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ORIGINAL STUDIES

EDITORIAL COMMENT: Expert Article Analysis For:
Protecting the kidneys

Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: A multicenter observational study of the DyeVert™ plus contrast reduction system

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Abstract

Objective: To evaluate contrast media (CM) volume (CMV) saved using the DyeVert™ Plus Contrast Reduction System (DyeVert Plus System, Osprey Medical) in patients undergoing diagnostic coronary angiogram (CAG) and/or percutaneous coronary interventional (PCI) procedures performed with manual injections.

Background: Current guidelines advocate for monitoring and minimization of the total volume of CM in chronic kidney disease (CKD) patients undergoing invasive cardiac procedures. The DyeVert Plus System is an FDA cleared device designed to reduce CMV delivered during angiography and permit real-time CMV monitoring.

Methods: We performed a multicenter, single-arm, observational study. Eligible subjects were ≥ 18 years old with baseline estimated glomerular filtration rate (eGFR) 20–60 mL/min/1.73 m^2. The primary endpoint was % CMV saved over the total procedure. A secondary objective was to evaluate adverse events (AEs) related to DyeVert Plus System or to CM use.

Results: A total of 114 subjects were enrolled at eight centers. Mean age was 72 ± 9 years, 72% were male, and mean body mass index was 29 ± 5. Baseline eGFR was 43 ± 11 mL/min/1.73 m^2. CAG-only was performed in 65% of cases. One hundred and five subjects were evaluable for the primary endpoint. Mean CMV attempted was 112 ± 85 mL (range 22–681) and mean CMV delivered was 67 ± 51 mL (range 12–403), resulting in an overall CMV savings of 40.1 ± 8.8% (95% CI 38.4, 41.8; $P < 0.0001$) per procedure. Image quality was maintained in all but one case where the system was turned off for one injection. No DyeVert Plus System-related AEs were reported. Acute kidney injury (AKI; defined as serum creatinine rise of >0.3 mg/dL from baseline) was reported in 11 cases with seven occurring in subjects with baseline eGFR < 30 and three AKI events were attributed to CM. AKI rates increased as CMV/eGFR ratios increased.

Conclusions: These data suggest DyeVert Plus System use in CKD patients undergoing CAG and/or PCI results in clinically meaningful CMV savings while maintaining image quality.

KEYWORDS

ANCO-angiography, angiographic/fluoroscopic, CONT-contrast agents, coronary, IAF-imaging, PCI-percutaneous coronary intervention, RDAC-renal disease-acute

Clinical Trial Registration Information: URL: http://www.clinicaltrials.gov. Unique identifier: NCT03715452.

1 | INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) is a common complication observed in patients undergoing invasive cardiac procedures and is associated with increased morbidity, mortality, and health care costs.[1–5] Current professional society recommendations support identification of at risk patients, appropriate periprocedural hydration, and minimization of contrast volume in at-risk patients as strategies to prevent CI-AKI.[6,7]

There appears to be a non-linear increase in risk of AKI with increasing doses of contrast media (CM) volume (CMV), and both in vivo data and clinical studies have demonstrated an association between high contrast volume and the risk of AKI.[8,9] While different authors have evaluated several contrast thresholds to guide safe contrast dosing, collaborative efforts to reduce the proportion of patients exceeding threshold targets have been associated with a reduction in the incidence of AKI.[10–15]

The DyeVert™ Contrast Reduction System (DyeVert System, Osprey Medical) was cleared by the Food and Drug Administration (FDA) for the purpose of reducing CMV delivered to patients during angiography procedures. Early experience with this device from European centers has demonstrated clinically and statistically meaningful reductions in CM delivered to the patient.[16–18] We report the results of a single-arm, observational study evaluating the safety and efficacy of the latest version of the product, DyeVert Plus System, which includes continuous CM threshold monitoring, across multiple participating sites.

2 | METHODS

2.1 | Study design and population

This was a prospective, multicenter, single-arm, observational study designed to evaluate CMV saved using the DyeVert Plus System in a cohort of subjects undergoing diagnostic coronary angiography (CAG) and/or percutaneous coronary interventional (PCI) procedures performed with manual injections. The study was performed at eight centers by 17 interventional cardiologists.

