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PERIPHERAL VASCULAR DISEASE

Original Studies

Contrast Induced-Acute Kidney Injury following Peripheral Angiography with Carbon Dioxide versus Iodinated Contrast Media: A Meta-Analysis and Systematic Review of Current Literature

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Objective: We conducted a meta-analysis to compare the incidence of acute kidney injury (AKI) with carbon dioxide (CO_2) versus iodinated contrast media (ICM). Background: Contrast induced-acute kidney injury (CI-AKI) is a known complication following endovascular procedures with ICM. CO_2 has been employed as an alternative imaging medium as it is nontoxic to the kidneys. Methods: Search of indexed databases was performed and 1,732 references were retrieved. Eight studies (7 observational, 1 Randomized Controlled Trial) formed the meta-analysis. Primary outcome was AKI. Fixed effect model was used when possible in addition to analysis of publication bias. Results: In this meta-analysis, 677 patients underwent 754 peripheral angiographic procedures. Compared with ICM, CO_2 was associated with a decreased incidence of AKI (4.3% vs. 11.1%; OR 0.465, 95% CI: 0.218-0.992; $P = 0.048$). Subgroup analysis of four studies that included granular data for patients with chronic kidney disease (CKD) did not demonstrate a decreased incidence of AKI with CO_2 (4.1% vs. 10.0%; OR 0.449, 95% CI: 0.165–1.221, $P = 0.117$). Patients undergoing CO_2 angiography experienced a higher number of nonrenal events including limb/abdominal pain (11 vs. 0; $P = 0.001$) and nausea/vomiting (9 vs. 1; $P = 0.006$). Conclusions: In comparison to ICM, CO_2 use is associated with a modestly reduced rate of AKI with more frequent adverse nonrenal events. In studies that use CO_2 as the primary imaging agent, the average incidence of AKI remained high at 6.2%—supporting the concept that factors other than renal toxicity from ICM may contribute to renal impairment following peripheral angiography.

Key words: contrast agents; angiography; peripheral/renal; acute kidney injury

Additional Supporting Information may be found in the online version of this article.

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Conflict of interest: Nothing to report.

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INTRODUCTION

Acute kidney injury (AKI) and more specifically, iodinated contrast induced-acute kidney injury (CI-AKI), remains a concern in patients undergoing invasive endovascular procedures. Most recent studies have suggested an incidence of AKI in the context of endovascular procedures to be at least 10% [1,2]. Given the well-established nephrotoxic effect of iodinated contrast media (ICM), the use of carbon dioxide (CO_2) imaging has emerged as an alternative method of peripheral vascular angiography [3]. The attractive qualities of CO_2 angiography include no potential for allergic reactions and no direct renal toxicity. However, concerns about air contamination, variable image quality, and induction of ischemic symptoms have all limited ubiquitous use of this modality. In general, there exists a paucity of randomized data reporting AKI outcomes with CO_2 as compared to ICM-based angiography. The purpose of this systematic review and meta-analysis was to collect and evaluate the published data regarding the comparative impact of each imaging medium on renal function and adverse reactions in patients undergoing abdominal and lower extremity endovascular procedures.

METHODS

Cohorts and Outcomes

The investigators developed a data extraction protocol that detailed the specific objectives, study selection criteria, clinical outcomes and statistical methods. This protocol was centered on three prospectively defined cohorts. The first cohort (cohort A) included randomized and nonrandomized double arm studies that compared outcomes with CO_2 versus ICM angiography, cohort B included single arm studies reporting outcomes with CO_2 as the primary imaging agent and cohort C included studies reporting outcomes with ICM as primary agent. The primary outcome studied was AKI as defined by each study. Secondary outcomes including nonrenal adverse events such as death, myocardial infarction, vapor lock phenomenon (obstruction of blood flow secondary to trapped bolus of gas in a blood vessel), nausea/vomiting, cholesterol emboli, and need for dialysis were also extracted where available. The following protocol was applied to all three cohorts.

Data Sources and Searches

We identified all published studies that reported outcomes for patients undergoing angiography with CO_2 and ICM using MEDLINE (1984 to week 2 of February 2016) and EMBASE (1985 to week 2 of February 2016) electronic databases. Search Terms included "AKI," "CO_2," "ICM," "CI-AKI," and "angiography." We supplemented our search strategy by manually reviewing all references in the retrieved articles.

Study Selection

Two reviewers (S.S.G and J.W) performed study selection. Studies were considered for an initial review if they met any of the following selection criteria: all randomized controlled trials (RCT) comparing primary outcomes with CO_2 in one arm and ICM in the other arm, all double arm prospective and retrospective observational studies comparing CO_2 and ICM, all single arm observational studies reporting incidence outcomes with CO_2 and all observational and randomized studies reporting incidence outcomes with ICM.

