Contrast-enhanced ultrasound and/or colour duplex ultrasound for surveillance after endovascular abdominal aortic aneurysm repair: a systematic review and economic evaluation

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Scientific summary

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Background

Endovascular abdominal aortic aneurysm repair (EVAR) consists of placing a stent–graft within the aneurysm via the femoral arteries. The purpose of the stent–graft is to reduce the risk of rupture by excluding the aneurysm from the influences of blood flow and blood pressure. Failure to obtain, or maintain, aneurysm exclusion, such that blood leaks into the aneurysm sac, is seen as a failure of the technique and is called ‘endoleak’. Although less invasive than open surgery, with a lower perioperative mortality rate, EVAR is associated with important complications, such as different types of endoleaks, stent–graft migration, distortion or kinking of the stent–graft, structural disintegration of the stent–graft and stent–graft thrombosis. Any complication leading to a loss of aneurysm exclusion risks the failure of treatment in the form of aneurysm rupture, whereas any complication leading to stent–graft thrombosis risks the failure of supplying blood to the patient’s legs. Post-EVAR surveillance is performed to detect complications and direct treatments with adequate surveillance relying on appropriate imaging strategies. Since the development of EVAR, computed tomography angiography (CTA) has been the most common modality adopted for surveillance; however, its use is associated with repeated radiation exposure and with the risk of contrast nephropathy. Modified surveillance protocols have recently been proposed as a way to minimise radiation exposure by eliminating unnecessary CTA examinations. Colour duplex ultrasound (CDU) and, more recently, contrast-enhanced ultrasound (CEU) have been suggested as possible, safer, alternatives to CTA.

Objective

To assess the current evidence for the clinical effectiveness and cost-effectiveness of strategies using either CDU or CEU alone or in conjunction with plain radiography compared with CTA for surveillance after EVAR.

Methods

Clinical effectiveness

Ovid MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Daily and Ovid MEDLINE, EMBASE, Science Citation Index, Scopus’ Articles-In-Press, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and the Health Technology Assessment (HTA) database were searched from 1996 onwards to identify reports of studies of interventions and systematic reviews of diagnostic studies.

The World Health Organization’s International Clinical Trials Registry Platform, Current Controlled Trials, and Clinical Trials.gov were also searched for ongoing studies, clinical experts and relevant websites were consulted and reference lists were perused.

Clinical effectiveness evidence was considered from randomised controlled trials, non-randomised comparative studies and/or prospective and retrospective cohort studies of different imaging modalities and follow-up strategies. In particular, we assessed the relative effectiveness of CEU or CDU, used alone or in conjunction with plain radiography, for the long-term surveillance following EVAR. The comparator modality was CTA. The population considered were adults undergoing surveillance following EVAR for abdominal aortic aneurysm (AAA).
Two reviewers independently selected studies for inclusion. One reviewer completed data extraction and assessed the risk of bias of included studies, and two reviewers independently cross-checked the details extracted by the first reviewer. A formal meta-analysis and metaregression of outcome data proved to be unfeasible, owing to the dearth of relevant comparative studies. Outcome data are summarised descriptively.

**Cost-effectiveness**

The evidence on cost-effectiveness was explored using a two-step approach: (1) a systematic review of economic evaluations, followed by (2) a de novo decision-analytic model.

The NHS Economic Evaluations Database, the HTA database, MEDLINE In-Process & Other Non-Indexed Citations, Epub Ahead of Print, EMBASE and Research Papers in Economics were searched from 1996 onwards for relevant economic evaluations. Clinical experts and relevant websites were consulted and reference lists were scanned. The titles and abstracts of all of the identified citations were screened by one reviewer. The full-text papers of potentially relevant studies were retrieved and assessed for inclusion.

A Markov model was developed to include five surveillance strategies:

1. annual CTA plus plain radiography
2. annual CDU plus plain radiography
3. annual CEU plus plain radiography
4. colour duplex ultrasound together with CTA and plain radiography at 1 year, followed by CDU and plain radiography on an annual basis
5. contrast-enhanced ultrasound together with CTA and plain radiography at 1 year, followed by CEU and plain radiography on an annual basis.

The parameter estimates were derived from the systematic review of clinical effectiveness, expert opinions and other UK-based sources. The model considered a cohort of 74-year-old men, a lifetime time horizon, a 6-month cycle length, a 3.5% discount rate and a NHS and Personal Social Services perspective. The costs were expressed in 2015–16 Great British pounds and the effectiveness was expressed in quality-adjusted life-years (QALYs) and incremental cost per QALY.

