

# DyeVert for reducing contrast media in coronary and peripheral angiography

Medtech innovation briefing

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## Summary

- The **technology** described in this briefing is DyeVert. It is intended to reduce the amount of contrast media given during coronary and peripheral angiographies.
- The **innovative aspects** are that DyeVert could reduce contrast media given to a patient, whilst maintaining image quality. This aims to reduce the incidence of contrast-induced acute kidney injury (CI-AKI).
- The intended **place in therapy** would be with current coronary and peripheral angiography equipment in people at risk of AKI, such as patients with moderate to severe chronic kidney disease, diabetes, older age, or heart failure.
- The **main points from the evidence** summarised in this briefing are from 6 studies: 2 randomised trials, 2 prospective non-comparative studies and 2 retrospective non-comparative studies. Included studies involved 381 adult patients, 274 of whom had DyeVert in a secondary care setting. The studies showed a reduction in the amount of contrast media given to the patient when DyeVert was used.

- **Key uncertainties** around the evidence are that evidence about how DyeVert effects the incidence of CI-AKI is limited. Most of the evidence is observational data and evidence with comparator arms is limited to single-site studies. Also, there is no published UK evidence.
- The cost of DyeVert system disposable components is £350 (exclusive of VAT) per patient. The reusable monitor is included in the cost of the first set of disposable components. The resource impact could be lower if DyeVert reduced the incidence and the number of adverse events associated with AKI. There is some evidence to support this but it is limited.

## The technology

DyeVert (Osprey Medical Inc) is a non-invasive system designed to reduce the amount of contrast media given during coronary and peripheral angiographies, when a manual or power injection of contrast media is needed. It is designed for patients at risk of acute kidney injury (AKI), including patients with moderate to severe chronic kidney disease, diabetes, and heart failure. By reducing the amount of contrast volume entering the patient's vasculature, DyeVert aims to reduce the risk of contrast induced-AKI (CI-AKI).

There are 2 DyeVert models: DyeVert Plus EZ and DyeVert Power XT. The DyeVert Plus EZ system consists of:

- Disposable module: attaches to any standard manifold configuration, has disposable tubing with different ports each controlled by opening or closing a valve, with a reservoir for storing excess contrast.
- Disposable smart syringe: connects to manifold to deliver dye injections.
- Reusable monitor: shows real-time dye delivery.

The DyeVert Plus EZ disposable module is positioned between the manual syringe (smart syringe) and the injection port (manifold). The clinician controls the injection of contrast manually and aspirates using the smart syringe. Excess contrast (approximately 40% of total) not needed for diagnostic or therapeutic purposes is moved from the patient's blood vessels into the reservoir in the device. This reduces the total contrast given while, according to the company, maintaining adequate visual quality. Bluetooth in the module and smart syringe allows wireless communication to the monitor, which gives a real-time display of total contrast given, and total diverted contrast. The monitor is included in the cost of the first set of disposables. Future disposables are provided without the monitor. The monitor is maintained and serviced by the company.

DyeVert Power XT is used for power contrast injections. It consists of:

- DyeVert Power XT assembly
- contrast collection bag.

The disposable module is positioned between the power injector (injects the contrast) and the angiographic catheter (to put the contrast media into the vascular system). The sterile waste bag collects diverted contrast. Similarly to the manual injection process, a modifiable valve responds to injection pressure and fluid pathway resistance to maintain a minimum flow rate. There is no reusable monitor for live contrast monitoring and no smart syringe in the DyeVert Power XT system.

## Current care pathway

NICE's clinical guideline on [acute kidney injury: prevention, detection and management](#) states that increasing volume of contrast agent is a risk factor for AKI. This means that patients who are going to have contrast agents should be assessed for their risk of AKI. Use of iodinated contrast agents in the past week should trigger investigation for AKI. Prevention strategies for patients having iodinated contrast include intravenous volume expansion.

A [clinical practice guideline on prevention of CI-AKI](#) also states that before any imaging using iodinated contrast media, risk factors for CI-AKI should be identified (unless very early imaging outweighs the risk of delaying the procedure). When patients are identified as high risk, this must be discussed with a renal physician to assess whether potential benefit from iodinated contrast outweighs the risk of CI-AKI. Preventative strategies include use of scanning without iodinated contrast or with the lowest possible volume, and intravenous volume expansion. The Kidney Disease, Improving Global Outcomes (KDIGO) [clinical practice guideline for AKI](#) recommends using either iso-osmolar or low-osmolar iodinated contrast media (rather than high-osmolar) in patients at increased risk of CI-AKI.