Data Extraction

Data extraction was carried out per the PRISMA (Providing Innovative Service Models and Assessment) criteria [4]. The reviewers independently extracted data on study (year of publication, PubMed ID, design, population demographics, comorbidities (smoking, coronary artery disease, diabetes mellitus, hypertension, chronic kidney disease [CKD]), type and details of procedure (diagnostic, therapeutic, anatomical site involved), type of contrast used (CO_2, ICM), amount of contrast used (ml), injection technique, and the definition of AKI used. If outcomes or relevant data were missing in the publication the reviewers contacted the primary authors for source data.

Statistical Analysis

Statistical analysis was carried out using Comprehensive Meta-Analysis software (Biostat; Englewood, NJ) version 3.3.070. We determined pooled Odds Ratio (OR) and corresponding 95% Confidence Intervals (CI) for the development of CI-AKI for cohort A. To calculate incidence data for cohorts B and C an aggregate effect size weighted by sample size was computed to provide overall effect size across studies. The adequacy of pooling data across studies was assessed using the Cochran Q and the Higgins and Thompson I^2 test for heterogeneity where a significant Q statistic suggests that the distribution of effect size around the mean is greater than would be predicted from sampling error alone, whereas I^2 provides an estimate of the proportion of the variance in the aggregate effect size that is attributable to between-studies heterogeneity [5]. We preferred to employ fixed effect model based on the Mantel–Haenszel method. Results from our analysis were compared to the random effects model (DerSimonian and Laird) [6]. In the absence of between study variance, the two methods give similar results. Random effects model was

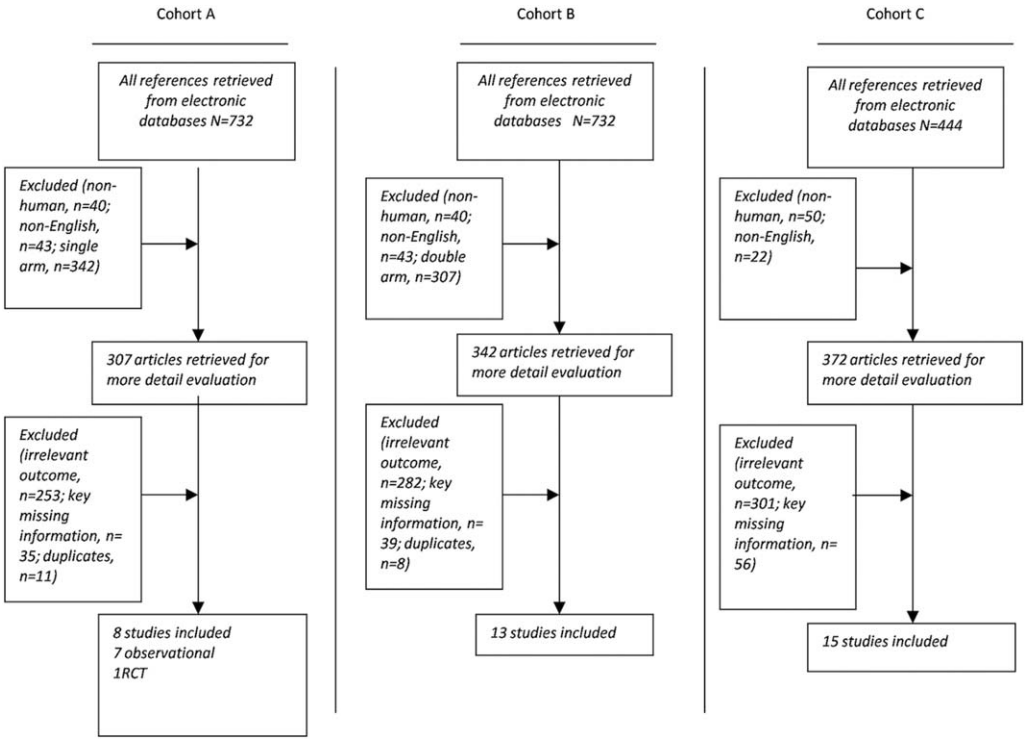

Fig. 1. Study selection for cohorts A, B, and C.

employed where interstudy heterogeneity was a concern. A probability value of <0.05 was considered statistically significant. Publication bias was addressed using funnel plots of effect size versus standard error and Eggers regression intercept where a P value of <0.20 was considered statistically significant for publication bias [7]. Subgroup analysis was performed for studies reporting data specific to patients with baseline CKD as defined in each study.

RESULTS

Study Identification and Selection

This meta-analysis included three different sets of studies identified as separate cohorts as described above. Figure 1 represents an illustration of the search strategy.