Local institutional review boards approved this study and all subjects provided written informed consent. Eligible subjects were ≥18 years old, scheduled to undergo CAG and/or PCI, and had a baseline estimated glomerular filtration rate (eGFR) of ≥20 and ≤60 mL/min/1.73 m^2. Subjects were excluded from participation if they: had acute ST-elevation myocardial infarction or known coronary artery fistulas, had a body mass index (BMI) >40, were currently pregnant, were undergoing a chronic total occlusion procedure or optical coherence tomography analysis, were planning to undergo transcatheter aortic valve replacement within 72 hr of the index procedure, or had a condition known to require large volumes of contrast (>10 mL) for each injection.

The specific type of CM, and the use of other renal protection strategies such as hydration, pre and post procedural laboratory studies, and continuation or discontinuation of specific medications were at the discretion of the study investigator and per local institutional policies. Similarly, the use of other contrast minimization techniques such as biplane angiography and use of adjunct imaging such as IVUS were per operator discretion and was not specified by the study protocol.

2.2 | Study device

The DyeVert Plus System interfaces with standard manifold systems to provide real-time contrast monitoring and reduce the amount of contrast used in catheterization procedures while maintaining fluoroscopic image quality. System components include a disposable, single-use, sterile DyeVert Plus Disposable Kit that contains a Smart Syringe and DyeVert Plus Module, which is connected to a standard manifold (Figure 1) and provides fluid pathway resistance modulation via a dedicated diversion valve. The diversion valve self-adjusts to the manual injection pressure to divert some of the CM into the reservoir chamber within the module. This diverted volume of CM does not enter the patient.

The second component of the system is a contrast monitoring wireless (CMW) display, which communicates with the DyeVert Plus disposable component to allow real-time monitoring and display of CMVs manually injected. The treating physician specified a maximum contrast dose threshold at their discretion prior to the procedure. This allowed determination of the percent of the predefined maximum CMV delivered to the patient. CM monitoring and volume accounting is completed via translation of Hall Effect sensors and pressure transducer voltage readings to volume readings in milliliters and accounting for whether contrast accounting for each injection was performed with the contrast accounting system on or off. At the end of the procedure, the CMW displays total procedure contrast volume used (mL, actual CMV delivered to the patient), % of physician-specified threshold, total procedure contrast volume saved (mL), and % contrast saved. The amount of CMV attempted to be delivered to the patient is the sum of the total procedure contrast volume used (mL) and total procedure contrast volume saved (mL).

Image quality was monitored by each operator during the procedure per standard practices. Any injection in which the DyeVert Plus System was turned off for the purpose of improving image quality was recorded.

2.3 | Endpoints

The primary endpoint of the study was the percentage of CMV saved over the total procedure as reported on the DyeVert Plus display at the end of each case.

Secondary endpoints were the evaluation of DyeVert Plus System-related adverse events (AEs) and CM-related AEs of anaphylaxis and AKI through discharge. Acute kidney injury events were defined as a >0.3 mg/dL increase in serum creatinine postprocedure through discharge compared to the baseline value or through the date of a secondary procedure for staged procedures. Investigators defined the etiology of each AKI event.