The European Society of Urogenital Radiology [guidelines on contrast media](#) recommends the lowest dose of contrast medium consistent with a diagnostic result and to use of low or iso-osmolar contrast media. For at-risk patients, the guidelines recommend considering an alternative imaging method without iodinated contrast media or preventative hydration.

## Innovations

DyeVert is a non-invasive technology to reduce contrast media, with real-time contrast media dose

monitoring. The company claims that DyeVert maintains adequate image quality, and that this is not possible with the current approach of manual slowing of the rate of injection.

## Population, setting and intended user

The technology is for adult patients at risk of AKI having coronary and peripheral angiography. An increased risk of AKI is associated with:

- chronic kidney disease (including those with coexisting diabetes)
- heart failure
- renal transplant
- hypovolaemia
- increasing volume of contrast agent
- intra-arterial administration of contrast agent.

DyeVert is for use in a cardiac catheter laboratory by consultant cardiologists, interventional cardiologists or catheter laboratory staff in secondary care. Catheter laboratory staff must set up and prime the DyeVert system before each use. Clinicians can turn DyeVert on or off for contrast agent counting or reduction. The company states that there is no training needed.

## Costs

### Technology costs

The costs are based on company estimates. The total cost for DyeVert (including disposables) per case is £350.00 (excluding VAT). The system monitor is multi-use and servicing (software maintenance and upgrades) is included in this price. The procedure cost of diagnostic angiography or percutaneous coronary intervention is estimated by the company to be £3,565.90. If DyeVert can reduce the incidence of CI-AKI and recurrent AKI after the procedure, it could be resource releasing.

The company have posted an [economic manuscript](#) of a study they plan to publish in a peer-reviewed journal. The evaluation assesses the DyeVert Plus EZ system based on patients with chronic kidney disease stage 3 to 4 having angiography. If DyeVert reduces the incidence of CI-AKI, it could reduce the cost of CI-AKI and related complications in the first 3 months after treatment,

and the cost of subsequent disease management. However, the company model is based on a number of assumptions and evidence to support these assumptions is limited.

## Resource consequences

DyeVert is currently being used by 5 hospitals in the UK according to the company. The company claims that DyeVert could be resource releasing, by reducing the incidence and adverse events associated with CI-AKI.

Potential adoption barriers raised by 2 commentators were the cost of the device and defining patient selection criteria, since it would not be needed for all patients.

## Regulatory information

DyeVert is a CE-marked class I medical device.

## Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Adult patients at risk of contrast-induced acute kidney injury (CI-AKI) are identified as the intended population. Older age is a risk factor for AKI, and people in this group could benefit from contrast media volume reduction. Age is a protected characteristic.

## Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting [mibs@nice.org.uk](mailto:mibs@nice.org.uk).

## Published evidence

Six studies are summarised in this briefing: 2 randomised trials, 2 retrospective non-comparative studies and 2 prospective non-comparative studies. The 6 studies involved 381 patients, 274 of

whom had DyeVert (9 had DyeVert Power XT, 173 had DyeVert Plus and 92 had DyeVert [that is, it did not specify which type of DyeVert system was used]). Included studies were done in Germany, Australia, US and Italy. These studies used DyeVert in coronary angiogram or percutaneous coronary intervention procedures.

[Table 1](#) summarises the clinical evidence as well as its strengths and limitations.

## Overall assessment of the evidence

There is limited high-quality published evidence on DyeVert. Only 2 of the included studies involve a comparator, making it difficult to conclude the efficacy of DyeVert compared with standard care. One of the included studies ([Bruno et al. 2019](#)) used the DyeVert Power XT device with an ACIST power injector, to allow for use with power contrast injections. Sample sizes are relatively small and there is no published UK evidence.

There is a need for larger prospective, UK-based, multicentre, randomised controlled trials using DyeVert compared with standard care. Important outcomes would include how the contrast media volume savings from DyeVert affect rates of contrast-induced acute kidney injury (CI-AKI), with follow up long enough to detect this, to see the device's efficacy at preventing this complication.

### Table 1 Summary of selected studies

<a href="#">Bruno et al. (2019)</a>	
Study size, design and location	A single-centre retrospective pilot study involving 9 patients having diagnostic or interventional invasive coronary angiography over 2 consecutive days in November 2018. Location: Germany.
Intervention and comparator(s)	Intervention: DyeVert Power XT System and ACIST CVi Contrast Delivery System (n=9). Comparator: None.

