NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

DyeVert Systems for reducing the risk of acute kidney injury in coronary and peripheral angiography

How medical technology guidance supports innovation

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

If the case for adopting the technology is supported, the specific recommendations are not intended to limit use of other relevant technologies that may offer similar advantages. If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Recommendations

1.1 DyeVert Systems show promise for reducing the risk of acute kidney injury (AKI) in coronary and peripheral angiography after using contrast media. However, there is not enough evidence to support the case for routine adoption. This is because there is not enough good-quality evidence that using the system reduces AKI incidence after receiving contrast media.

1.2 A randomised controlled trial is recommended to compare DyeVert Systems with standard care. The aim of this research would be to address uncertainties about whether using DyeVert Systems reduces AKI

incidence and rate of renal replacement therapy after using contrast media. This should include people with stage 4 chronic kidney disease (with an estimated glomerular filtration rate [eGFR] under 30 ml/min/1.73 m^2) who are at risk of AKI and need an elective coronary or peripheral angiography.

Find out details of required outcomes in further research.

Why the committee made these recommendations

Current standard care to reduce the risk of AKI in people having contrast dye (media) during coronary and peripheral angiography involves giving them fluids.

Clinical evidence shows that DyeVert Systems reduce the amount of contrast that enters the blood vessel. Contrast dye is thought to increase the risk of AKI in people at risk. There is some evidence to suggest the system could reduce AKI but more is needed to be certain. Also, almost all the evidence is from coronary angiography, which may not apply to peripheral angiography.

Because of the uncertainty about whether DyeVert Systems reduce AKI, any potential cost savings are also uncertain.

Therefore NICE recommends further research.

2 The technology

Technology

2.1 DyeVert Systems are designed to reduce the amount of contrast media given during coronary and peripheral angiography in a cardiac catheterisation or vascular radiology suite. The system uses a pressure-responsive valve to divert excess contrast medium while maintaining image quality, to reduce the risk of contrast-induced acute kidney injury (AKI).

2.2 There are 2 models of the DyeVert System. DyeVert Plus EZ Contrast Reduction System is compatible with manual contrast injectors. A smart

syringe connects to a standard manifold and is manually operated by the clinician to inject the dye into the module that contains the diversion valve. A monitor displays the total administered and total diverted contrast volume using Bluetooth communication with the smart syringe. DyeVert Power XT Contrast Reduction System is compatible with power injectors. There is no reusable monitor but the contrast collection bag has a digital display showing the diverted dye volume.

Care pathway

2.3 People having contrast agents for non-emergency imaging should be assessed for their risk of AKI. Chronic kidney disease should be investigated by measuring estimated glomerular filtration rate (eGFR) or by checking an eGFR result from the past 3 months. Emergency imaging should not be delayed but clinicians should be aware who is at increased risk of developing contrast-induced AKI. Risk reduction strategies including oral hydration before and after procedures and intravenous volume expansion with isotonic sodium bicarbonate or 0.9% sodium chloride should be considered in anyone at risk. DyeVert Systems are designed to be used in addition to these risk reduction strategies.

Innovative aspects

2.4 The company says that DyeVert Systems are non-invasive technologies which reduce contrast media, with real-time contrast media dose monitoring. The system reduces the total contrast media volume delivered during coronary or peripheral imaging while maintaining adequate image quality.

Intended use

2.5 DyeVert Systems would be used to reduce the total contrast media volume delivered during coronary or peripheral imaging in people identified as at risk of contrast-induced AKI. It can be added to the equipment currently used for angiography procedures.

Costs

2.6 The DyeVert Systems cost £350 (excluding VAT) per procedure. This includes the diversion module, contrast collection bag, smart syringe (for DyeVert Plus EZ) and reusable monitor (for DyeVert Plus EZ).

For more details, see the website for DyeVert Systems.

3 Evidence

NICE commissioned an external assessment centre (EAC) to review the evidence submitted by the company. This section summarises that review. Full details of all the evidence are in the project documents on the NICE website.

Clinical evidence

The main clinical evidence comprises 19 studies

3.1 The EAC assessed 19 studies. Eight were full text publications: 1 randomised controlled trial, 3 prospective studies (2 of which were comparative), and 4 retrospective studies (2 of which were comparative). One abstract reported results from a randomised controlled trial, and 8 abstracts and posters reported retrospective studies. Two posters reported results from the same acute kidney injury (AKI) reduction programme. Two unpublished papers were included: 1 retrospective comparative study and 1 prospective comparative study. For full details of the clinical evidence, see section 3 of the assessment report.