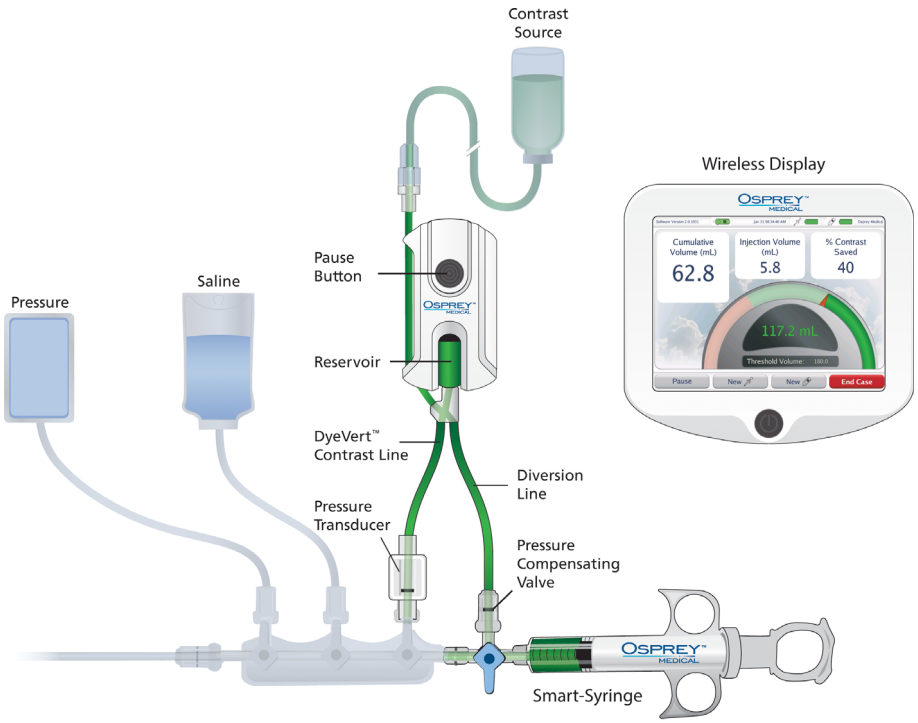

FIGURE 1 The DyeVert™ Plus System [Color figure can be viewed at wileyonlinelibrary.com]

2.4 | Statistical analysis

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). The primary endpoint analysis was based on the population of evaluable subjects and used a one sample *t*-test against a fixed null hypothesis. Successful rejection of the null hypothesis will demonstrate that the percentage of CMV saved is statistically greater than 30%. The expected percentage of CMV saved was estimated to be at least 35% ± 16%; therefore, a sample size of 100 evaluable subjects was estimated to be required (80% power, one-sided 0.025 alpha). To account for attrition, 114 subjects were enrolled.

Subjects were deemed unevaluable for primary endpoint analysis if any of the following criteria were met; the DyeVert Reservoir was inadvertently turned off due to user error for >1 injection, the DyeVert Reservoir was turned off for >1 injection due to an AE not related to the device, the display did not provide contrast accounting details at the end of a case due to device deficiency, a contrast accounting error due to user error occurs for >1 injection as defined in the procedure case report form, or the treating physician determines that a Bluetooth disconnection occurred resulting in inaccurate contrast accounting.

All available data were used for the secondary endpoints.

3 | RESULTS

A total of 114 subjects were enrolled between July through December 2017. Patient and procedure characteristics are listed in Table 1. Baseline eGFR was 43 ± 11 mL/min/1.73 m^2 with 18 (16%) subjects having a baseline eGFR of 20–30 mL/min/1.73 m^2. Baseline serum creatinine was 1.6 ± 0.5 mg/dL. Nearly all subjects had history of hypertension (96%) and 100 (88%) subjects had three or more comorbidities in addition to chronic kidney disease (CKD). Twenty-five (22%) subjects had New York Heart Association functional classification of heart failure Stage III (moderate) or IV (severe). Subjects were, on average, at a moderate risk for AKI according to the Mehran risk score.

Most procedures were CAG only (65%) and were performed using femoral access (63%) and 6 Fr (73%) catheters. Mean pre-defined physician CM threshold per procedure was 122 ± 50 mL and were set using criteria of eGFR x < 2 not to exceed 3[14] in 66% of procedures, eGFR x < 3.7[19] in 24% of procedures, and other methods in 11% (ePRISM or physician discretion). Cath lab staff reported the DyeVert Plus System setup and priming added 3.3 ± 2.9 min to procedure preparation.

Staged PCI was performed in 11 subjects. Post-procedure serum creatinine measurement was obtained in 54 (47%) subjects as part of routine clinical care. Same-day discharge occurred in 63 (55%) subjects, 27 (24%) subjects were discharged the day after the procedure, five (4%) subjects were discharged 2 days after the procedure and 19 (17%) subjects were discharged three or more days after the procedure.