Adverse events and complications during surveillance were generically named as ‘abnormalities’. These were divided into those conditions that would trigger an elective intervention (abnormal I) and those that, on clinical assessment, would require a closer follow-up (abnormal II – e.g. type II endoleaks with sac expansion of < 5 mm in 6 months or with limbs with kinking or partial thrombosis). The first category was further subdivided into two: abnormal Ia includes non-endoleak-triggered interventions (e.g. limb occlusions, graft infections) and abnormal Ib accounts for the endoleak-prompted interventions (e.g. types I, III and IV, type II or endotension with sac expansion of > 5 mm).

**Results**

**Clinical effectiveness**

The evidence for this assessment is derived from two non-randomised comparative studies (including 750 participants, 694 participants in one study and 56 participants in the other), 25 cohort studies (including 7196 participants) and nine systematic reviews of diagnostic test accuracy (including 174 primary studies). Surveillance protocols based on a combination of CTA and CDU or CEU were assessed.

The study duration ranged from 3 years to 16 years. The mean duration of follow-up ranged from 14 months (interquartile range 7–27 months; range 1–46 months) to 54.8 months (standard deviation 35.9 months). Patient characteristics and the type of aneurysm varied between studies.
The two non-randomised comparative studies compared a surveillance protocol based on a combination of CTA and CDU, with a simplified protocol based on CDU for long-term surveillance. In the largest comparative study (694 participants), no significant differences between the two surveillance strategies were observed during the 3-year follow-up in terms of reinterventions, clinical complications, mortality and adverse effects, including renal impairment.

All studies included CDU as part of their surveillance protocols, apart from one study that followed up patients using CEU and/or CTA. Studies that used CDU for annual long-term surveillance were published more recently than those that used a combination of CTA and CDU for long-term surveillance. In the majority of the included cohort studies (n = 10), surveillance was based on a combination of CTA and CDU throughout follow-up. Eight studies used CTA and/or CDU for early and mid-term assessments and CDU for long-term surveillance. Two studies used CTA for long-term surveillance (i.e. CTA at discharge, CDU at 6 months and then CTA at 12 months and annually thereafter). Three studies adopted a protocol based exclusively on CDU after EVAR and two studies included CEU together with CTA as part of their surveillance strategy.

Overall, the proportion of participants requiring reintervention after EVAR ranged from 1.1% during a mean follow-up of 24 months to 23.8% in a cohort that included high-risk patients with hostile neck anatomy who underwent a secondary procedure after a mean follow-up period of 32 months. Reintervention was required mainly for the treatment of limb occlusion (<1% to 7.2% of participants), thrombosis/stenosis (<1% to 5.6% of participants), type I endoleaks (<1% to 8.3% of participants), type II endoleaks (<1% to 3.6% of participants) and type III endoleaks (<1% to 1.6%). Across the studies, all-cause mortality ranged from 2.7% (mean follow-up period of 24 months) to 42% among a cohort that included a proportion of high-risk patients with hostile neck anatomy (mean follow-up period of 54.8 months). In the four cohort studies that reported it, aneurysm-related mortality occurred in <1% of the participants.

The studies that used a combination of CTA and CDU throughout follow-up reported the highest all-cause mortality (42%) and the highest proportion of participants who required reinterventions for complications after EVAR (23.8%). However, it is worth noting that the study that reported the highest all-cause mortality (42% of patients) and the highest proportion of patients requiring reinterventions (23.8%) focused on high-risk patients, some of whom presented with features of hostile neck anatomy. Apart from this study, the remaining studies based on early and mid-term CTA and/or CDU and long-term CDU surveillance were broadly comparable with those based on a combination of CTA and CDU throughout follow-up in terms of clinical complications, reinterventions and mortality.

The findings of the nine systematic reviews of diagnostic accuracy show that for CDU the pooled sensitivity for detection of all types of endoleaks ranged from 65% to 96% and the pooled specificity ranged from 90% to 97%, whereas for CEU the pooled sensitivity ranged from 81% to 98% and the pooled specificity ranged from 78% to 88%. CEU accuracy improved when only studies that utilised the second generation of contrast agents were considered.

Cost-effectiveness

Five economic studies were identified. All of the studies were cohort studies and they compared a surveillance strategy based on the use of CDU or CEU with a strategy based on CTA and assessed the reduction in costs as a result of fewer CTA scans in accordance with a modified surveillance protocol. Although all of the studies fairly agree on the clinical outcomes of interest (i.e. endoleaks, AAA size and the need for secondary interventions), the reporting of costs and cost methods was disparate. None of the studies used a preference-based measure of effectiveness and the time horizon chosen was not long enough to allow for all relevant costs and consequences. Consequently, as a result of insufficient information for decision-making, a decision-analytic model was developed.

