

# evidence | *note*

In response to an enquiry from Andrew Tambyraja, Edinburgh Vascular Service, Royal Infirmary of Edinburgh

Number 78 May 2018

**What is the clinical and cost-effectiveness of complex endovascular aneurysm repair in patients with juxta-renal or thoraco-abdominal aortic aneurysm compared with open surgical repair, and how should these technologies be delivered in NHSScotland?**

## Key points

- A single prospective observational study compared 30-day outcomes of fenestrated/branched endovascular aneurysm repair (F/B-EVAR) with open surgery repair (OSR) for the treatment of complex aortic aneurysm anatomies: para/juxta-renal aortic aneurysm (PRAA/JRAA) and thoraco-abdominal aortic aneurysm (TAAA). There was no statistically significant difference in 30-day mortality between the F/B-EVAR cohort and OSR cohort (6.7% versus 5.4%,  $p=0.40$ ).
- After stratification by aneurysm anatomy, the F/B-EVAR and OSR mortality rates were not significantly different for PRAA/JRAA (4.3% versus 5.8%,  $p=0.26$ ) and supra-diaphragmatic TAAA (11.9% versus 19.7%,  $p=0.70$ ), and significantly higher with F/B-EVAR for infra-diaphragmatic TAAA (11.9% versus 4.0%,  $p=0.01$ ).
- In an extension study, 2-year mortality did not significantly differ between the groups (14.9% with F/B-EVAR vs. 11.8% with OSR,  $p=0.15$ ) and F/B-EVAR was associated with a higher rate of readmissions per patient (2.2 vs. 1.7,  $p = 0.001$ ).
- Additionally, three systematic reviews and one Health Technology Assessment (HTA) reported pooled outcome estimates for various complex EVAR techniques in populations with different aneurysm anatomies. These were based on low quality evidence - generally retrospective case series reporting short-term outcomes - within which patient cohorts are unlikely to be comparable in terms of urgency of treatment (elective/non-elective), aneurysm anatomy, risk profile, and other demographics. The systematic reviews reported a 30-day mortality for the treatment of JRAA ranging from 1.4% to 4.1% with F-EVAR, 3.1% to 4.1% with OSR, and 5.3% with chimney-EVAR (Ch-EVAR).

- Significantly higher postoperative major complication rates were reported for OSR compared to the endovascular techniques included across the systematic reviews identified. However, the endovascular techniques have a higher rate of re-intervention and their durability is uncertain due to the general lack of long-term follow-up data.
- High volume hospitals and surgeons performing higher number of procedures are associated with lower levels of perioperative mortality. A policy document from NHS England recommends that providers of these techniques should have a projected annual case load in excess of 24-30 cases to maintain high levels of expertise in all professionals involved in the care pathway.
- Complex EVAR procedures are costly; the cost of the stent graft alone is in the region of £12,000- £30,000 in the UK depending on the device used. One prospective observational study reported significantly higher costs for F/B-EVAR compared to OSR but no statistical significant difference in 30-day and 2-year mortality. However, due to the short-term follow-up, high heterogeneity between the cohorts and lack of quality-of-life data, no clear conclusions can be made about the cost effectiveness of these procedures based on this study.

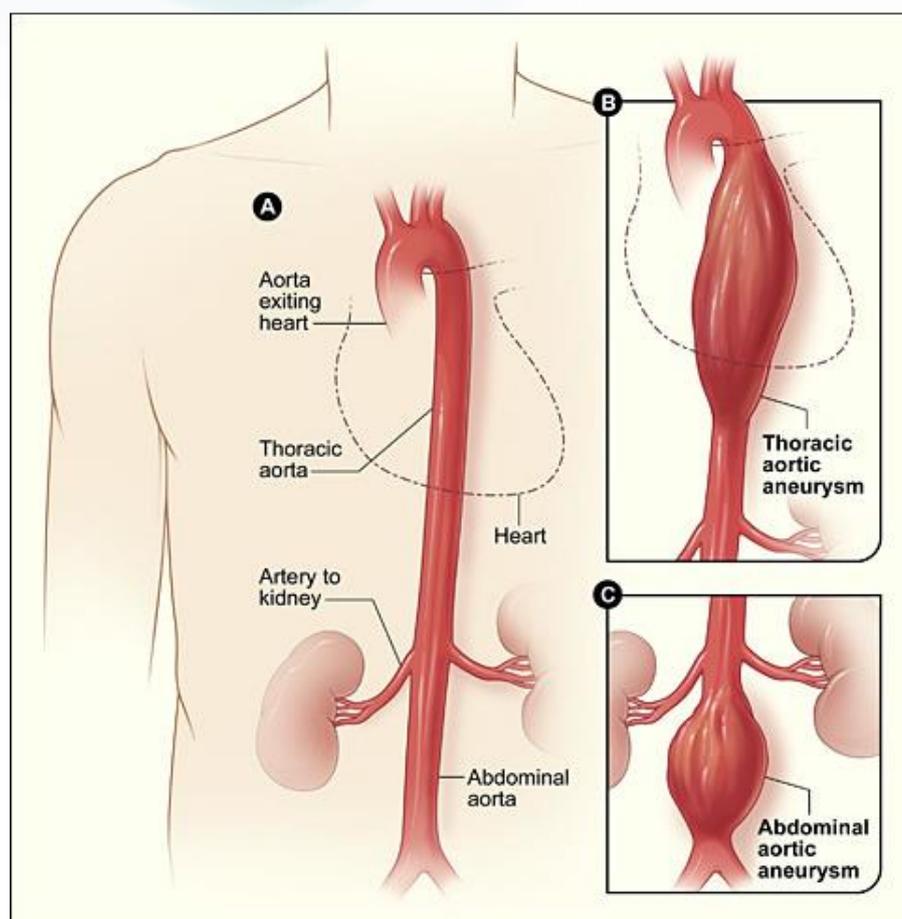
## What is an evidence note?

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

## Definitions

**Aortic aneurysm (AA):** A permanent and localized enlargement (dilation) of the aorta by  $\geq 50\%$  of its normal vessel diameter.<sup>1</sup> Most aortic aneurysms occur in the abdominal aorta below the kidney arteries (infra-renal); these are termed abdominal aortic aneurysms (AAAs). A further classification are para-renal aortic aneurysm (PRAA) which include two types of AAA: juxta-renal (JRAA) and suprarenal (SRAA). Aneurysmal degenerations that occur in the thoracic aorta above the kidney arteries are termed thoracic aortic aneurysms (TAAs). TAAs may be located in the ascending aorta, arch, descending aorta or thoraco-abdominal aorta, which originates in the descending aorta and extends to the abdominal aorta.<sup>2</sup> See Figure 1 for a graphical representation of the two main types of aortic aneurysms.