3.1 | Primary endpoint

Nine subjects were excluded from the primary endpoint analysis per the protocol. In eight cases, the DyeVert Plus System was not used for more than one injection during the case due to user or technical error. In one case, the subject met study exclusion criteria for BMI but was inadvertently enrolled in the study. Therefore, 105 subjects were evaluable for the primary endpoint.

TABLE 1 Patient and procedural characteristics

Patient characteristics	
Age (years)	72 ± 9
Gender	
Male	82 (72)
Female	32 (28)
Race	
Caucasian	86 (75)
African American	25 (22)
Asian	1 (1)
American Indian	1 (1)
Other	3 (3)
BMI	29 ± 5
eGFR (mL/min/1.73 m^2)	43 ± 11
Serum creatinine (mg/dL)	1.6 ± 0.5
Comorbidities	
Hypertension	110 (96)
Coronary artery disease	86 (75)
Prior PCI	60 (53)
Diabetes	60 (53)
Congestive heart failure	54 (47)
Prior coronary artery bypass graft	40 (35)
Prior myocardial infarction	39 (34)
Anemia	33 (29)
Angina	30 (26)
Mehran risk score[a] (using eGFR)	9.0 ± 3.9
Procedure characteristics	
Vascular access route	
Femoral	72 (63)
Radial	42 (37)
Procedure type	
CAG only	74 (65)
CAG + PCI	30 (26)
PCI only	10 (9)
CM type used	
Visipaque 320	63 (55)
Omnipaque 350	20 (18)
Omnipaque 300	16 (14)
Isovue	8 (7)
Visipaque 270	7 (6)
Fluoroscopy time (min)	12.8 ± 14.4
# Lesions treated	
0	74 (65)
1	29 (25)
2	7 (6)
3	2 (2)
4	1 (1)
5	0 (0)
6	1 (1)
Maximum catheter size (per subject)	
4F	1 (1)
5F	20 (18)
6F	79 (73)
7F	9 (8)
Catheter size (total reported for all cases)	
4F	1 (1)
5F	42 (22)
6F	141 (73)
7F	10 (5)

Data are n (%) or mean ± SD.

[a] Intra-aortic balloon pump use and hypotension were not collected in this study; risk score integers were assumed 0 for these factors.

The mean predetermined CMV threshold in the primary endpoint cohort was 119 ± 48 mL (range 40–236 mL). The mean CMV attempted was 112 ± 85 mL (range 22–681 mL) and mean CMV delivered was 67 ± 51 mL (range 12–403 mL) resulting in an overall CMV savings of 40.1 ± 8.8% (95% CI 38.4, 41.8; $P < 0.0001$) per procedure (Figure 2). In 91 (87%) cases, the CMV delivered was less than the predefined CM threshold.

When the primary analysis was additionally performed using all cases (inclusive of the excluded cases), the overall CMV savings was 39.4 ± 9.1% (95% CI 37.7, 41.1; $P < 0.0001$) per procedure.

Image quality was maintained in all but one CAG + PCI case, in which the physician turned off the DyeVert Plus System for one injection for the purpose of obtaining a better image, and then resumed using the DyeVert Plus System for the remainder of the case.

Prespecified subgroup analyses were performed to assess if contrast savings varied within access approach (radial vs. femoral), BMI (<30 kg/m^2 vs. ≥30 kg/m^2), physician user, and procedure type (Table 2). While a large average contrast savings was observed in all subgroups, there were significant differences in contrast savings ($P < 0.05$) for subgroups defined by BMI and procedure type, with more savings observed for those with a lower BMI and for diagnostic procedures. Contrast savings also varied significantly between physician users ($P = 0.0029$).