Analysis

Cohort A (comparative studies of ICM vs. CO_2). The characteristics of eight studies are shown in Table I and Table S1 (Supporting Information), respectively. Overall, we identified seven nonrandomized comparative studies and 1 RCT. These eight studies contained a total of 677 patients who underwent 754 procedures, year of publication ranged from 1995 to 2015. Of the 677 patients, the number of individuals in the CO_2 and ICM groups was 185 and 492, respectively. The mean age for the CO_2 group was 69 ($\pm$ 6.1) years while that for ICM group was 69.5 ($\pm$ 4.8) years. As shown in Table I, the definition of CI-AKI varied across studies with the majority ($n = 4$, 50%) of them using more than 25% rise in serum creatinine from baseline as a parameter and 48 hr as the cutoff for measuring post procedure creatinine. As shown in Table S1 Supporting Information, all studies employed use of preprocedure hydration, however, volume and technique was variable and often not precisely reported. Gross incidence of AKI for CO_2 was 4.3% while that for ICM was 11.1%. Pooled odds ratio favored CO_2 over ICM (OR 0.465; CI 0.218–0.992; $P = 0.048$) as shown in Fig. 2. Test for heterogeneity showed a Q value of 6.998, $P = 0.429$ and $I^2 < 0.001$ and since there was no evidence of heterogeneity we used the fixed model analysis for this cohort. Overall, six studies reported a decreased incidence of AKI in the CO_2 group when compared to the ICM group. A subgroup analysis (Fig. 3) of four studies that included patients with baseline CKD (defined as serum creatinine > 1.5 mg/dl in two studies, >1.8 mg/dl in one study, and not defined in one study) did not show a statistically significant difference between the two contrast media (4.1% vs. 10.0%; OR 0.449; CI 0.165–0.1221; $P = 0.117$).

Patients undergoing CO_2 angiography experienced a higher number of nonrenal adverse events versus ICM, such as limb/abdominal pain (11 vs. 0, OR 77.185; CI

TABLE I. Procedural Details for Cohort A

Study	Type	Group	*n*	Anatomy	Procedure	CI-AKI definition	F/u renal function(hr)	Mean CO2 Volume(ml)	ICM type	Mean ICM volume(ml)
Stegemann et al., 2015 [8]	R	**CO2**	37	IF=21, Pop=6, BTK=10	PTA=53	rise in serum creatinine of >25% or >0.5 mg/dL.	48	31.9	iodixanol	34
		ICM	154	IF=126, Pop=7, BTK=21	PTA=203	rise in serum creatinine of >25% or >0.5 mg/dL.	48	*	iodixanol	113
Knipp et al., 2010 [9]	R	**CO2**	4	Abd=4	Evar=4	Not Defined	24	443	*	*
		ICM	7	Abd=7	EVAR=7	Not Defined	24	33	ICM	110
Chao et al., 2007 [10]	R	**CO2**	16	Abd=16	EVAR=16	>20% rise in serum Creatinine at 24 hours	24	50	iopamidol	27
		ICM	84	Abd=84	EVAR=84	>20% rise in serum Creatinine at 24 hours	24	*	iopamidol	148
Liss et al., 2005 [11]	RCT	**CO2**	37	Renal=37	Diagnostic=10, PTA=27	increase in serum creatinine ofmore than 25%	48	191	ioxaglate	35.1
		ICM	45	Renal=45	Diagnostic=13, PTA=32	increase in serum creatinine ofmore than 25%	48	*	ioxaglate	88.4
Dowling et al., 2003 [12]	R	**CO2**	51	Abd=7, Renal=2, IF=36, Pop=1, BTK=0	Diagnostic=51	rise in creatinine of 1.0 mg/dL over baseline	48	380	*	*
		ICM	49	Abd=22, Renal=3, IF=37	Diagnostic=49, PTA=10	rise in creatinine of 1.0 mg/dL over baseline	48	380	iodixanol, iohexol	37
Sterner et al., 2001 [13]	R	**CO2**	8	Abd=4, Renal=4	Diagnostic=4, PTA=8	rise in serum creatinine of >25%	336	*	*	*
		ICM	110	Abd=21, Renal=24, IF=29, Other=35	Diagnostic=48, EVAR=37, PTA=73	rise in serum creatinine of >25%	336	*	iohexol, iodixanol	16
Spinosa et al., 1999 [14]	P	**CO2**	24	Renal=24	Diagnostic=15, PTA=10	Increases in serum creatinine of more than 0.5 mg/dl	48	40	*	*
		ICM	25	Renal=25	Diagnostic=12, PTA=13	Increases in serum creatinine of more than 0.5 mg/dl	48	*	ICM	*
Frankhouse et al., 1995 [15]	R	**CO2**	8	IF=8	Diagnostic=8	rise in serum creatinine of >25%	24	250	*	*
		ICM	18	Renal=2, IF=15, BTK=2	PTA=19	rise in serum creatinine of >25%	24	*	ICM	39