Figure 1: Various aortic aneurysm anatomies

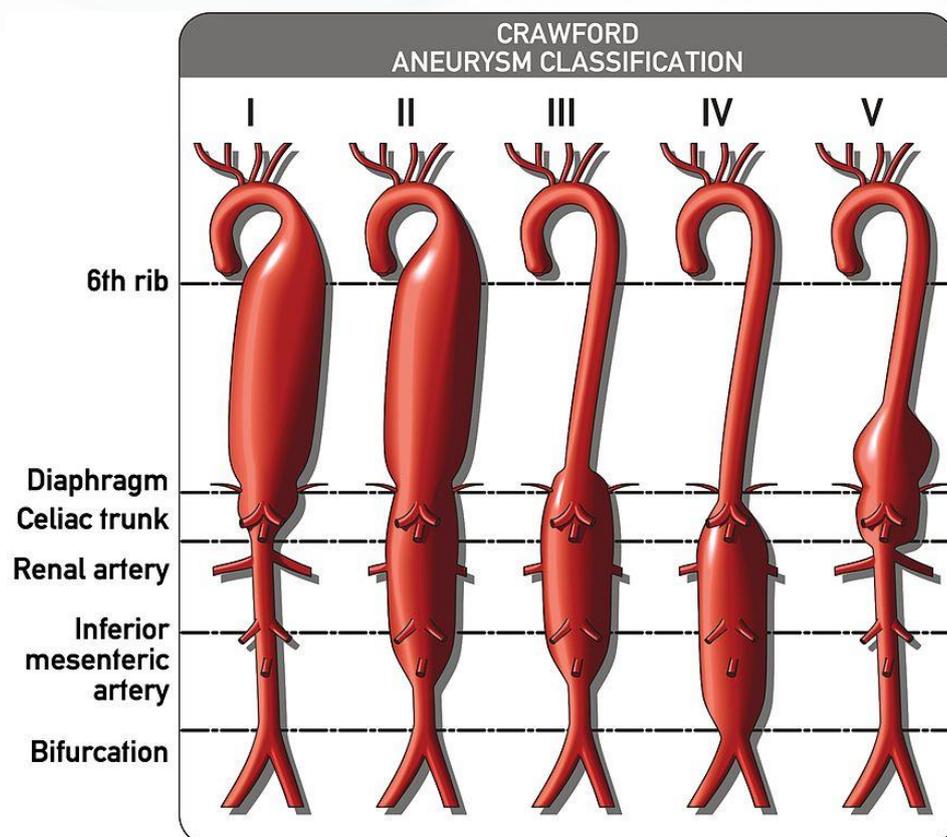


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**Juxta-renal aortic aneurysm (JRAA):** A type of AAA extending up to but not involving the renal arteries.<sup>3</sup> An important concern relating to endovascular repair regards the length of the proximal neck between the renal artery and the aneurysm which tends to be short in the case of JRAA providing a lower sealing zone margin. In case of a para-renal aortic aneurysm (PRAA), there is no aortic neck beneath the renal arteries.

**Thoraco-abdominal aortic aneurysm (TAAA):** Aneurysms of the descending thoracic aorta extending into the abdominal aorta and involving the celiac, superior mesenteric, and renal arteries.<sup>4</sup> These are difficult aneurysms to treat and are relatively uncommon in general vascular practice. TAAAs are stratified using the Crawford Classification System based on their distribution within the aorta and this is illustrated in Figure 2<sup>2</sup>. According to their relative position in relation to the diaphragm these can be further classified into supra-diaphragmatic and infra-diaphragmatic.

Figure 2: Crawford Classification of Thoraco-Abdominal Aortic Aneurysms

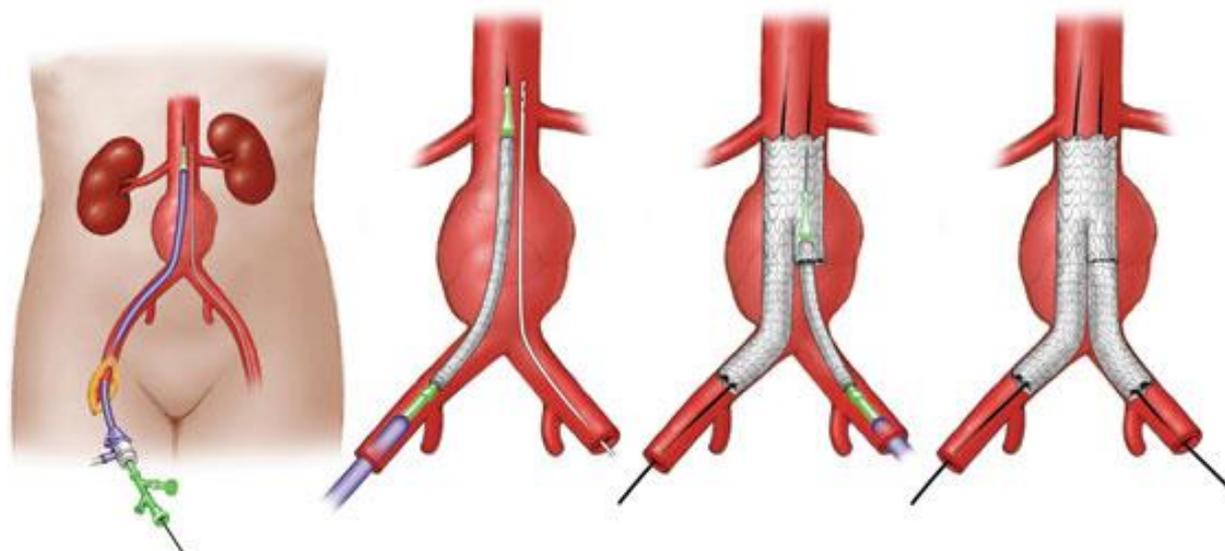


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**Open surgery repair (OSR) for aortic aneurysm:** Open surgery is a well-established gold standard treatment for aortic aneurysms, including JRAA, in low-surgical-risk patients.<sup>3</sup> For patients with severe comorbidities and/or deemed to be at high surgical risk for OSR, endovascular repair is a potential non-invasive alternative.