3.2 | Secondary endpoints

All enrolled subjects contributed to the secondary endpoint analysis. No DyeVert Plus System-related AEs or cases of contrast-related anaphylaxis were reported. Acute kidney injury (>0.3 mg/dL increase in serum creatinine postprocedure through discharge) was reported in 11 subjects for an observed AKI rate of 9.6% (11/114). The adjusted AKI rate, including only those subjects with a post-procedure serum

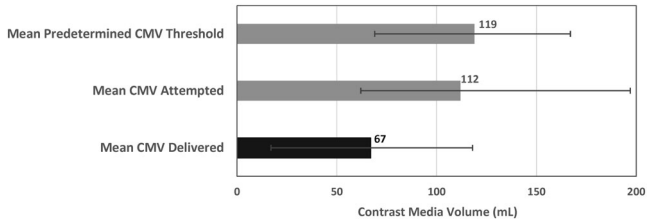

FIGURE 2 Mean contrast media volume attempted (total procedure contrast volume delivered + total procedure contrast volume saved) versus delivered to the patient

TABLE 2 Contrast volume savings, subgroup analyses

Variable	Percent contrast savings	*P*-value[a]
Access location		0.1558
Femoral	39.2 ± 8.6 (68)	
Radial	41.8 ± 9.0 (37)	
BMI		0.0398
<30	41.6 ± 8.0 (61)	
≥30	38.0 ± 9.5 (44)	
Physician		0.0029
Physician user 1	32.7 ± 7.5 (18)	
Physician user 2	42.3 ± 5.4 (16)	
Physician user 3	41.5 ± 12.3 (15)	
Physician user 4	41.5 ± 8.2 (14)	
Physician user 5	35.9 ± 5.1 (5)	
Physician user 6	44.9 ± 5.4 (5)	
Physician user 7	48.6 ± 5.0 (5)	
Physician user 8	40.7 ± 7.4 (4)	
Other users[b]	40.6 ± 8.0 (23)	
Procedure type		0.0057
Diagnostic only	41.9 ± 8.4 (70)	
Diagnostic + PCI	37.4 ± 8.7 (25)	
PCI only	34.1 ± 7.8 (10)	

Data are presented mean ± std (n).
[a] *P*-value based on two sample t-test or ANOVA for subgroup variables with more than two levels.
[b] Physicians with fewer than four cases were combined into Other Users.

creatinine value, was 20.4% (11/54). Seven AKI events occurred in subjects with baseline eGFR <30. Investigators attributed the AKI events to the following causes: five (4.4%) were fluid management related (over- or under-diuresis, diuretic use/congestive heart failure), three (2.6%) were contrast-related, one was related to a diabetic complication, one was due to a recent prior surgery, and in one case, the cause was unknown.

Using an AKI definition of ≥0.5 mg/dL increase in serum creatinine postprocedure through discharge, six AKI events were reported for an observed AKI rate of 5.3% (6/114) and an adjusted rate of 11.1% (6/54). Based on an imputed Mehran risk score[20] (hypotension and use of IABP were assumed to be 0 for all subjects since these variables were not prospectively collected) calculated for this cohort, the predicted risk of AKI (defined as an elevation in serum creatinine of >0.5 mg/dL) for the overall cohort and the patients with follow up serum creatinine data was 14%.

Use of the DyeVert Plus System was associated with a lower observed CMV/eGFR ratios for the study cohort compared to the attempted CMV/eGFR ratios (reflective of the amount of contrast the subject would have been given without the use of DyeVert Plus); therefore, a substantial proportion of subjects moved into lower CMV/eGFR deciles (Figure 3). At lower CMV/eGFR ratios, the use of DyeVert Plus increased the percentage of subjects with ratios ≤1 from 7% (attempted) to 33% (actual) and with ratios ≤2 from 42% (attempted) to 75% (actual). Conversely, at higher CMV/eGFR ratios, the use of DyeVert Plus reduced the percentage of subjects with ratios >2 from 58% (attempted) to 25% (actual).

Observed AKI rates increased with increasing CMV/eGFR ratios (Figure 4), with an observed AKI rate of 0% for subjects with a CMV/eGFR of ≤1 and 22.2% for subjects with a CMV/eGFR >3 although the number of AKI events and number of subjects with a high CMV/eGFR was limited.