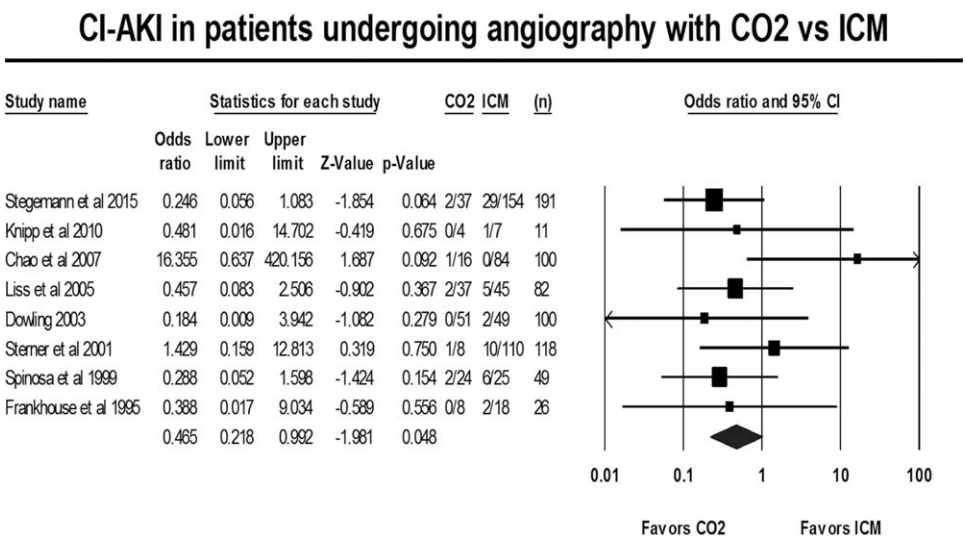

Fig. 2. CI-AKI in patients undergoing angiography with CO_2 versus ICM.

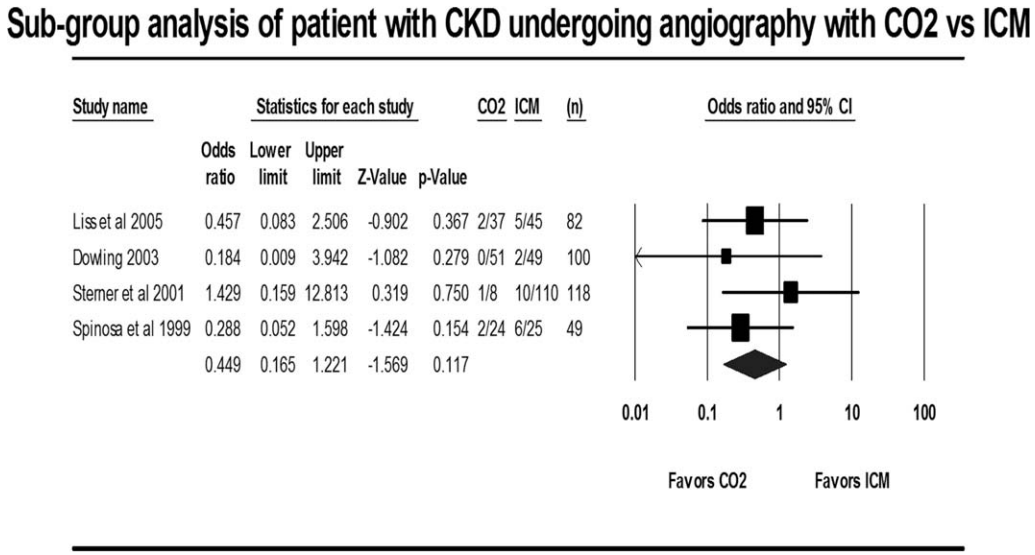

Fig. 3. Subgroup analysis of patients with CKD undergoing angiography with CO_2 versus ICM.

8.905–668.981, $P = 0.001$), nausea/vomiting (9 vs. 1, OR 12.306; CI 2.081 vs. 72.773 $P = 0.006$), with no differences in death (2 vs. 2, OR 3.271; CI 0.495–21.633, $P = 0.219$). No statistical differences were noted between CO_2 and ICM regarding the need for renal replacement therapy (0 vs. 2, OR 0.384; CI 0.037–4.009, $P = 0.424$). Meta-regression analysis between incidence of AKI and multiple covariates including year of publication ($P = 0.758$), supplemental ICM dose ($P = 0.991$) and definition of CI-AKI used ($P = 0.258$) did not show any significant associations. Egger's regression analysis for cohort A revealed a P value of 0.248. Hence there was no evidence of publication bias. Figure S1 Supporting Information shows the corresponding funnel plot. Given the possibility that AKI pathophysiology has changed overtime, an addition analysis was conducted with studies published after the year 2000, no significant changes were found in the results, data is not reported.