**Endovascular aneurysm repair:** Standard endovascular aneurysm repair (EVAR) is a non-invasive alternative to open surgical repair (OSR) in which an endograft (stent) is inserted into the affected section of the aorta through the femoral artery under fluoroscopic guidance.<sup>5</sup> Complex endovascular aneurysm repair techniques have been developed to deal with cases in which standard EVAR is unfeasible (for example in the case of JRAA, the short proximal neck is generally considered a contraindication for standard endovascular approaches). An illustration of endovascular aneurysm repair is given in Figure 3.

Figure 3: Endovascular aneurysm repair



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## Literature search

A systematic search of the secondary and primary literature was carried out between 21–28 August 2017. Key websites were searched for policy documents, reviews, economic studies and ongoing trials.

Medline, Medline in process, Embase and Web of Science databases were searched using the OVID SP platform. Concepts used in all searches included: thoraco abdominal and juxta renal aortic aneurysm, Fenestrated Endovascular Aneurysm Repair (FEVAR); Branched Endovascular Aneurysm Repair (BEVAR); Chimney-EVAR and Snorkel-EVAR. A full list of resources searched and search strategies are available on request.

Review of the literature in this evidence note was restricted to health technology assessments (HTAs), systematic reviews, economic evaluations, randomised controlled trials (RCTs) and observational studies from 2007 onwards.

An additional search for patient issues was carried out between 3–8 November 2017. The Medline, Medline in process, Embase and Web of Science databases were searched using the search terms and a patient issues filter designed by the Scottish Intercollegiate Guidelines Network (SIGN). Additional patient information sources such as the Picker Institute, Patient Opinion and National Voices were searched. A full list of resources searched is available on request.

## Introduction

Open surgical repair (OSR) has traditionally been seen as the gold standard treatment for aortic aneurysms; however, endovascular techniques are becoming increasingly used, particularly in patients deemed high risk for morbidity and mortality with open repair<sup>6</sup>. Patients with abdominal aortic aneurysms (AAAs) may be treated with conventional endovascular aneurysm repair (EVAR), which has become the standard of care in many hospitals for patients with suitable anatomy. Past clinical evidence indicated that EVAR was associated with superior perioperative outcomes and similar long-term survival compared with open repair, also shown in an SHTG technologies scoping report published in 2012.<sup>5</sup> However, more recent clinical evidence suggests that, while an early survival benefit of EVAR may still be

present, beyond eight years follow-up the survival benefit following OSR may become superior to EVAR; also the durability for EVAR is inferior and associated with a higher rate of re-intervention compared with OSR<sup>7</sup>.

Approximately 20% to 30% of otherwise eligible patients are ineligible for standard EVAR because of aortic neck morphology.<sup>8</sup> Most of these patients have an aortic neck situated in the vicinity of the aortic side branches, requiring extensive open surgery. In the past few years, complex endovascular stent grafts have increasingly been used to manage anatomically challenging aneurysms, and experiments with off-label use of stent grafts — such as chimney techniques — have been performed.<sup>6</sup>

While multiple high-quality, randomised controlled trials with long-term follow-up have now been published that compare standard EVAR to OSR, evidence on the use of complex grafts is still in its infancy. Previous work by National Services Scotland (NSS) looked at the state of the evidence for anatomically challenging aneurysms, noting the general lack of evidence in a 2007 review of the TAAA services within NHSScotland<sup>2</sup>. In another NSS review of the TAAA services in NHS Lothian<sup>9</sup>, the review group concluded that patients with TAAA in which open surgery is the treatment of choice should only be treated in the designated national specialist centre in Edinburgh, and that the national service should also offer a comprehensive list of complex endovascular repair techniques.

The aim of this evidence note is to summarise the post-2007 published evidence around the relative clinical effectiveness, safety and cost effectiveness of complex EVAR techniques compared with OSR or non-surgical management in patients with a juxta-renal or thoracoabdominal aortic aneurysm. The outcomes of interest are survival, freedom from adverse events, re-intervention rate, and cost effectiveness. Issues around the method of delivery of these procedures in NHSScotland were also explored.

## Health technology description

The current evidence review addresses three types of complex endovascular aneurysm repair techniques for the treatment of juxta-renal and thoraco-abdominal aortic aneurysms. These are:

- Fenestrated endovascular aneurysm repair (F-EVAR)
- Branched endovascular aneurysm repair (B-EVAR)
- Chimney endovascular aneurysm repair (Ch-EVAR)

There are various manufacturers that produce the stent grafts (Cook, Vascutek, Jotec) used in these techniques. It should be noted that the evidence base does not consider the relative effectiveness of different manufacturers' devices, rather it considers the procedure as a whole compared to open surgery repair.