Key outcomes	The average volume of CM delivered to patients was 80.6 ml (range 45.5 ml to 211.9 ml). Attempted delivery was 127.8 ml (range 71.6 ml to 304.9 ml), resulting in average CM savings of 38.9% (range 31.0% to 47.0%). Ratio of total CM volume to creatinine clearance was reduced from 1.84 (attempted approach, array 1.03 to 4.41) to 1.12 (delivered approach, array 0.73 to 3.04). There were no DyeVert Power XT system failures. A physician assessment results and reported no loss of angiograph quality.
Strengths and limitations	Four different physicians did the procedure and used the device, helping to reduce potential bias. No statistical analysis of results. Small sample size. Coexisting use of device with ACIST power injector, uncertain over the efficacy of DyeVert with other power injectors. No random allocation and no control group. Reduced contrast media dose was estimated, and subjective unblinded assessment of image quality by the physicians may have introduced bias. Not in UK so may not be generalisable to the NHS. Author reports to have received speaking fee from company.
<u>Desch et al. (2018)</u>	
Study size, design and location	A prospective, single-centre, open-label randomised controlled trial of 96 patients having diagnostic coronary angiography from April 2016 to May 2016. Location: Germany.
Intervention and comparator(s)	Intervention: DyeVert with standard care for diagnostic coronary angiograms (n=48). Comparator: Standard diagnostic coronary angiogram (n=48).
Key outcomes	There was a 41.0% reduction in CM volume in DyeVert group compared with comparator group (36.9±10.9 ml versus 62.5±12.7 ml, p<0.001). Image quality using DyeVert system was not inferior compared with control (p=0.03). There were no device-related adverse events.

Strengths and limitations	A randomised controlled trial is good-quality evidence. Randomisation method was permuted block randomisation stratified by access site using a computer to generate random numbers, to prevent bias. However, physicians doing the procedures were aware of randomisation results and blinding was not possible because of visual differences with the tubing set. Image quality assessment was done by independent reviewer who was blinded to treatment allocation. Study was powered for primary (different in CM volume) and secondary (image quality) end points, but not for incidence of serious adverse device effects. The study was not in the UK so may not be generalisable to the NHS. Study sponsored by the company. Author is a consultant to the company.
<u>Sapontis et al. (2017)</u>	
Study size, design and location	A multicentre prospective, single arm clinical pilot study involving 44 patients having coronary diagnostic or PCI procedures. Location: Australia and Germany.
Intervention and comparator(s)	Intervention: DyeVert system (n=44). Comparator: None.
Key outcomes	The mean CM volume attempted to be injected versus actual volume injected were 173±117 ml versus 89±57 ml respectively. The mean volume saved by DyeVert was 47% (p<0.0001). Mean volume savings were similar for diagnostic (47±9%) and PCI (50±9%) procedures (p=0.26). Image quality was good in 43 out of 44 patients (98%). In 1 patient, the clinician judged image quality to have a "washed out appearance" and so DyeVert was turned off for 2 injections. Clinician-rated device acceptability was high (95% to 98%).
Strengths and limitations	Power calculation performed to calculate sample size. Patients who, in the investigator's opinion DyeVert was not appropriate for, were excluded. This is subjective and may have introduced bias. Subjective assessment of image quality by the clinician doing the procedure, which is unblinded and prone to bias. No comparator to compare outcomes with standard care. The CM used varied, which may have affected results. One of the authors is a consultant to the company. The company was the contract grant sponsor.
<u>Gurm et al. (2018)</u>	