Cohort B (CO_2 only outcomes). Thirteen studies identified a total of 1,414 patients who underwent 2,006 procedures using CO_2 as the primary imaging agent. The characteristics of the studies are shown in Table II and

TABLE II. Procedural Details for Cohort B

Study	Type	*n*	Anatomy	Procedure	CI-AKI Definition	f/u renal function (hours)	Mean Volume of CO2 (ml)	ICM used	Mean ICM volume (ml)
Kawasaki et al., 2015 [16]	R	18	Renal=18	PTA=18	increase of 20% in the serum creatinine	48	244	none	*
Fujihara et al., 2015 [17]	P	98	Renal=16, If=93	PTA=109	increase in creatinine level 0.5 mg/dL or greater than 25%.	72	281.4	yes	15
Palena et al., 2015 [18]	P	36	IF=14, Pop=33, BTK=17	Diagnostic=72, PTA=72	rise in serum creatinine of >0.5 mg/dL.	24	395	yes	54
Sueyoshi et al., 2015 [19]	P	40	Abd=40,	Diagnostic=40	Not defined	24	*	yes	128
Scalise et al., 2015 [20]	P	40	IF=25, BTK=15	DIagnostic=40	Not defined	48	240	yes	150
Penzkofer et al., 2014 [21]	P	5	Renal=5	DIagnostic=5	Not defined	24	*	none	*
Moos et al., 2011 [22]	R	991	Abd=527, Renal=164, IF=347, Venous=375, Other=296	Diagnostic=1, 007, EVAR=62, PTA=94, Other=343	rise in serum creatinine of >0.5 mg/dL.	48	186	yes	8.5
Lee et al., 2010 [23]	P	17	Renal=17	EVAR=17	Not defined	24	*	yes	59
Criado et al., 2008 [24]	R	18	Renal=23	EVAR=18, Other=5	increase in creatinine level 0.5 mg/dL or greater than 25%.	24	363	yes	44
Spinosa et al., 2001 [25]	P	95	Renal=95	Diagnostic=26, PTA=69	rise in serum creatinine of >0.5 mg/dL.	48	250	none	*
Fitridge et al., 1999 [26]	P	28	Renal=7, IF=21	Diagnostic=28, PTA=8	rise of serum creatnine by 0.044 mmol/litre or an overall increase of 20%	72	23	yes	23
Caridi et al., 1999 [27]	P	15	Renal=23	PTA=23	rise in serum creatinine of >0.5 mg/dL.	48	129	yes	15
Spinosa et al., 1998 [28]	P	13	Abd=11, IF=2	Diagnostic=9, PTA=4	rise in serum creatinine of >0.5 mg/dL.	24	40	none	*

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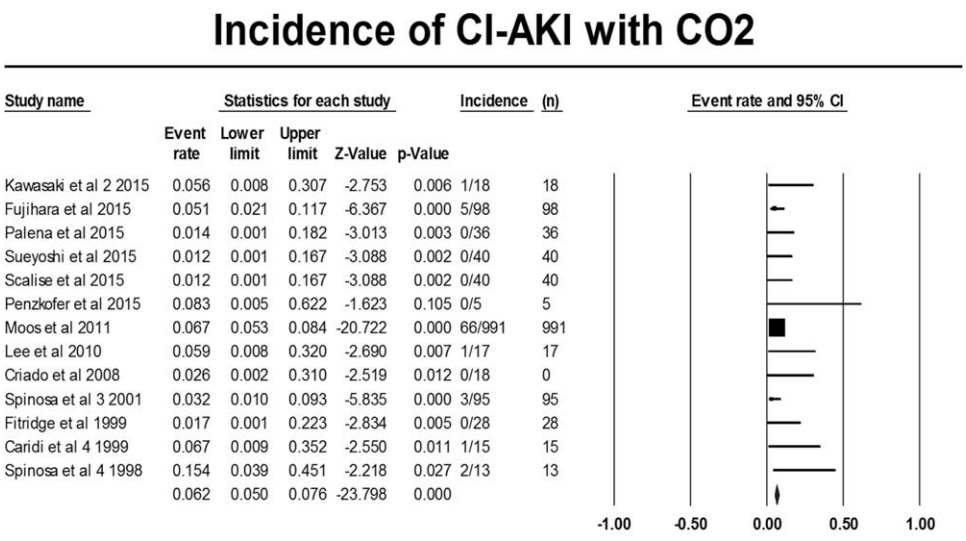

Fig. 4. Incidence of CI-AKI with CO_2.

Supporting Information Table S2, respectively. Studies were published from the year 1998 to 2015. The meta-analysis found an overall event rate of AKI in patients undergoing angiography with CO_2 of 6.2% (95% CI 0.050–0.076; $P < 0.001$) as shown in Fig. 4. Heterogeneity was low (Q value= 9.070, $I^2 < 0.001$) hence we used the fixed effect analysis for this cohort. Egger's regression analysis for cohort B demonstrated a P value of 0.05 which suggested publication bias. Figure S2 Supporting Information shows the corresponding funnel plot.