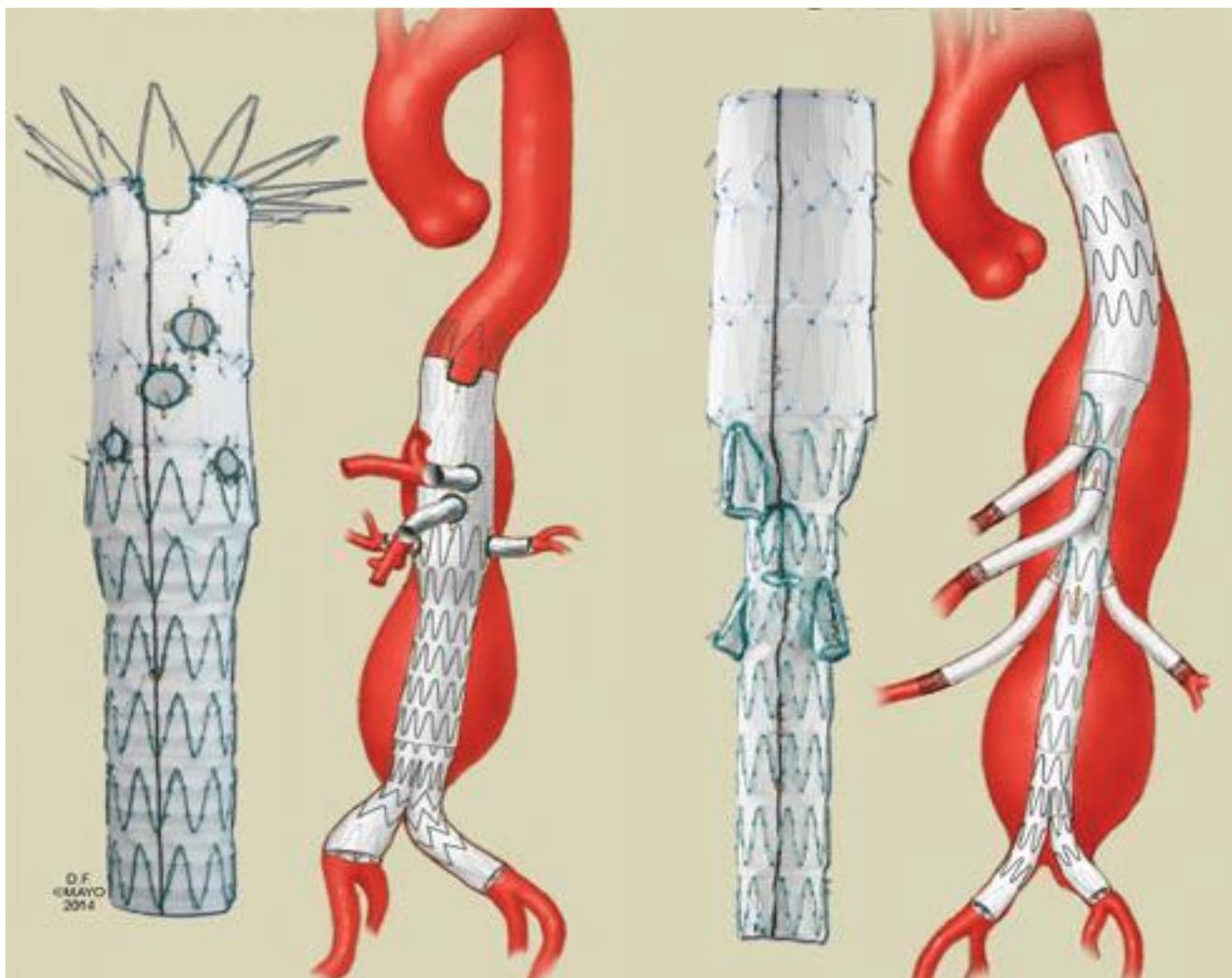
F-EVAR is a complex endovascular aneurysm repair technique that uses fenestrated grafts which overcome the problem of an insufficient infra-renal neck for stent graft implantation in patients with juxta-renal or supra-renal aortic aneurysms.<sup>6</sup> These grafts are designed to allow the proximal sealing zone of the stent to incorporate the aorta at the level of the renal and visceral vessel ostia.<sup>10</sup> The flow to the side branches is preserved through fenestrations in the stent-graft fabric.

B-EVAR is a technique which uses branched stent grafts for aneurysms that involve vital aortic side branches such as supra-renal and Type 4 thoraco-abdominal aneurysms or even the pre-cerebral vessels (aortic arch aneurysm).<sup>10</sup> Unlike the fenestrated grafts, which have only pre-made windows for the visceral and renal artery origins, branched grafts have branches already attached to the body of the

endograft that are themselves deployed into the visceral and renal arteries. The essential difference between F-EVAR and B-EVAR is that the latter is more suitable when the aneurysm extends in the visceral segment.

An illustration of the F-EVAR and B-EVAR techniques is provided in Figure 4. The stents used in these two techniques are generally custom made using imaging techniques to determine the aneurysm anatomy. The manufacturing of the stents may take 4 to 6 weeks.

**Figure 4: Fenestrated (left) and branched (right) endovascular aneurysm repair**

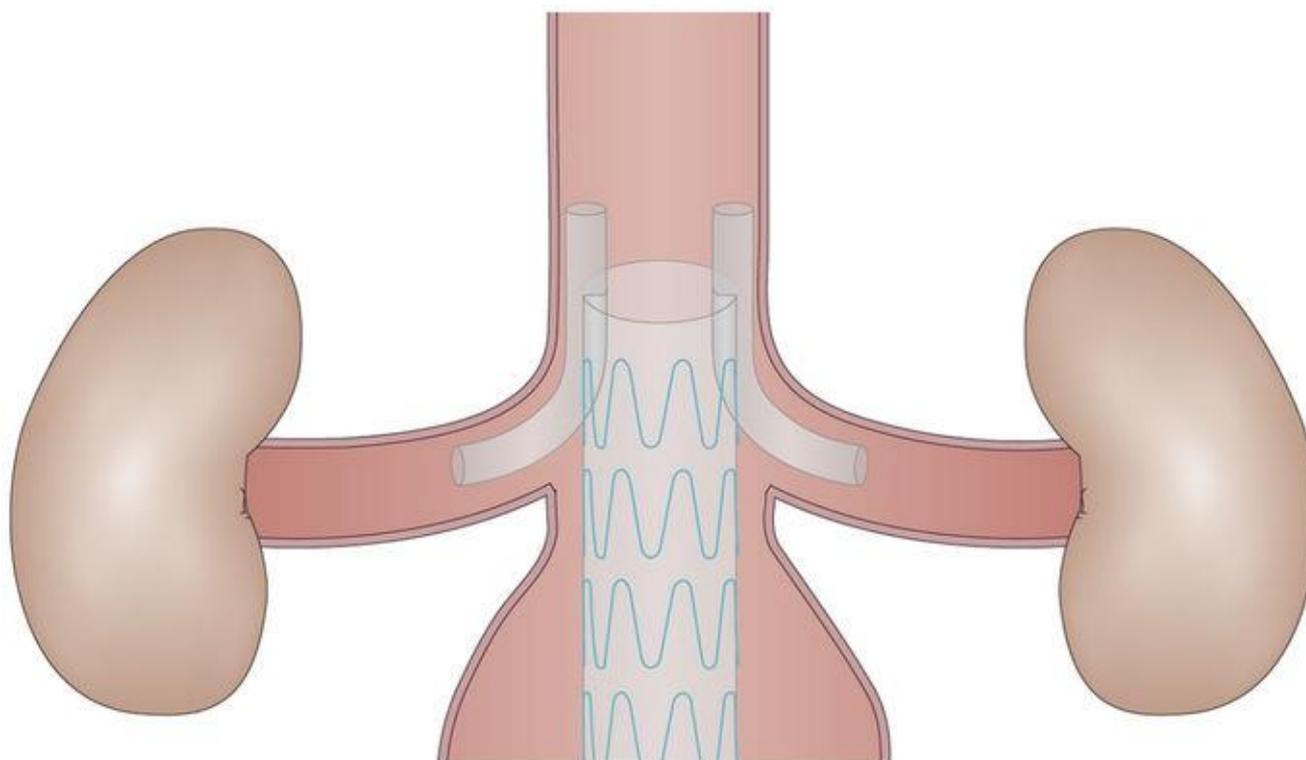


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Not all patients with complex aneurysms are suitable for F-EVAR or B-EVAR. Vascular specialists have developed the chimney graft technique (Ch-EVAR, also known as the periscope or snorkel technique) for patients who are deemed unfit for open surgery, but who require urgent intervention and a custom-made stent cannot be designed within the time available. As previously noted, F-EVAR requires manufacturing of a stent-graft, which can easily take 4 to 6 weeks or more so is not suitable for non-elective cases, while Ch-EVAR utilises off-the-shelf stents.