The Markov model base-case analysis results shows that annual follow-up with CDU only is the strategy with the lowest expected cost (£3791), followed by CTA only (£3828) and CEU only (£4709). The strategies with higher expected costs are those that use CDU (£4732) or CEU (£5644) in conjunction with CTA at the start.
of follow-up. A CTA-only strategy produces the lowest expected QALYs (6.552) and is dominated by CDU only (6.553). Moreover, adding CTA to CDU or CEU at the start of follow-up results in more QALYs than using only one imaging modality, but these strategies are either dominated or the incremental cost for an additional QALY is well above the accepted cost-effectiveness threshold (i.e. £30,000). CEU-based strategies result in higher expected QALYs (i.e. 6.559 and 6.560) than all of the other strategies, although the incremental cost-effectiveness ratios to adopt any of these are well above the £30,000 threshold.

The probabilistic analyses show that, for willingness-to-pay (for an extra QALY) values of up to £50,000, annual follow-up with CDU only has a > 58% probability of being cost-effective, with CTA having a probability of between only 32% and 42% and CEU having a probability of between only 0.1% and 4.1%. CTA added to CDU or CEU has zero probability of being cost-effective.

The sensitivity analyses showed that a CEU-only strategy became cost-effective at very high rates of test sensitivity and specificity (e.g. when it was assumed to produce perfect information – sensitivity and specificity of 100% and no indeterminate results) and for a cost difference between CDU and CEU of < £55. A further sensitivity analysis explored the effect of surveillance in a very high-risk group. At an annual incidence rate of 7% for the abnormal Igb group (e.g. type I and III endoleaks, together with type II endoleaks with a > 5-mm sac expansion and other conditions commonly detected by non-X-ray modalities), CEU-based surveillance becomes cost-effective. Although in clinical practice it is unlikely to observe an incidence of 7% for type I or type III endoleaks, an incidence of 7% for type II endoleaks with sac expansion is, perhaps, possible.

Limitations

The majority of the studies were rated as being at a high or moderate risk of bias.

There was considerable heterogeneity in terms of imaging modality and the frequency of imaging, the duration of follow-up, outcome measures, definition of the outcomes (e.g. the definition of decreased aneurysm size) and the time points at which the outcomes were assessed. Owing to the observed clinical heterogeneity, a statistical synthesis of the relevant outcomes was considered to be inappropriate.

Studies comparing protocols based on CDU with those based on CEU were not found. The majority of surveillance protocols were based on a combination of CTA and CDU. Data from studies that exclusively used a CDU-based surveillance (three studies) and from studies that used CEU as part of their imaging protocol (two studies) were scarce.

The economic model was hindered by a lack of suitable data. The identification and selection of input data were particularly challenging, with key model parameter values being based on expert opinions.

Conclusions

The current evidence assessing the effects of surveillance after EVAR is very heterogeneous, with protocols being based on different imaging modalities, frequency of imaging and length of follow-up. No firm conclusion can be drawn with regard to the optimal surveillance strategy after EVAR. There is a need to improve current protocols to reduce radiation exposure, the risk of contrast nephropathy and costs, while ensuring that patients are adequately followed up to minimise their risk of secondary complications, especially aneurysm rupture. CDU may be a safe alternative to CTA, with CTA being reserved for abnormal or inconclusive CDU cases that require further investigation. Further research is required, however, to validate the safety of modified protocols based on the use of CDU and/or CEU. Access to modern equipment and highly experienced operators remains a crucial requirement for the adoption of CDU surveillance. The economic evaluation shows that CDU is the most cost-effective option, with a 63% probability of being cost-effective at a £30,000 willingness-to-pay-per-QALY threshold. Strategies based on CEU produce more QALYs, but are also more expensive and might be cost-effective for only higher-risk patients.
Suggested research priorities

- Further research is needed to assess the value of targeted surveillance (i.e. patients with a greater risk of complications may receive more frequent surveillance, whereas those with uncomplicated EVAR may undergo less-frequent assessments or be discharged from surveillance).
- If surveillance is to be targeted, is CDU and/or CEU surveillance satisfactory for all patient groups or are there groups for which CTA is required to avoid excessive risk?
- The criteria used for identifying patients at high risk of complications (e.g. use of validated score systems, risk prediction models) require further investigation.
- The role of plain radiography as part of EVAR surveillance needs to be clarified. If CTA is to be performed less frequently or avoided, should plain radiography be mandatory or reserved for patients with abnormalities on ultrasound imaging?
- Future research should explore the effects of the information generated by the imaging modalities used for surveillance and incorporate this within economic analyses.

Study registration

This study is registered as PROSPERO CRD42016036475.

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