Study size, design and location	<p>A prospective, multicentre, single-arm observational study enrolling 114 patients (105 patients in primary end point analysis, 114 patients in secondary end point analysis) having diagnostic coronary angiogram or PCI procedures done with manual injections between July 2017 to December 2017.</p> <p>Location: US.</p>
Intervention and comparator(s)	<p>Intervention: DyeVert Plus System.</p> <p>Comparator: None.</p>
Key outcomes	<p>Mean CM volume attempted was <math>112 \pm 85</math> ml (range 22 ml to 681 ml) and mean CM volume given was <math>67 \pm 51</math> ml (range 12 ml to 403 ml), resulting in overall CM volume savings of <math>40.1 \pm 8.8\%</math> (95% CI 38.4 to 41.8; <math>p &lt; 0.0001</math>) per procedure. Image quality was maintained in 104 patients, with 1 patient having the system turned off for 1 injection. No adverse events were reported. AKI was reported in 11 patients, with 7 in patients with baseline eGFR less than <math>30 \text{ ml/min/1.73 m}^2</math>. There were 3 AKI cases attributed to CM. There were significant differences in contrast savings for subgroups defined by BMI (<math>p = 0.0398</math>) and procedure type (<math>p = 0.0057</math>). Contrast savings were also significantly different between different physicians (<math>p = 0.0029</math>). At lower CMV/eGFR ratios, DyeVert Plus increased the percentage of subjects with ratios of 1 or lower from 7% (attempted) to 33% (actual) and with ratios of 2 or lower from 42% (attempted) to 75% (actual). Conversely, at higher CMV/eGFR ratios, DyeVert Plus reduced the percentage of subjects with ratios of more than 2 from 58% (attempted) to 25% (actual). Observed AKI rates increased with increasing CMV/eGFR ratios, with no patients with a CMV/eGFR ratio of less than 1 developing AKI. Catheter laboratory staff reported DyeVert Plus system setup and priming added <math>3.3 \pm 2.9</math> minutes to procedure preparation time. 55% (63 patients) were discharged on the same day. 17% (19 patients) were discharged 3 or more days after the procedure.</p>

Strengths and limitations	Multicentre trial with procedures performed by 17 different interventional cardiologists helps to reduce bias. Reasonably good sample size which was powered to detect CM volume savings of 35%±16%. Good range of outcomes including rates of CI-AKI. However, study states that data on rates of CI-AKI should be 'hypothesis-generating' as post-procedure laboratory data were not available for all patients, suggesting that results may not be accurate or generalisable to real-life practice. No comparator group means no comparison to standard of care. The type of CM, and use of other renal protection strategies such as hydration and discontinuation of medications, were at discretion of study investigator. This makes it difficult to attribute changes in outcomes to DyeVert. CM saved was the value shown on the DyeVert contrast monitoring system, with no quality assurance comparator to check accuracy. Study sponsored and funded by the company. Of the authors, 2 are consultants for the company and 1 received research funding from the company.
<u>Corcione et al. (2017)</u>	
Study size, design and location	A retrospective analysis of 10 patients having coronary or peripheral invasive procedures from an institutional clinical database when DyeVert Plus was used.  Location: Italy.
Intervention and comparator(s)	Intervention: DyeVert Plus (n=10).  Comparator: None.
Key outcomes	All procedures were completed with adequate and high-quality angioscopic and angiographic images. One patient had CI-AKI. Mean CM volume was 79.9±48.8 ml (95% CI 53.2 to 109.4), with a mean absolute saving of 55.8±31.9 ml (95% CI 39.1 to 76.7, p<0.05), and a relative saving of 41.8±7.3% (95% CI 37.5 to 46.4, p<0.05). The mean theoretical total CM volume was 135.7 ml (95% CI 95.2 to 186.7). Comparison of CM volume estimates between DyeVert Plus versus manual measurements showed a mean absolute difference of -1.6 ml (95% CI -2.9 to -0.4, p<0.05) and a relative difference of -1.9% (95% CI -3.5 to 0.2, p>0.05).

Strengths and limitations	Statistical analysis of results, with a good range of outcomes. Procedures are as per device indications, meaning results are generalisable to the target population. Different types of CM used, which may have affected results, so outcomes are difficult to attribute solely to DyeVert. Very small sample size limits reliability of study findings. Not in UK so may not be generalisable to an NHS setting. Retrospective observational study which is low quality evidence.
<u>Bath et al. (2019)</u>	
Study size, design and location	A randomised study involving 108 patients at increased risk of CI-AKI having diagnostic angiography with or without DyeVert Plus. Location: US.
Intervention and comparator(s)	Intervention: Diagnostic angiography with DyeVert Plus (n=49). Comparator: Diagnostic angiography without DyeVert Plus (n=59).
Key outcomes	When comparing DyeVert Plus arm with standard of care arm, mean cumulative CM volume was 62.7±9.5 ml (95% CI) versus 87.6±110 ml (95% CI) respectively, resulting in a 28.4% (p=0.0004) reduction in CM volume with DyeVert Plus. CM given through DyeVert Plus was 43.8% below the threshold volume (eGFR ×3) for the cohort as compared to 31.4% in the standard of care arm (p=0.05). Contrast savings of 34.9±3.0% (95% CI) were seen in the DyeVert Plus arm.
Strengths and limitations	Randomised study design helps to reduce bias and allows comparison of outcomes to standard of care. Relatively good sample size. Abstract from a poster presentation is low-quality evidence and lacks details of study methodology. There is no information regarding baseline characteristics, how study participants were selected, how they were randomised and whether there was any loss to follow up. Outcomes such as image quality were not assessed. Not in UK so not generalisable to an NHS setting.
Abbreviations: AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; CM, contrast media; CMV, contrast media volume; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate.	