4 | DISCUSSION

Our study demonstrates the feasibility of using the DyeVert Plus System to achieve a meaningful reduction in contrast volume delivered to

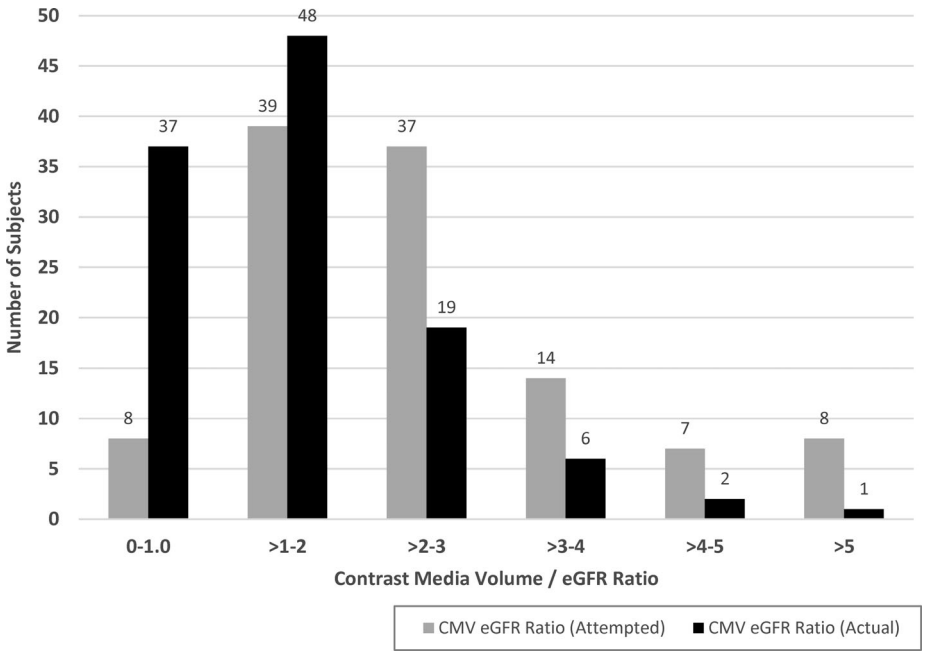

FIGURE 3 Contrast media volume/baseline estimated glomerular filtration rate ratio attempted (total procedure contrast volume delivered + total procedure contrast volume saved) versus delivered to the patient (actual) using DyeVert Plus

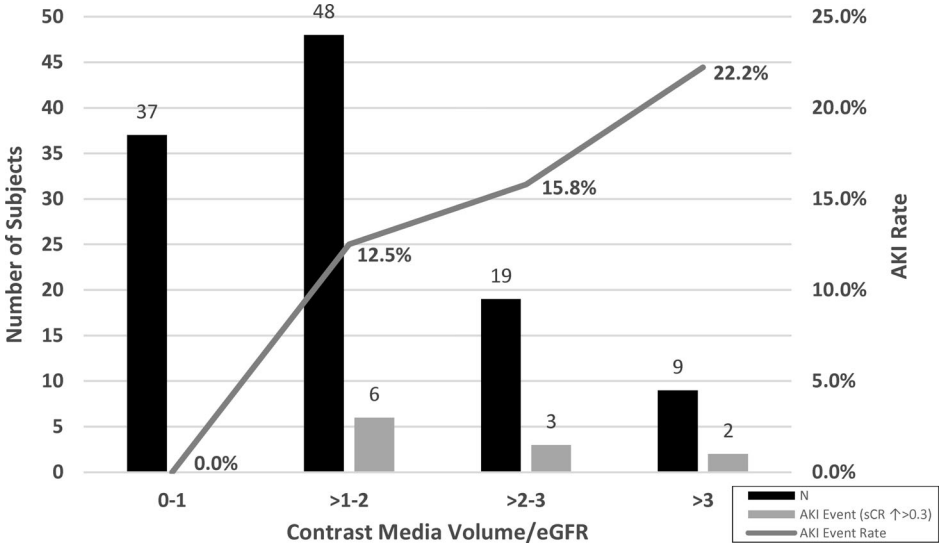

FIGURE 4 Acute kidney injury rates by contrast media volume to baseline estimated glomerular filtration rate ratio