In the case of a juxta-renal aneurysm, covered stents are first deployed in the renal arteries usually via the axillary artery and out into the aorta in an upward direction (appearance is like that of a chimney under fluoroscopy) into proximal aorta as in Figure 5. Following this, a conventional bifurcated stent graft is deployed in line with the covered stents.<sup>10</sup>

**Figure 5: Chimney graft**



Source: Buck et al.<sup>6</sup>

## Epidemiology

The prevalence of AAA is approximately 4% to 8% in screening studies worldwide (various age groups, typically over 65 years old), predominantly affecting males.<sup>11</sup> However, AAAs found on screening are generally small, and larger AAAs measuring  $\geq 5.5$  cm or greater are found in only 0.4% to 0.6% of those screened. The annual incidence of AAA diagnoses is approximately 0.4% to 0.67% in Western populations. Both the prevalence and incidence tend to significantly increase with age. There is also a strong relationship between aneurysm size and rupture risk as indicated in Table 1.

**Table 1: Annual AAA rupture risk in relation to size (adapted from Law et al., 1994)<sup>12</sup>**

Aneurysm size (cm)	Risk of rupture per year (%)
< 3.0	0
3–3.9	0.4
4–4.9	1.1
5–5.9	3.3
6–6.9	9.4

According to the latest key performance indicators of the Scottish AAA National Screening Programme, 97% of men who turned 66 in the year ending March 2016 were invited for screening before their 66<sup>th</sup> birthday.<sup>13</sup> Uptake of the AAA screening programme was high with 84% of men in Scotland tested before age 66 and 3 months. Of the 25,500 men tested, 376 (1.5%) had a positive result (an aneurysm of 3.0cm or greater). Of the men having a positive result 81.1% were found to have a small aneurysm (3.0 to 4.4cm), 12.2% medium (4.5 to 5.4cm) and 6.6% large (5.5cm or greater). The data in the report were not further classified by aneurysm type.

Epidemiological data on specific types of aortic aneurysms are limited. It is reported that AAA account for 75% of all aortic aneurysms and are located below the renal arteries.<sup>2</sup> Juxta-renal aortic aneurysms (JRAA) account for approximately 15% of AAAs.<sup>14</sup> The proportion of thoracic aortic aneurysms that occur in the thoraco-abdominal aorta is 15%. The true incidence of thoraco-abdominal aortic aneurysms (TAAA) is unknown. The estimated adjusted incidence varies from 2.2 to 3 cases per 100,000 person-years.<sup>2</sup>

## Clinical effectiveness

For ease of reference, the evidence base is summarised in Table 2. A more detailed description of each study follows.

**Table 2: Main characteristics of the evidence base summarised for the JRAA population**

Study	Year	Type	Population	Interventions	Mortality
<b>Michel <i>et al.</i><sup>15</sup></b>	2018	Prospective cohort study	JRAA/PRAA TAAA	F-EVAR/B-EVAR OSR	F-EVAR/B-EVAR: 14.9% <sup>a</sup> OSR: 11.8% <sup>a</sup>
<b>Michel <i>et al.</i><sup>16</sup></b>	2015	Prospective cohort study	JRAA/PRAA TAAA	F-EVAR/B-EVAR OSR	F-EVAR/B-EVAR: 6.7% <sup>b</sup> OSR: 5.4% <sup>b</sup>
<b>Rao <i>et al.</i><sup>17</sup></b>	2015	Systematic review and meta-analysis of case series	JRAA	F-EVAR OSR	F-EVAR: 4.1% <sup>c</sup> OSR: 4.1% <sup>c</sup>
<b>Katsargyris <i>et al.</i><sup>18</sup></b>	2013	Systematic review and pooled data analysis	JRAA	F-EVAR Ch-EVAR OSR	F-EVAR: 2.4% <sup>b</sup> Ch-EVAR: 5.3% <sup>b</sup> OSR: 3.4% <sup>b</sup>
<b>Nordon <i>et al.</i><sup>19</sup></b>	2009	Systematic review and pooled data analysis	JRAA	F-EVAR OSR	F-EVAR: 1.4% <sup>b</sup> OSR: 3.6% <sup>b</sup>
<b>Health Quality Ontario<sup>20</sup></b>	2009	HTA	JRAA	F-EVAR OSR	F-EVAR: 1.8% <sup>b</sup> OSR: 3.1% <sup>b</sup>

<sup>a</sup>2-year mortality

<sup>b</sup>30-day mortality

<sup>c</sup>pooled 30-day and in-hospital mortality

The only prospective comparative evidence comes from a recent multicentre case-control study which compares 30-day outcomes and costs of F/B-EVAR with OSR for the treatment of complex AAA and TAAA<sup>16</sup>. The primary endpoint was 30-day mortality. Secondary endpoints included severe complications, length of stay, and costs. The study included 268 prospective cases from the multicentre registry

WINDOW and 1,678 controls (retrospective) extracted from the French national hospital discharge database for the years 2010-2012. The prospective cases were significantly older than the controls and comorbidities were generally more frequent within the prospective cases, but there was no statistical difference in Charlson comorbidity index between the two cohorts. However, mortality was derived by regression analysis using pre and post-operative characteristics to match for differences between the two cohorts. The results of the analysis found that there was no statistically significant difference in 30-day mortality between F/B-EVAR and OSR (6.7% versus 5.4% respectively,  $p=0.40$ ). After group stratification within the AAA population, mortality was similar across treatment arms for PRAA/JRAA (4.3% versus 5.8% respectively,  $p=0.26$ ) and supra-diaphragmatic TAAA (11.9% versus 19.7% respectively,  $p=0.70$ ), and higher with F/B-EVAR for infra-diaphragmatic TAAA (11.9% versus 4.0%,  $p=0.01$ ).

