr>
<th>MBS item number</th>
<th>Description</th>
<th>Fee</th>
<th>Benefit 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>34509</td>
<td>ARTERIOVENOUS ANASTOMOSIS OF UPPER OR LOWER LIMB, not in conjunction with another venous or arterial operation</td>
<td>$977.55</td>
<td>$733.20</td>
</tr>
<tr>
<td>34512</td>
<td>ARTERIOVENOUS ACCESS DEVICE, insertion of</td>
<td>$1,075.40</td>
<td>$806.55</td>
</tr>
</tbody>
</table>
Ethical, cultural, access or religious considerations

No ethical, cultural or religious considerations were identified that may limit the use of this technology.

The literature reports waiting periods in excess of 3 months for surgical AVF creation. Consequently, this increases the time patients are required to use central venous catheters for haemodialysis, which are associated with an increased risk of infection and death. Endovascular systems may improve patient access to AVF creation by increasing the number and types of physicians (including endovascular surgeons, interventional radiologists and interventional nephrologists) who can perform the procedure.

Evidence and Policy

Safety and effectiveness

Two case series studies (level IV interventional evidence) were eligible for inclusion in this Technology Brief. One is in conference abstract form and the other is a full peer-reviewed document. The conference abstract reported the use of the Ellipsys device in 10 patients. The peer-reviewed case series study reported the use of the everlinQ device in 33 patients.

Table 3: Study details for included studies

<table>
<thead>
<tr>
<th>Study; Location</th>
<th>Study design</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>N</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajan et al 2015 Canada</td>
<td>Case series</td>
<td>everlinQ</td>
<td>Patients requiring long-term haemodialysis; candidacy for native surgical AVF; advanced (stage 4/5) CKD; elective haemodialysis; ≤ 2 mm between target vein and artery; target vein/artery diameter ≤ 2 mm; not pregnant; age ≥ 18 years; estimated life expectancy &gt; 1 year; ability to consent.</td>
<td>33</td>
<td>6 months</td>
<td>Primary endpoints Technical success (creation of a patent AVF between an arm artery and vein); dilation (maturation) of the vessel over time assessed monthly by Doppler US; adverse events assessed by clinical examination and/or US or angiography. Secondary endpoints Haemodialysis via the AVF for ≥ 75 per cent of sessions over a 1-month period.</td>
</tr>
<tr>
<td>Hull et al 2014 Colombia</td>
<td>Case series (Abstract)</td>
<td>Ellipsys</td>
<td>Patients with a proximal radial artery and adjacent vein diameter ≥ 2.0 mm with adequate (&gt;2.0 mm) venous outflow.</td>
<td>10</td>
<td>6 weeks</td>
<td>Technical success (creation of AVF); clinical success (maturation); adverse events.</td>
</tr>
</tbody>
</table>

AVF: arteriovenous fistula; CKD: chronic kidney disease; US: ultrasound.
This prospective case series study investigated the feasibility of creating fistulae with the everlinQ endoAVF system and evaluated the utility of AVFs made through the skin (percutaneous) in providing haemodialysis access. Inclusion criteria and primary and secondary endpoints are reported in Table 3.

A total of 61 consecutive patients were screened to participate in this study, 33 of whom were prospectively enrolled. The mean age of the included patients was 51 years (standard deviation [SD] 11.4). Fifty-eight per cent of patients were diabetic and 6 per cent had peripheral vascular disease.

**Safety**

There were a total of four deaths over the study period, all of which were unrelated to AVF creation. The causes of death included myocardial infarction, gangrenous intestine, diabetic foot infection with sepsis and heart arrhythmia. Three of the four deaths occurred within 2 months of the procedure.

Among the 33 patients there were six (18%) device- or procedure-related adverse events reported, one of which was considered serious. In this patient, a pseudoaneurysm, or a pooling of blood between the two outer layers of an artery, 3 cm in length was noted at 1 month follow-up and successfully treated with thrombin injection. The five minor adverse events included: a small (< 1 cm in length) pseudoaneurysm which did not require intervention; two cases of small collections of blood at the brachial artery access site (haematomas) that resolved spontaneously; detachment of the venous catheter’s tip upon withdrawal requiring an incision for removal; and arm swelling and venous hypertension in a patient with pre-existing central vein narrowing. Blood clot formation (thrombosis) was noted in the patient with swelling 3.5 months post-procedure.

There was no evidence of inadequate blood flow to the lower arm (arterial steal) or damage to the peripheral nerves (peripheral neuropathy) in any patient.