DyeVert Systems reduce contrast volume received during angiographic procedures

3.2 The evidence from comparative studies showed that using DyeVert Systems reduced the amount of contrast media injected by between 17% (Sattar et al. 2018) and 41% (Desch et al. 2018) compared with standard coronary angiography. A company meta-analysis estimated that contrast volume received by the patient was lower by 39.43% when using DyeVert

Systems compared with when they were not used (calculated from 5 single-arm studies and 3 comparative studies).

Image quality is maintained while using DyeVert Systems

3.3 Seven published studies reported no loss to image quality with DyeVert Systems (Desch et al. 2018, Gurm et al. 2019a, Briguori et al. 2020, Bruno et al. 2019, Sapontis et al. 2017, Corcione et al. 2017, Zimin et al. 2020) and 2 abstracts (Amoroso et al. 2020, Rao et al. 2019). A company meta-analysis estimated that image quality was 98.2% of that when the system was not used (calculated from 6 published clinical studies and 1 abstract).

Evidence on AKI risk reduction is limited

3.4 Evidence on the risk reduction in AKI was from 1 published paper (Briguori et al. 2020) and 5 abstracts and posters (Sattar et al. 2018, Kutschman et al. 2019, Bunney et al. 2019, Cameron et al. 2020, Turner and Tucker 2020). These studies reported outcomes from people who were identified as having chronic kidney disease (CKD) stages 2 and 3 before their angiography procedure. Briguori et al. (2020) was a single-centre, observational, non-randomised design, which used a control group of patients treated in the same centre. Propensity score matching was used to match the control group to the DyeVert group, resulting in 90 patients in each group. This study reported AKI in 8% of the DyeVert Systems group and 19% of the control group (p=0.047). A company meta-analysis estimated the relative risk of contrast-induced AKI in a DyeVert Systems group compared with a control group to be 0.59, calculated from Briguori et al. (2020) and 3 comparative studies reported as an abstract or poster.

Study designs and insufficient reporting of outcomes limited the assessment of AKI incidence

3.5 The evidence presented was limited because measurements were only taken during the procedure in the studies that looked primarily at contrast

volume used or reduced and image quality. In the studies that followed up after the procedure, the methodology around collecting and reporting of the outcomes was not clear. Briguori et al. (2020) did report serum creatinine for 72 hours after the procedure, and AKI incidence and major adverse events within 1 month of the procedure. But the studies were limited by their retrospective design, which meant not all AKI incidents could be identified.

Evidence on the Power XT version of the DyeVert System is limited

3.6 The only evidence on the DyeVert Power XT device was on the first version of the system and from 1 full text single-arm retrospective study (Bruno et al. 2019) and 1 retrospective study presented as an abstract (Amoroso et al. 2020). This was from a total of 35 people having angiography procedures. No studies included the current version of the Power XT system.

Evidence on DyeVert Systems for peripheral angiography is limited

3.7 The evidence presented was mostly for coronary angiography, with only 2 studies (Corcione et al. 2017 and Rao et al. 2019) including 9 people having peripheral angiography.

Cost evidence

The company's cost model is based on a published cost–utility analysis

3.8 The company presented 1 published UK-based cost–utility analysis (Javanbakht et al. 2020) and 3 economic studies based in the US. Javanbakht et al. (2020) found DyeVert Systems were cost saving by £435 and estimated a quality-adjusted life year (QALY) gain of 0.028 over an individual's lifetime compared with current practice. The company's cost model was based on an updated version of this published model. For full details of the cost evidence, see section 4 of the assessment report.

The company's model uses a decision tree and Markov model

3.9 The company's model included people with CKD stages 3 and 4. It used a decision tree for the first 3 months after the procedure, then a Markov model for the remainder of the individual's lifetime. The Markov model transitions between 6 health states in 3-month cycles. The company's model had some differences to Javanbakht et al. (2020). The relative risk reduction of AKI because of DyeVert Systems use was increased from 21.4% to 41% (based on the company meta-analysis results). Unit costs were also updated, peripheral angiography procedures included in the population, and the age of the cohort entering the model was reduced from 72 years to 65 years.