## Recent and ongoing studies

- [DyeVert System use for contrast monitoring and minimisation in at-risk patients undergoing angiography procedures: a real-world registry \(DYEMINISH\)](#). ClinicalTrials.gov identifier:

- NCT03825094. Status: enrolling by invitation. Indication: patients undergoing cardiac angiography who are at risk for contrast-induced acute kidney injury. Devices: DyeVert Contrast Reduction Systems. Last update posted: 7 August 2019. Location: US.

The company states that UK-based evidence about contrast use and clinician satisfaction data is pending publication.

## Specialist commentator comments

Comments on this technology were invited from clinical specialists working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

None of the 3 specialists were familiar with or had used this technology before.

## Level of innovation

All commentators considered DyeVert to be innovative with no competing alternatives, although 1 commentator advised that it has not been compared with standard care in a randomised controlled and blinded study. Another commentator noted an alternative system is available and used by some clinicians. The system promotes diuresis and monitor's the patient's urine output to enhance contrast washout from the kidney and prevent contrast-induced acute kidney injury (CI-AKI). However, the commentator acknowledged that DyeVert uses a different method of limiting the contrast load rather than promoting diuresis.

## Potential patient impact

Patients who would particularly benefit include those with moderate to severe pre-existing kidney disease, patients with diabetes and those with heart failure needing invasive cardiac intervention such as percutaneous coronary intervention or transcatheter aortic valve implantation. Potential patient benefits included reduced AKI, reduced costs, reduced morbidity and mortality, reduced need for dialysis and shorter length of stay secondary to less contrast. However, 1 commentator stated that the current evidence does not completely show these improved outcomes and another commentator advised that rates of CI-AKI may actually be less than historically reported.

## Potential system impact

System benefits included reduced cost from contrast and treating CI-AKI, less follow-up renal

function testing, less renal replacement therapy, shorter length of stay and potential to increase availability of interventional cardiac procedures for patients with advanced chronic kidney disease. Additional resources included the need for the disposable equipment, for example, tubing and contrast reservoir, and the reusable console for contrast volume monitoring. Opinions on costs varied. One commentator thought that DyeVert would cost more than any downstream savings, whilst another commentator thought that if it was proven to be effective, it could reduce costs. The third commentator could not comment on this because of lack of evidence comparing DyeVert with standard care.

No commentators were aware of any safety concerns. All commentators thought that DyeVert would be used in addition to standard care. One commentator had concerns about image quality with reduced contrast volumes. They suggested that variables such as force of injection, contrast viscosity, guide catheter engagement, patient hydration should be considered. Potential adoption barriers raised by 2 commentators were the cost of the device and patient selection criteria, since it would not be needed for all patients.

## General comments

Commentators thought that training for the device would be needed to set up DyeVert in the catheter laboratory. This should be a straightforward addition to the manifold system.

It was estimated by 1 commentator that CI-AKI occurs in up to a third of all at-risk cardiac patients having percutaneous coronary intervention, and so DyeVert may be an option in this patient population.

All commentators identified further research that is needed in the form of randomised controlled blinded trials compared with standard care. Important outcomes would be potential to reduce CI-AKI, ability to maintain image quality, hospital length of stay and persistent reduction in renal dysfunction. Health economic evaluations would also be needed as evidence.

## Specialist commentators

The following clinicians contributed to this briefing:

- Dr Nick Selby, associate professor of nephrology, Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine University of Nottingham, did not declare any interests.

- Dr Amarjit Sethi, consultant cardiologist, Imperial College Healthcare NHS Trust, did not declare any interests.
- Dr Shahid Aziz, consultant interventional cardiologist, North Bristol NHS Trust, did not declare any interests.

## Development of this briefing

This briefing was developed by NICE. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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