**Effectiveness**

Technical success was achieved in 97 per cent of patients (32/33) and AVF patency was confirmed by Doppler ultrasound at 24 hours for all patients. In the one technical failure, no fistula was created and there was no evidence (ultrasound or angiographic) of blood leakage or vessel injury.

All of the living patients in whom the procedure was a technical success (n=28) were considered to have mature haemodialysis access at an average of 58 days post-procedure (range 37 to 168; SD 32). The access was used successfully to deliver haemodialysis at 6 months in 24 patients of these patients. Four patients were not receiving haemodialysis at 6
months due to: no longer requiring it despite patent AVFs (n=2), death (n=1) and hypertension and arm swelling (n=1; patient had pre-existing central vein narrowing).

Two patients did not have use of their AVFs for all of their dialysis sessions due to cannulation injuries that resulted in haematomas (all resolved). Despite this, all patients used their AVFs for more than 75 per cent of their dialysis sessions (secondary endpoint).

Table 4  Study results reported by Rajan et al (2015) using the everlinQ device.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical fistula success at 24 hours</td>
<td>97% (32/33)</td>
</tr>
<tr>
<td>Vein maturation at 3 months</td>
<td>96% (27/28)</td>
</tr>
<tr>
<td>Fistula patency at 6 months</td>
<td>100% (26/26)</td>
</tr>
<tr>
<td>Dialysis initiation/ready with AVF</td>
<td>96% (27/28)</td>
</tr>
<tr>
<td>Receiving dialysis with AVF &gt; 1 month</td>
<td>96% (25/26)</td>
</tr>
<tr>
<td>Mean time to fistula maturation</td>
<td>58 days (n=28)</td>
</tr>
</tbody>
</table>

AVF: arteriovenous fistula

* Differing results are reported for some outcomes (fistula patency at 6 months and mean time to fistula maturation) in tabular versus narrative form in the full text document. As such, the narrative version of results is reported above.

Hull et al 2014

This case series study, presented in abstract form, reported the initial clinical experience with an electrocautery-based catheter (the Ellipsys Vascular Access System) for the creation of percutaneous AVFs. Ten patients with advanced CKD were eligible for inclusion.

Technical success was defined as the creation of a fistula and clinical success (or maturation) was defined as a fistula with a venous outflow of at least 400 mL per minute at 6 weeks or the occurrence of successful dialysis. The complications considered included uncontrolled bleeding, haematoma, thrombosis, pseudoaneurysm, infection, nerve damage and death.

A duplex ultrasound examination was performed at 24 hours and 1, 2 and 6 weeks post-procedure to evaluate vessel patency, size and flow.

Safety

Three patients (30%) experienced venous thrombosis in their AVFs, with no long-term adverse consequences noted; there were no other complications reported.

Effectiveness

Technical success with the Ellipsys system was achieved in all 10 patients and clinical success was achieved in 70 per cent. The mean proximal venous outflow of the fistulae was 804 mL per minute (range 131 to 720; SD 614).
Economic evaluation

No cost-effectiveness or economic analyses were identified in the retrieved literature regarding the use of the everlinQ or Ellipsys endovascular AVF systems.

Ongoing research

Searches of trial registers (clinicaltrials.gov) found the following manufacturer-sponsored clinical trials using endovascular AVF creation systems.\(^{16, 19-21}\) Three of the four trials are complete, with results yet to be published.\(^{16, 19, 21}\)

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Ongoing trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial ID and location</strong></td>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td>NCT02036671 16 Australia; Canada; New Zealand</td>
<td>Multicentre case series</td>
</tr>
<tr>
<td>NCT02363972 21 USA</td>
<td>Multicentre case series</td>
</tr>
<tr>
<td>NCT02682420 20 Germany; Netherlands; UK</td>
<td>Multicentre case series</td>
</tr>
<tr>
<td>NCT02816398 19 Location(s) NR</td>
<td>Case series</td>
</tr>
</tbody>
</table>

AVF: arteriovenous fistula; NA: not applicable; NR: not reported; UK: United Kingdom; USA: United States of America.

Other issues

All of the included studies and ongoing trials had conflicts of interest; therefore, interpretation of their findings should proceed with caution. Although not acknowledged therein, the first author of the conference abstract is the founder of and a stockholder in Avenu Medical, Inc.

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies 2
Total number of Level IV studies 2
Search criteria to be used (MeSH terms)
(Arteriovenous fistula AND creation) AND (arteriovenous fistula AND endovascular)

Search date
18th November 2016

References
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