DyeVert Systems remain cost saving in the EAC's update to the model

3.10 The EAC agreed with the company's cost model overall. The EAC corrected small errors in the model and parameter inflation costs, lowered the relative risk of contrast-induced AKI, and differentiated the costs of fatal and non-fatal myocardial infarctions. The EAC found that DyeVert Systems remained cost saving by £23 with a QALY gain of 0.013.

If the baseline risk of contrast-induced AKI is below 8.2% DyeVert Systems are no longer cost saving

3.11 The EAC updated the company's model and applied a baseline risk of contrast-induced AKI of 8.74% for people with CKD stage 3 and 4 aged 65. The EAC considered the company's stated risk of 30% to be too high if people are appropriately hydrated. The EAC estimated that if the risk of contrast-induced AKI was below 8.2%, DyeVert Systems would no longer be cost saving.

The reduction in relative risk of contrast-induced AKI after using DyeVert Systems is uncertain

3.12 The company's model used a relative risk reduction of contrast-induced AKI after DyeVert Systems use of 41% based on its meta-analysis results. The EAC accepted the statistical validity of the meta-analysis but noted

that the strength of the included studies was low to moderate. The EAC did sensitivity analysis around the risk reduction of contrast-induced AKI from DyeVert Systems and found that the break-even relative risk reduction was 38.5%, assuming a baseline AKI risk of 8.74%.

4 Committee discussion

Clinical-effectiveness overview

DyeVert Systems are effective in reducing contrast media volume but more evidence is needed on acute kidney injury incidence

4.1 There is consistent evidence that DyeVert Systems can reduce contrast volume received by the patient by up to 40%. Clinical experts said that using DyeVert Systems can maintain the pressure of the injection needed to preserve image quality, while reducing the overall amount of contrast given. The committee heard that the cause of acute kidney injury (AKI) is multifactorial and complex. It understood that contrast media is 1 risk factor for AKI, but it can be difficult to identify its direct cause (or causes), given other confounding factors such as comorbidities (which are often significant in people having angiography) and procedural complexities. The committee also heard conflicting views on the causal relationship between contrast agent and AKI. Two experts pointed out that clinical guidelines say that contrast volume is a risk factor for AKI, and that contrast volume is a modifiable parameter that could help to reduce AKI risk. However, 1 expert maintained that contrast-induced AKI has not been proven clinically, and that the link between contrast agent and AKI may only be an association. This was a key uncertainty, and as a result the committee was not confident that a reduction in contrast dye received would lead to reduced incidence of AKI. It felt that the strength of evidence on AKI incidence reduction using DyeVert Systems was not robust enough to address these concerns, and it could not be confident in the results of the meta-analyses (see section 4.4).

The evidence for coronary angiography is not generalisable to peripheral angiography

4.2 The evidence presented on peripheral angiography included 9 people in 2 studies. Clinical experts explained that it was unlikely that the evidence for coronary angiography was transferable to peripheral angiography procedures. Types of peripheral angiography procedure vary. Different volumes of contrast dye and different injection pressures are needed, making comparisons with coronary angiography difficult. The committee also heard that peripheral angiography can be done without using contrast media, for example when used for diagnosis.

Generalisability of the evidence for the PLUS EZ device to the Power XT device is uncertain

4.3 The evidence presented on the Power XT version of the DyeVert System included 2 studies on 35 people and was based on an older model of the system. The company said that the PLUS EZ and Power XT versions work in a similar way, with both devices responding to pressure going through the valve. Clinical experts thought that the power injector was more likely to be used in peripheral angiographies, especially when large volumes of contrast dye are needed to be given quickly. The committee was uncertain if the evidence on the PLUS EZ device was generalisable to the Power XT device. It felt that more evidence was needed before the devices could be considered comparable.

The meta-analyses are statistically robust, but the risk of bias is uncertain

4.4 The company submitted meta-analyses for several parameters, which the EAC said were statistically valid. However, some of the analyses, such as a reduced risk of AKI because of DyeVert Systems use, predominantly used data from abstracts and posters. The committee was concerned that it was difficult to assess the methodological quality of some studies, making it difficult to quantify the size and direction of bias in the meta-analysis. This made the reliability of the outcome measures uncertain.

Outcome measures

Better quality long-term follow up is needed to identify most cases of AKI

4.5 Most of the clinical evidence was limited by only having data from during the procedure. If AKI incidence was reported not all may have been identified because the studies were retrospective. Clinical experts said that most AKI events happen 4 days to 5 days after the contrast exposure, and sometimes as late as 7 days to 10 days afterwards. Incidence of AKI may be difficult to track because serum creatinine measurements may not be done routinely and there may not be consistent post-procedure renal monitoring. Overall, the committee felt that more long-term evidence on AKI incidence was needed.