Cohort C (ICM only outcomes). The 15 studies identified a total of 11,354 patients who underwent 11,525 procedures with the use of ICM as the contrast agent. The characteristics of the studies are shown in Table III and Supporting Information Table S3, respectively. Studies were published between 2003 and 2016. The meta-analysis found an overall event rate for AKI of 9.4% (95% CI 0.068–0.127) in patients undergoing angiography with ICM as shown in Fig. 5. This indicated an incidence of 9.4 for every 100 (or 9.4%) patients undergoing angiography with ICM. Heterogeneity was high in this cohort (Q value = 177.364, $I^2 = 92.10$) hence the random effect analysis was used. Egger's regression analysis for cohort C demonstrated a P value of 0.002, suggesting publication bias. Figure S3 Supporting Information shows the corresponding funnel plot.

DISCUSSION

This is the first meta-analysis to describe the renal and safety outcomes of ICM and CO_2 and their clinical application as contrast agents for peripheral angiography. Cohort A, our primary cohort, suggests a modest decrease in the incidence of AKI with CO_2 as compared to ICM (OR 0.465, $P = 0.048$). The overall incidence of AKI as reported separately (cohorts B, C) following CO_2 and ICM angiography was 6.2% and 9.4%, respectively. There was no significant difference in AKI between CO_2 and ICM angiography in patients with baseline CKD. The analysis also demonstrated a higher incidence of nonrenal events including limb and abdominal pain, nausea and vomiting with CO_2 as compared to ICM. There was no difference in mortality between the two modalities.

CO_2 as an Imaging Agent

As the prevalence of diabetes, CKD, and peripheral arterial disease (PAD) continues to rise, an increasing number of patients will present for endovascular therapy and be exposed to the risk of CI-AKI [44]. The use of digital subtraction imaging with ICM remains the most common angiographic approach in patients with symptomatic PAD [45]. Pharmacologic measures to reduce the incidence of CI-AKI have been largely ineffective—with volume expansion and minimization of ICM as the most adopted techniques to prevent this complication.

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TABLE III. Procedural Details for Cohort C

Study	Type	*n*	Procedure (*n*)	Procedure type	CI-AKI definition	F/u renal function (hours)	ICM type	Mean ICM volume (ml)
Peng et al., 2016 [29]	P	204	204	Peri=204	Increase in serum creatinine level ≥ 25% or ≥ 0.5 mg/dL at 72 hours post procedure	72	Iodixanol	138.7
Kim et al., 2015 [30]	R	240	240	Peri=240	Increase in serum creatinine level ≥ 25% or ≥ 0.5 mg/dL	48	Iodixanol	158.4
Yang et al., 2014 [31]	P	305	305	Peri=305	Increase in serum creatinine level ≥ 25%	48	Iohexol Iodixanol	97.7
Arora et al., 2013 [32]	R	684	744	Peri=744	Acute Kidney Injury Network (AKIN) criteria	192	Iodixanol	*
Hafiz et al., 2012 [33]	RCT	320	320	Coro=195, Peri=105, Other=20	Increase in serum creatinine level > 25% or > 0.5 mg/dL	48	Iodixanol Iopamidol Ioversol	110
Karlsberg et al., 2011 [34]	P	253	253	Peri=253	Increase in serum creatinine level ≥ 25%	24	Iodixanol Low osmolar contrast	235
Plaisance et al., 2011 [35]	R	7, 769	7, 769	Peri=7, 769	Increase in serum creatinine level > 0.5 mg/dL	*	*	*
Sadat et al., 2011 [36]	RCT	40	40	Peri=40	Increase in serum creatinine level > 25%	72	Iopamidol	73
Karlsberg et al., 2010 [37]	P	250	250	Peri=250	Increase in serum creatinine level > 25%	24	Iodixanol Iopamidol Ioversol Iohexol Iopromide	235
Lawlor et al., 2007 [38]	RCT	78	78	Peri=78	Increase in serum creatinine level ≥ 25% or increase of ≥ 0.5 mg/dL	48	*	162
Sandhu et al., 2006 [39]	RCT	106	106	Visc=32, Peri=74	Increase in serum creatinine level ≥ 25% or increase of ≥ 0.5 mg/dL	48	Iodixanol Iopamidol	137
Erley et al., 2004 [40]	RCT	11	11	Peri=11	Decrease in estimated glomerular filtration rate of > 50%	48	iohexol	49
Rashid et al., 2004 [41]	RCT	94	94	Peri=94	Increase in serum creatinine level > 20%	48	iohexol	143
Srodon et al., 2003 [42]	P	191	302	Peri=302	Increase in serum creatinine level > 25%	72	Iohexol Iodixanol	*
Alamartine et al., 2003 [43]	P	809	809	Coro=404, Peri=138, Other=266	Increase in serum creatinine level > 25%	*	Iomeprol Oxaglic acid Iodixanol Oxitalamic acid	80gm