An extension of the above study compared the outcomes between the same cohorts at 2 years<sup>15</sup>. Mortality was not significantly different between the groups (14.9% with F/B-EVAR vs. 11.8% with OSR,  $p=0.15$ ) after two years. Similar results were found for patients with PRAA/JRAA (11.2% vs. 11.4%,  $p=0.96$ ), patients with infra-diaphragmatic TAAA (17.1% vs. 8.4%,  $p=0.09$ ), and patients with supra-diaphragmatic TAAA (28.6% vs. 31.0%,  $p=0.79$ ). Within the study, mortality was due to the aneurysm in the majority of deaths (53.8% in patients treated with f/b EVAR and 57.1% in patients treated with OSR). Additional analyses in the form of multivariate Cox regressions that control for predictive characteristics did not find a significant association between 2-year mortality and treatment. Finally, across the two treatment groups, similar proportions of patients were readmitted to hospital at least once (69.7% with F/B-EVAR vs. 64.2% with OSR,  $p=0.096$ ) but F/B-EVAR patients had more readmissions on average (2.2 vs. 1.7,  $p=0.001$ ).

The rest of the evidence identified as relevant to this review includes three systematic reviews<sup>17-19</sup> and one HTA<sup>20</sup> comparing pooled clinical outcomes estimates for various complex EVAR techniques with OSR in patients with JRAA. The primary studies included in these reviews were case series, retrospective and non-comparative in nature. The main outcome studied was peri-operative mortality (30-day and in-hospital mortality rate). Other outcomes reported were procedure time, blood loss, hospital length of stay (LoS), endoleak events, re-intervention rates, renal events, and long-term mortality.

There was variation in the interventions compared across the studies, including F-EVAR, Ch-EVAR and OSR. Although some of the reviews reported comparative pooled outcome estimates for multiple procedures, all estimates were in fact based on non-comparative case series with a large degree of heterogeneity between the patient groups. Moreover, there was overlap among the primary studies included in the reviews identified. The 30-day mortality following F-EVAR ranged from 1.4% to 2.4% in three papers<sup>18-20</sup>. The 30-day mortality for Ch-EVAR, 5.3% reported in one review<sup>18</sup>, was considerably higher than for F-EVAR. For OSR, three reviews reported a 30-day mortality ranging from 3.1% to 3.6%. Another review<sup>17</sup> found a peri-operative mortality (pooled 30-day and in-hospital mortality) of F-EVAR not significantly different than that of OSR at 4.1% for both groups.

The 2015 systematic review by Rao *et al.*<sup>17</sup> compared elective treatment for JRAA by OSR and F-EVAR. A total of 21 case series of OSR (1,575 interventions) and 14 of F-EVAR (751 interventions) were identified and a meta-analysis of the results was performed. Mean age was 71 in the OSR group and 73 in the F-EVAR group, while mean aneurysm diameter was 6.1 cm in the OSR studies and 6 cm in the F-EVAR studies. The pooled 30-day and in-hospital mortality rate was 4.1% (CI 3.1% to 5.3%) in the OSR group and 4.1% (CI 2.8% to 5.9%) in the F-EVAR group. The odds ratio for OSR compared with F-EVAR was 1.059 (CI 0.642 to 1.747;  $p=0.82$ ) and not statistically significant. F-EVAR patients had higher rates of secondary re-intervention, renal impairment during follow-up, and a lower long-term survival compared with open repair patients, but this may be due to F-EVAR being offered to higher-risk patients. The F-EVAR patients

were older on average than those undergoing open repair, with higher rates of preoperative renal impairment, diabetes, cardiovascular disease, and respiratory insufficiency. There was also significant clinical and methodological heterogeneity among the studies which may confound the interpretation of these outcomes.

Katsargyris *et al.*<sup>18</sup> carried out a systematic review to compare the outcomes with open, fenestrated and chimney graft repair of JRAA. The search found 20 studies with a total of 1,725 patients (76% men; mean/median age range was 66–74 years) undergoing OSR, 10 studies with a total of 931 patients (87.6% men; age range 72–75 years) receiving F-EVAR, and five studies with a total of 94 patients (75% men; age range 68–82) reporting on Ch-EVAR. Mean and median aneurysm maximum diameter was 5.8 and 6.7 cm respectively in the OSR group and 5.5 to 6.8 cm respectively in the F-EVAR group. The main outcomes are summarised in Table 3. 30-day mortality seems to be in favour of F-EVAR but the differences did not reach statistical significance. F-EVAR was also associated with better outcomes relating to renal impairment and endoleaks.

**Table 3: Main outcomes reported in Katsargyris *et al.*<sup>18</sup>**

	Open	F-EVAR	Ch-EVAR	p-value
<b>30-days mortality</b>	3.4%	2.4%	5.3%	NS
<b>Renal impairment</b>	18.5% <sup>a</sup>	9.8% <sup>a</sup>	12%	<0.01
<b>Early proximal type I endoleak</b>	NA	4.3%	10%	<0.01
<b>Estimated blood loss, L</b>	1-3.2	0.2-0.8	0.35-0.4	NA
<b>ICU LOS, days</b>	2.1-8.9	0.8-1	1	NA
<b>Hospital LOS, days</b>	6.8-24	3-9	4-8	NA

NS: not significant

NA: not applicable

<sup>a</sup>indicates the pairs compared

A systematic review by Nordon *et al.*<sup>19</sup> looked at the outcomes of fenestrated technology and makes a comparison with open repair. Eight cohort studies reporting 368 F-EVAR cases and 12 cohorts reporting 1,164 open repairs of JRAAs were identified. The outcome measures assessed were 30-day mortality, renal impairment, target vessel patency, length of stay and secondary re-intervention rate. Cumulative 30-day mortality following F-EVAR was 1.4% (CI 0.4 to 3.1) and 3.6% (CI 2.7 to 4.9) following OSR. The relative risk (RR) of OSR versus F-EVAR was 1.03 (CI 1.01 to 1.04,  $p=0.02$ ), confirming increased mortality risk associated with open repair in these reports. No difference was identified in postoperative permanent dialysis dependence (RR 1.00, CI 0.99 to 1.01,  $p=1$ ). Transient renal impairment was more common following open repair (RR 1.06, CI 1.01 to 1.12,  $p=0.03$ ). Early re-interventions were less common following open repair (RR 0.87, CI 0.83 to 0.91,  $p<0.01$ ).