Longer-term follow up is needed to collect data on secondary end points

4.6 Because the clinical evidence was limited by the follow-up evidence, the committee thought that further data collection was needed to capture secondary end points. This includes the need for temporary or end-stage dialysis and hospital stay.

NHS considerations overview

DyeVert Systems may be of most benefit to people with chronic kidney disease stage 4 and over

4.7 The clinical experts said that people with chronic kidney disease (CKD) stage 4 and over (estimated glomerular filtration rate [eGFR] less than 30 ml/min/1.73 m^2) would most benefit from DyeVert Systems and are likely to be the target population in clinical practice. Evidence presented on DyeVert Systems was in people with CKD stages 2 and 3 (eGFR 30 ml/min/1.73 m^2 to 89 ml/min/1.73 m^2), so the evidence on people with CKD stage 4 and over was limited. The company said that the population included in the studies had additional comorbidities, making them at greater risk of developing AKI after a contrast procedure.

Procedure type and anticipated contrast volume use should be considered when deciding whether to use DyeVert Systems

4.8 Clinical experts said that some procedures, such as diagnostic angiographies, are lower risk for AKI than more complex procedures, such as percutaneous coronary intervention. This is because the more complex procedures need larger volumes of contrast dye. The clinical experts felt that procedure type and anticipated volume of contrast dye needed should be taken into account when deciding whether to use DyeVert Systems.

Cost modelling overview

The cost model for DyeVert Systems is well constructed

4.9 The cost model for DyeVert Systems used a well-constructed decision tree and Markov model, with appropriate outcomes based on NICE clinical guidelines, and an appropriate time horizon. The clinical experts thought that the EAC's revised assumption of a relative risk of AKI of 8.74% was reasonable.

Because the link between reduced risk of contrast-induced AKI and using DyeVert Systems is not certain, the cost savings are not certain

4.10 The committee considered that the most robust evidence for DyeVert Systems was on surrogate markers, such as contrast volume reduction, rather than AKI incidence. According to clinical experts the causal relationship between contrast agent and AKI is not certain (see section 4.1). The results of the cost analysis were sensitive to the reduction in relative risk of AKI from using DyeVert Systems. Three of the 4 studies that reported that DyeVert Systems reduced the relative risk of AKI were abstracts or posters. These were included in the meta-analysis that provided the values used in the economic model. Including these studies meant the robustness of and risk of bias in the meta-analysis were uncertain. The reduction in relative risk of AKI for DyeVert was reported as 42% in the 1 full text published study and 41% in the meta-analysis. The EAC's sensitivity analysis found the break-even reduction in relative

risk to be 38.5%. Because the economic model was very sensitive to this parameter, there was uncertainty around whether using DyeVert Systems would lead to a cost saving.

Further research

Further good-quality research is needed to address uncertainties about the clinical efficacy of DyeVert Systems

4.11 The committee concluded that further research is needed to address uncertainties in the clinical effectiveness of DyeVert Systems compared with standard care. It concluded that, although there is clear evidence that DyeVert Systems can reduce contrast volume received while maintaining image quality, the evidence around AKI incidence was weaker. The committee concluded that a randomised controlled trial was needed. It should collect data on AKI incidence, renal replacement therapy, hospital stay and biochemical markers of kidney injury, and should follow up for enough time to capture these outcomes. The population should include people having an elective procedure who have an eGFR less than 30 ml/min/1.73 m^2. Further evidence should be collected to resolve the uncertainties around the generalisability between the 2 DyeVert devices. The committee noted that collecting evidence for DyeVert in peripheral angiography will be more difficult because of the different ways the procedure is done. It concluded that for peripheral angiography it may be appropriate to trial the system in procedures that use a consistent volume of contrast, such as endovascular aneurysm repair.

Real-world evidence may be difficult to interpret because of confounding factors

4.12 The committee thought that confounding factors make interpreting real-world evidence challenging. Comorbidities and procedural factors affect the risk of developing AKI after a contrast procedure, and these may not be clearly reported. There may also be inconsistencies in routine post-

procedure renal monitoring, including timing and frequency of serum creatinine measurements.

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technologies advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technologies advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more health technology assessment analysts (who act as technical leads for the topic), a health technology assessment adviser and a project manager.

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