patients undergoing CAG and/or PCI. This was accomplished by a lowering of the CMV-to-eGFR ratio; and thus, a left-ward shift of the renal function-based contrast dose curve. The overall magnitude of the CMV saved was both clinically meaningful and statistically significant. The device was easy to set up and use and no device related complications were observed. In the majority of cases, the CMV delivered was less than the predefined CMV threshold. The observed AKI rate in this study was significantly lower than predicted and adds to the large body of data suggesting that strategies to reduce CMV can result in improved patient outcomes.

Diagnostic CAG and PCIs are among the most common procedures using intra-arterial CM and AKI remains one of the most common and expensive complications in this population. There is a large body of data suggesting that higher renal function-adjusted CM dose is associated with a higher risk of AKI.[4,19–27] While the exact threshold for defining renal safety remains debatable, it is clear that patients who receive higher CM doses are at greater risk of AKI, compared with those who receive lower doses. Furthermore, recent data suggest that collaborative efforts to reduce CMV have been associated with a reduction in the incidence of AKI.[13–15]

Current PCI performance standards support careful ascertainment of CMV in patients undergoing PCI although this practice remains far from universal. A recent landmark study of over 1.3 million PCIs by Amin et al. demonstrated inconsistent and significant variation in contrast use among physicians and minimal reduction in CMV for patients at higher risk for AKI.[28] In a recent physician survey carried out by SCAI, 40% of respondents reported estimating CMV without using a measurement technique and 40% of respondents reported not using CMV threshold limits for patients at risk of AKI.[29]

The average volume of CM administered to the patients in this study (67 mL) compares favorably with the volume administered in recent randomized controlled trials (median of 85 mL reported in the PRESERVE trial[30]) or in routine clinical practice (mean of 198 mL reported by Amin et al.[28] and 168 mL reported by Gurm et al.[31]). Concurrent with the reduction in CMV, the use of DyeVert Plus resulted in a shift in the actual versus attempted CMV/eGFR ratio. Since the association between AKI and CMV/eGFR is non-linear, a left-ward shift would be expected to significantly reduce the incidence of AKI. Indeed, none of the patients in whom the CMV/eGFR ratio was less than 1, developed AKI. Further studies to explore the utility of this threshold in high risk patients are warranted.

The DyeVert Plus System probably impacts contrast dose via two related yet equally important mechanisms. First, by minimizing wasted reflux into the aortic root, the system directly reduces the CMV administered to the patient. Second, by providing direct monitoring of the total CMV delivered to the patient, the system provides direct feedback to the operator and permits modifying the procedure to ensure that the predetermined CM threshold is not exceeded. Finally, the DyeVert Plus System attunes the entire catheterization laboratory to the importance of CM thresholds and CMV minimization and potentially helps drive renal safety in the catheterization laboratory.

4.1 | Study limitations

We used an objective performance criterion based on published literature instead of a concurrent control group. Additionally, data on CI-AKI should be construed as hypothesis-generating as postprocedure laboratory data were not available on all patients and CI-AKI was based only on clinically available subject data. AKI events were not available beyond discharge and were not centrally adjudicated. However, the system did significantly reduce administered CM dose, which has been shown to directly correlate with CI-AKI in prior studies.

5 | CONCLUSION

These data suggest DyeVert Plus System use in CKD subjects undergoing CAG and/or PCI procedures results in statistically significant and clinically meaningful CMV savings while maintaining image quality. CMV savings resulted in a meaningful proportion of subjects moving to lower contrast volume-to-eGFR ratios and exploratory analyses

showed that CI-AKI event rates were significantly lower in subjects with lower contrast volume-to-eGFR ratios.

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CONFLICT OF INTEREST

H Gurm: Consultant—Osprey Medical, Research funding—NIH, Blue Cross Blue Shield of Michigan Foundation.

JL Thomas: Research funding—Osprey Medical.

G Kumar: Consultant-Osprey Medical.

None of the other authors have a direct conflict related to this study.

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