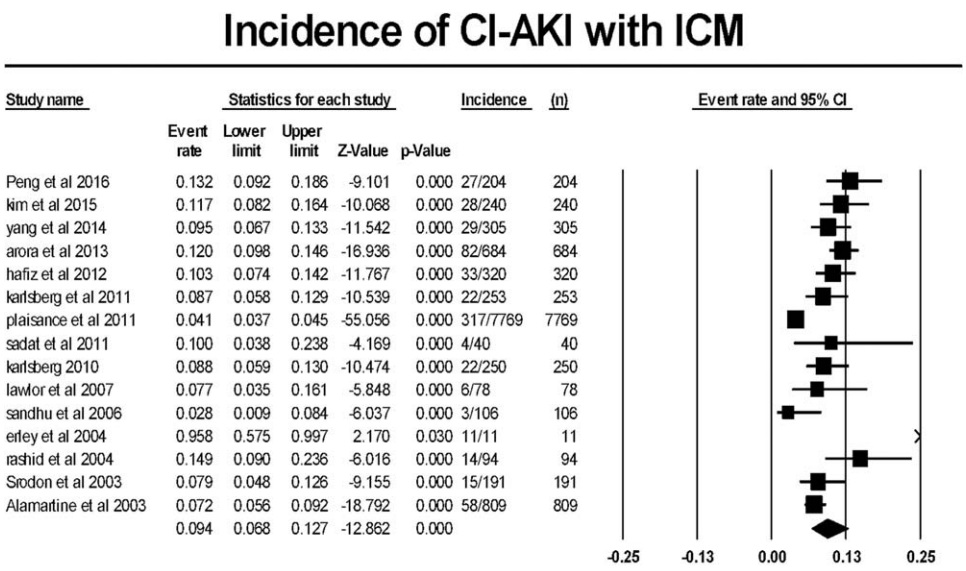

Fig. 5. Incidence of CI-AKI with ICM.

The renal toxicity of ICM has been well described and for these reasons CO_2 represents an attractive alternative contrast medium. The ability of CO_2 to provide vascular imaging is related to its chemical properties, which permits it to rapidly dissolve into the target vessel lumen where it displaces the blood pool, allowing for a negative X-ray image to be produced [17]. Due to potential neurotoxicity and risk of cardiac arrhythmias, it is avoided in the thoracic aorta, coronary arteries and cerebral circulation.

Initially employed in radiologic procedures to outline retroperitoneal structures, CO_2 gained use in the 1970s to support imaging during infra-diaphragmatic procedures of the lower extremity, abdominal, renal and hepatic vasculature [3,46]. More recently it has been explored as an alternate contrast medium of choice for peripheral angiographic procedures in patients who are high risk for CI-AKI [3].

Review of Literature: Incidence of CI-AKI across Multiple Levels of Evidence

While the aforementioned theoretical advantages of CO_2 are clear, implementation of this imaging modality into clinical practice has been limited. Few well-constructed studies are available to guide the utility of CO_2 angiography with the aims of AKI prevention and to rigorously vet safety and image quality. In the literature review, we found three RCTs that compared renal outcomes between CO_2 and ICM. Despite variable definitions for AKI, these studies appeared to favor the use of CO_2 with regards to renal injury [11,47,48]. A small number of nonrandomized prospective and retrospective studies have also compared the two contrast agents. In 2015, Stegemann et al. studied the safety and efficacy of CO_2 and found that the supplemental use of CO_2 decreased the total volume of ICM used for each procedure [8].

Single arm retrospective or prospective studies make up the larger body of reported literature with respect to CO_2. While four contemporary studies have reported 0% incidence of AKI in their subjects, Fujihara et al. recently reported the results of a multicenter prospective registry of patients undergoing peripheral angiography with CO_2 as the primary contrast agent. This study noted the incidence of AKI with CO_2 to be 5.1% [17]. These findings are comparable to data from Moos et al. who reported outcomes in 991 patients undergoing various vascular procedures with CO_2 as the only contrast or used in supplement with ICM. These authors found an overall 6.6% incidence of CI-AKI [22]. The etiology of AKI in patients receiving CO_2 as the primary imaging medium is not clear. CO_2 does not have direct renal toxicity and as a physiologic corollary supporting this statement, Palm et al. studied medullary blood flow in the rat kidney after injection of CO_2 or ICM (ioxaglate), and noted a pronounced decrease in medullary blood flow and renal O_2 concentration after injection of ICM while this effect was not seen with CO_2 [49]. There are, however, numerous practical considerations which may

explain AKI development following the use of CO_2 in patients. The vapor lock phenomena, which occurs when rapid or excessive administration of gas leads to air trapping within the vascular column subsequently causing obstruction of blood flow, could lead to organ ischemia and air trapping involving the renal arteries. Nearly ubiquitous and poorly characterized is the phenomenon of atheroembolization, which occurs as a result of catheter and equipment manipulation in the peripheral circulation. Showering of debris into the systemic circulation and into the renal vascular bed may be an important mechanism of AKI—independent of contrast administration [50]. In addition, in our analysis with cohort A, the average amount of ICM used for the ICM only arm was 78.7 (± 48.8) ml, while the average adjunctive ICM use for the CO_2 arm was 32.1 (± 4.3) ml. The adjunctive use of ICM with CO_2 likely still exposes patients to some degree of renal toxicity—the magnitude of this effect remains unclear.