A 2009 Canadian HTA looked at F-EVAR for JRAA, comparing it with OSR<sup>20</sup>. The HTA included evidence published from 2004 to 2008 inclusive, with 13 studies identified that met the inclusion criteria: one comparative study presented at an international seminar, five single-arm studies on F-EVAR, and seven studies on OSR (one prospective and six retrospective). The pooled estimate for 30-day mortality was 1.8% among the F-EVAR studies and 3.1% among the OSR studies that reported data for the repair of JRAA separately, while the pooled estimate for late mortality was 12.8% and 23.7% for F-EVAR and OSR respectively. Hospital data indicated a cost for the F-EVAR procedure in the range of \$24,395–\$30,070 (£18,453–£22,746).

## Ongoing studies

ISRCTN85731188 is a UK prospective comparison study of open surgery, minimal invasive surgery and medical management for complex aortic aneurysms that is expected to run until June 2022 at the Royal Liverpool University Hospital.

The following ongoing non-UK trials are expected to contribute to the evidence base:

- NCT01937949 (United States, Minnesota): Complex Aortic Aneurysm Repair With Fenestrated Stent Grafts (IDE#1)
- NCT02050113 (United States, Massachusetts): Complex Aortic Aneurysm Repair Using Physician Modified Endografts and Custom Made Devices (CARPE-CMD)
- NCT03342755 (Italy): Evaluation of Staged Endovascular Aneurysm Repair in the Management of Thoracoabdominal Pathology by Means of Branched and Fenestrated Devices (STEAR)
- NCT00583050 (United States, Ohio): Endovascular Exclusion of TAAA/AAA Utilizing Fenestrated/Branched Stent Grafts

## Patient and social aspects

No studies were identified that reported specifically on patient preferences or experiences in relation to the use of complex endovascular aneurysm repair techniques versus open repair in a JRAA/TAAA population.

A 2008 report<sup>21</sup> addressed patient preferences regarding surgical techniques for abdominal aortic aneurysm repair. A total of 237 patients (all men; aged 65 and over; aneurysm diameter between 4.0 and 5.5cm; not currently considered for imminent aneurysm repair) on the AAA screening programmes at two English acute hospital trusts were asked to state their preference between EVAR and OSR based on an objective information pack.

Overall, patients were more than twice as likely to prefer EVAR (46%) to OSR (18%), 14% percent of patients were equally happy with either treatment and 20% were unsure which of the two methods they preferred. Very few statistically significant variations were identified between patients in different age groups or based on differences in health or carer status, although the following findings may be worth consideration:

- Patients in all age groups preferred EVAR to OSR, but younger patients were marginally more likely to prefer EVAR
- Patients with a long-term illness or disability were more likely to prefer OSR
- Patients that were providing care for others were more likely to prefer EVAR.

The main factor influencing patient preferences was 'the advice of the doctor', while medical history or existing condition, invasiveness of surgery, and the risk of post-operative complications were also frequently cited but to a much lesser extent. Just over a third of patients preferred 'less invasive surgery even with a possible increased risk of post-operative complications' and just under a third said they preferred a lower risk of post-operative complications, even with the need for more invasive surgery, while the other third had no particular preference. Other influencing factors included shorter recovery time, avoiding a stay in intensive care and a shorter hospital stay, and least importance was placed on the size of the scar and the risk of impotency.

## Safety

Major adverse events and complications were well reported in all the clinical effectiveness studies identified for inclusion above.

In Michel *et al.*<sup>16</sup>, compared to OSR, patients treated with F/B-EVAR had higher rates of spinal cord ischemia (4.1% vs. 1.0%,  $p < 0.01$ ), an increased number of myocardial infarctions (3.1% vs. 1.2%,  $p = 0.019$ ), strokes (4.2% vs. 0.7%,  $p < 0.01$ ), and re-interventions (15.3% vs. 10.3%,  $p = 0.017$ ), while there was no difference in the occurrence of renal failure (13.4% vs. 17.2%,  $p = 0.12$ ). The reported adverse events and complications are reported in Table 4.

**Table 4: Adverse events reported in Michel *et al.*<sup>16</sup>**

	F/B-EVAR (n=262)	OSR (n=1,678)	p-value*
Major amputation	1 (0.4%)	4 (0.2%)	0.67
Myocardial infarction	8 (3.1%)	20 (1.2%)	0.019
Stroke	11 (4.2%)	12 (0.7%)	<0.01
Paraplegia	8 (3.1%)	16 (1.0%)	<0.004
Mechanical ventilation $\geq$ 7 days	18 (6.9%)	124 (7.4%)	0.76
Severe ischemic colitis and bowel infarction	7 (2.8%)	51 (3.0%)	0.75
Permanent hemodialysis	35 (13.4%)	289 (17.2%)	0.12
Re-intervention	40 (15.3%)	173 (10.3%)	0.017

\* Chi-square test (or the Fisher exact test depending on the number of observations)

Rao *et al.*<sup>17</sup> reported that the open repair studies included in their review had a significantly higher postoperative major complication rate compared with F-EVAR (25.0% versus 15.7%;  $p < 0.01$ ). These included cardiac events (myocardial infarction, arrhythmias), pulmonary infections, ischemic colitis, pulmonary embolism, and wound complications. However, F-EVAR was offered to older and higher risk patients and there was considerable heterogeneity across the studies included in the review.

Table 5 compares the post-operative complication rates between OSR, F-EVAR and Ch-EVAR presented in Katsargyris *et al.*<sup>18</sup>. OSR was found to be associated with a higher rate of patients requiring new-onset dialysis and a higher rate of cardiac and pulmonary complications compared with the two endovascular techniques. In the case of Ch-EVAR, ischemic stroke was significantly higher compared to the other two approaches.