CO_2 Use in Patients with CKD

Patients with CKD are vulnerable to CI-AKI and the use of preventive measures and/or alternative contrast has been extensively studied for these individuals [51]. Depending on risk factors and definition, the incidence of CI-AKI in patients with CKD undergoing invasive angiography is reported to be as high as 40–50% [52]. In the present meta-analysis, we did not find any statistical difference in the incidence of AKI between CO_2 and ICM in patients with baseline CKD. This finding should be taken in light of some limitations. The cumulative sample size for the studies with specific data on subgroup of patients with CKD was relatively small ($n = 349$). Granular details on overall AKI risk for the subjects, specifics on periprocedural hydration and medication management were not provided in these studies.

Nonrenal Adverse Events with CO_2

Our analysis of the literature noted a higher incidence of limb and abdominal pain as well as nausea and vomiting in patients receiving CO_2 versus ICM. Fujihara et al. reported an overall 17.3% rate (17 events out of 98 cases) of nonrenal events (limb pain/abdominal pain)—including two deaths attributable to CO_2 use [17]. Kawasaki et al. reported that 14.6% of patients undergoing CO_2 angiography complained of transient lower extremity pain, while Madhusudan reported this incidence to be 4.8% employing the use of a customized delivery system for intra-arterial injections [53,54]. The mechanisms underlying these effects in individual studies were not elucidated but likely involved either the vapor lock phenomenon or transient symptoms from blood displacement. It should be noted that potential air contamination of gas has also remained a concern with CO_2 injection and can contribute to the development of more severe ischemic effects.

Imaging Quality with CO_2

A challenge with CO_2 has been inferior imaging quality when compared to ICM-based angiography. The use of quantitative contrast opacification analysis or blinded qualitative review of CO_2-based images has not been performed in the majority of studies [2]. Fujihara et al. attempted semiquantitative analysis of angiographic sequences using two independent observers and graded the images from Types 1–3 (Type 1: the vessel and stenosis are completely visualized, Type 2: the vessel can be evaluated but the degree of stenosis cannot be measured, Type 3: no evaluation can be made). The authors reported that clinically acceptable evaluation of the vessel lumen and stenosis (Type 1 angiograms) by CO_2 alone in the majority (63%) of the superficial femoral artery cases [17]. However, only 22.6% of aortoiliac and 31.2% of renal artery stenosis angiograms had Type 1 angiograms—with an overall Type 3 (uninterpretable) rate of 12%. The need for adjuvant contrast administration and augmentation of lesion interrogation by intravascular ultrasound and pressure wires was required in several cases. The authors also noted that the limitations in the abdominal imaging (aortoiliac and renal beds) were often due to the presence of bowel loops and gas. It has been observed that in many studies, above the knee CO_2 imaging results are superior to infra-popliteal imaging—with diagnostic accuracy reported as low as 50% in this latter anatomical region [21,23]. However, Palena et al. reported 89.8% accuracy in patients with severe infra-popliteal arterial disease (vs. 94.4% for supra-popliteal lesions)—attributing this higher accuracy to the use of an automated CO_2 injection system as opposed to a conventional hand injection system [18]. Despite the lack of rigorous image analysis in the literature, the sum of the data would suggest that CO_2 angiography has significant challenges with respect to consistent high quality vessel imaging.

Study Limitations

The present meta-analysis has a number of limitations—including a lack of available data from RCTs with respect to outcomes with CO_2. Given the paucity of data, we had to pool the outcomes from all available observational and randomized trials that were available in published literature. Second, we also found that some authors chose not to report incidences of nonrenal events including limb ischemia/pain, nausea, vomiting, allergic reactions and mortality rate. Many studies also lacked data on subject baseline characteristics, periprocedural

hydration, management of diuretics and potential nephrotoxins, hemodynamic state, and ICM type and volume. We found variable criteria used for AKI—although most studies tend to use a rise in serum creatinine > 25% from baseline as the definition. In the previously reported literature, the definition of AKI can significantly impact the reported outcomes and can make it difficult to interpret comparative data. Last, we were unable to obtain patient level data and relied on published data only.

CONCLUSIONS

In comparison to ICM, CO_2 angiography is associated with a modestly decreased overall incidence of AKI—with more frequent nonrenal adverse events. There is no evidence in the present meta-analysis that CO_2 imaging reduces the occurrence of AKI in patients with CKD. In studies that use CO_2 as the primary imaging agent, the average incidence of AKI was 6.2%—supporting the concept that factors other than renal toxicity from ICM may also contribute to renal impairment following peripheral angiography.

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