**Table 5: Adverse events reported in Katsargyris *et al.*<sup>18</sup>**

	Open	F-EVAR	Ch-EVAR	p-value
New-onset dialysis	3.9% <sup>a</sup>	1.5% <sup>a</sup>	2.1%	<0.01
Cardiac complications	11.3% <sup>a</sup>	3.7% <sup>a</sup>	7.4%	<0.01
Pulmonary complications	16.1% <sup>a,b</sup>	2.3% <sup>a</sup>	3.2% <sup>b</sup>	0.01 <sup>a,b</sup>
Ischemic stroke	0.1% <sup>a</sup>	0.3% <sup>b</sup>	3.2% <sup>a,b</sup>	<0.01 <sup>a</sup> , 0.012 <sup>b</sup>

NS: not significant

NA: not applicable

<sup>a,b</sup> indicates the pairs compared

## Volumes and outcomes

Within their study, Katsragyris *et al.*<sup>22</sup> reviewed the literature to investigate the effect of volume of procedures within each hospital on aortic aneurysm repair outcomes. The majority of studies identified found that high-volume hospitals were associated with lower perioperative mortality of AAA, TAA and TAAA aortic aneurysm repair. A similar advantage is shown for surgeons who perform a large number of procedures. The volume advantage appears to be less evident for simple endovascular procedures (EVAR), compared to more complex endovascular (F/B-EVAR) and open surgical procedures. Superior outcomes observed in high-volume hospitals may be explained simply by surgeons undertaking a high volume of cases (i.e. greater experience), but also by more effective management of intra and postoperative complications. Confounding factors to be taken into account are the timing of the studies in relation to positive evolution of outcomes in several high-risk procedures, and patient cohorts selected in regions with very low and very high-volume hospitals only.

A policy document from NHS England recommends the provision of complex EVAR techniques in arterial centres with a catchment of two million people (typically performing at least 100 aortic procedures annually), and which have a projected annual case load for these specific interventions in excess of 24-30 cases in order to maintain high levels of expertise in all professionals involved in the care pathway<sup>23</sup>.

## Cost effectiveness

The cost-effectiveness evidence for these procedures is very limited. The cost of these stent devices alone is high, ranging from £12,000 to £30,000 in the UK<sup>23</sup> depending on the stent used, while the total cost for the procedure is even higher and can vary substantially. Within the Canadian HTA, hospital data indicated a cost for the F-EVAR procedure in the range of \$24,395-\$30,070 (£18,453-£22,746).<sup>20</sup> It is important that available resources are targeted to those patients who are able to gain most benefit from their use and that they are not exposed to unnecessary risks.

The case-control study by Michel *et al.* also looked at the 30-day costs of F/B-EVAR in comparison with OSR for the treatment of complex AAA and TAA<sup>16</sup>. Costs were higher with F/B-EVAR (€38,212 (£33,522) compared with €16,497 (£14,472) for OSR,  $p < 0.01$ ) per procedure. After group stratification, costs were higher with F/B-EVAR for PRAA/JRAA (€34,425 (£30,256) versus €14,907 (£13,102),  $p < 0.01$ ) and infra-diaphragmatic TAAA (€37,927 (£33,334) versus €17,530 (£15,407),  $p < 0.01$ ), but not different for supra-diaphragmatic TAAA (€54,710 (£48,084) versus €44,163 (£38,815),  $p = 0.18$ ). A cost-effectiveness analysis was conducted to assess incremental costs per incremental death averted with F/B-EVAR versus OSR. F/B-EVAR had a higher cost than OSR for a similar clinical outcome (as detailed in the clinical effectiveness section).

In the extension study<sup>15</sup>, 2-year costs (including acute hospital admissions, statutory health insurance, complementary health insurances, and patients' out of pocket expenditures) were higher in the F/B-EVAR group compared with the OSR group (€46,039 (£40,866) versus €22,779 (£20,220),  $p < 0.001$ ). At 2 years, F/B-EVAR was dominated (i.e. more expensive and less effective) by OSR, except in the supra-diaphragmatic TAAA subgroup where it is not expected to offer good value for money.

## Conclusion

Based on the low quality evidence summarised in this review, F/B-EVAR techniques are a viable option when it comes to treating complex aneurysm anatomies such as JRAAs and TAAAs owing to an acceptable short-term mortality rate which is similar to OSR. However, the absence of longer term head-to-head comparison data and the high heterogeneity between cohorts, in particular the higher risk

profile of those receiving endovascular treatment versus open repair, makes it difficult to conclude whether F/B-EVAR techniques provide a clinical advantage over OSR. Moreover, the rate of re-intervention for endovascular repair is high and these devices are generally more costly compared to OSR. For some patients, in whom OSR is unfeasible due to surgical risk, F/B-EVAR or non-surgical management might be the only options.

Initial findings relating to Ch-EVAR demonstrate higher mortality and higher complications rates compared with F/B-EVAR and OSR techniques, based on a limited number of reports and short-term data. Furthermore, the risk profile is not consistent across all techniques because some published case series of Ch-EVAR contain non-elective cases as well as elective. Ch-EVAR is feasible in patients at high risk from open repair requiring urgent treatment (non-elective) who cannot wait for the manufacture of a custom stent graft.

No clear conclusions can be made about the cost-effectiveness of complex EVAR. One case-control study<sup>16</sup> reported significantly higher costs for F/B-EVAR compared to OSR and it did not seem to offer good value for money. Although the study tried to control for the differences between the two cohorts, F/B-EVAR was given to higher risk patients compared to OSR. In the longer-term, F/B-EVAR in high risk patients seems to offer similar 2-year mortality to OSR performed in lower risk patients but at a higher cost. Further studies are necessary to evaluate the cost-effectiveness in patients with comparable risk.

Regarding consensus on how these technologies should be implemented in clinical setting, the evidence is very limited. According to a national multicentre, cross-disciplinary consensus model in which more than 90% of the UK F-EVAR centres participated<sup>24</sup>, there is agreement that F-EVAR should be used when there is moderate risk from open repair and need for suprarenal clamping, but it was less likely to be indicated in patients aged 85 years or more with 5.5-6 cm aneurysms, or short-necked infra-renal aortic aneurysms.

There appears to be a volume advantage associated with high-volume centres (in excess of 20-30 procedures per year) with regards to perioperative mortality. For countries like Scotland, with a relatively small population, consideration should be given to offering complex EVAR services in a small number of centres.

### Identified research gaps

Based on the IDEAL framework for assessment of surgical interventions<sup>25</sup>, complex EVAR is at an early stage of evidence development. Most studies are non-comparative case series aimed at increasing technical (surgical) skills and experience of the procedure (stage 2a development). Therefore future research should focus on randomised controlled trials (RCTs) or prospective comparative observational studies that compare the various complex EVAR techniques with OSR in patients with a juxta-renal or thoraco-abdominal aortic aneurysm. Studies should focus on capturing long term survival, quality of life, and costs. The follow-up should be sufficient to establish the health-related outcomes of complex EVAR and help inform cost-effectiveness analyses that are applicable to the UK setting.

### Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on [www.healthcareimprovementscotland.org](http://www.healthcareimprovementscotland.org)

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A glossary of commonly used terms in Health Technology Assessment is available from [htaglossary.net](http://htaglossary.net).

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