Carbon dioxide as a promising alternative to iodinated contrast media for lower extremity endovascular procedures (Review)

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Abstract. Carbon dioxide (CO_2) angiography has emerged as an alternative contrast agent for arterial endovascular procedures, particularly in patients at increased risk of complications from iodinated contrast media (ICM). The present review evaluates the clinical circumstances in which carbon dioxide (CO_2) angiography can reduce the use of iodinated contrast media (ICM) during arterial endovascular procedures, with particular attention to renal-risk reduction, image quality, anatomical limitations, and procedure-related complications. A narrative literature review was performed using PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and CENTRAL. Search terms included carbon dioxide angiography, CO_2 contrast, ICM, peripheral artery disease, endovascular intervention, chronic kidney disease (CKD), contrast-associated acute kidney injury (AKI), digital subtraction angiography, and digital variance angiography. Peer-reviewed clinical studies, systematic reviews, technical reports, and guideline documents relevant to vascular applications of CO_2 were included. Additional PubMed-indexed studies were incorporated to strengthen the discussion of kidney-risk terminology, lower-extremity outcomes, and contemporary evidence. The most consistent evidence supports CO_2 angiography as an ICM-sparing strategy for iliac and lower extremity interventions, especially in patients with CKD, previous post-contrast AKI, or ICM hypersensitivity. CO_2 reduces iodine exposure and may contribute to reducing contrast-associated renal complications while preserving procedural success in selected lesions. However, image quality is influenced by buoyancy, catheter position, patient positioning, vascular orientation, and post-processing. Evidence for abdominal aortic and transplant renal artery applications is less uniform, and mesenteric use is limited by clinically important ischemic complications. Arterial use above the diaphragm remains contraindicated due to the risk of cerebral or coronary gas embolism. CO_2 angiography should not be regarded as a universal substitute for ICM. Its strongest role is as a renal-sparing alternative or adjunct in infra-diaphragmatic peripheral arterial interventions, particularly in lower extremity disease. Safe implementation requires appropriate patient selection, closed or automated delivery systems, standardized injection protocols, pain management, and awareness of anatomical contraindications.

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Abbreviations: AKI, acute kidney injury; CA-AKI, contrast-associated acute kidney injury; CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; DSA, digital subtraction angiography; DVA, digital variance angiography; eGFR, estimated glomerular filtration rate; EVAR, endovascular aneurysm repair; ICM, iodinated contrast media; NOMI, non-occlusive mesenteric ischemia; PC-AKI, post-contrast acute kidney injury; rAAA, ruptured abdominal aortic aneurysm; SNR, signal-to-noise ratio

Key words: carbon dioxide angiography, iodinated contrast media, peripheral artery disease, endovascular intervention, chronic kidney disease, contrast-associated acute kidney injury, digital subtraction angiography

Contents

1. Background

In 1924, Brooks reported the first clinical application of sodium iodide as a contrast agent for lower extremity angiography to determine amputation levels in patients with peripheral vascular disease (1). Since then, iodinated contrast media (ICM) have become the standard contrast agents for diagnostic angiography and endovascular interventions due to their high X-ray attenuation and reliable vascular opacification. However, despite their widespread use, ICM administration has been associated with adverse effects, including renal injury potentially mediated by osmotic load, viscosity, and other patient- and procedure-related factors (2). Contrast-associated acute kidney injury (CA-AKI), previously termed contrast-induced acute kidney injury (CI-AKI), remains a clinically relevant concern, particularly among patients with pre-existing chronic kidney disease (CKD) and other risk factors, including diabetes mellitus, advanced age, heart failure, hypotension, and nephrotoxic medication exposure. The terminology used to describe kidney injury after contrast exposure has evolved. Older vascular and radiology literature frequently used contrast-induced nephropathy or CI-AKI, implying a direct causal relationship between ICM and renal injury. More recent consensus documents from radiology and nephrology groups recommend distinguishing CI-AKI from post-contrast acute kidney injury (PC-AKI) or CA-AKI, because postoperative renal deterioration often reflects multiple interacting factors rather than contrast toxicity alone (3-5). This terminology is particularly relevant in peripheral vascular interventions, where renal dysfunction may be influenced by baseline CKD, diabetes, hypotension, congestive heart failure, atheroembolism, infection, nephrotoxic medication, and perioperative dehydration.

This conceptual shift does not diminish the clinical importance of iodine reduction. Intra-arterial contrast exposure occurs in patients who may already have reduced renal reserve and systemic vascular disease. Moreover, ICM volume is one of the few modifiable procedural variables. Even when AKI is multifactorial, minimizing unnecessary ICM remains a reasonable strategy, especially when it does not compromise procedural success. In this context, CO_2 angiography is best understood as a component of renal-risk mitigation rather than as a stand-alone guarantee of renal protection.

Patients most likely to benefit are those with advanced CKD, previous PC-AKI, diabetes with reduced estimated glomerular filtration rate (eGFR), repeated planned interventions, or severe ICM hypersensitivity. Conversely, patients with normal renal function and straightforward anatomy may obtain limited incremental benefit from complete CO_2 substitution if ICM offers faster, clearer, and more reliable imaging. The decision should therefore be individualized, incorporating baseline eGFR, urgency of revascularization, lesion anatomy, expected need for branch visualization, availability of adjunctive imaging, and operator experience.

A practical renal-sparing strategy may combine pre-procedural risk assessment, hydration when indicated, avoidance of nephrotoxic drugs when clinically feasible, low-osmolar or iso-osmolar ICM when iodine is necessary, CO_2 as the primary contrast agent, and a predefined threshold for bailout ICM. Such a multimodal approach is more consistent with contemporary AKI concepts than a binary choice between CO_2 and ICM. The aim of this review is to explore under what circumstances carbon dioxide contrast can replace iodine contrast.

2. Physical and physiological characteristics of CO_2

CO_2 differs fundamentally from ICM. Iodinated agents are liquid, radiopaque materials that opacify vessels by positive contrast. CO_2 is a gas that displaces blood and produces negative contrast visualization on digital subtraction angiography (DSA). Its low viscosity allows passage through small catheters and stenotic segments, while its high solubility promotes rapid intravascular clearance (6-9). These properties underpin the renal-sparing value of CO_2 but also explain many of its limitations.

The buoyancy of CO_2 is clinically relevant. After injection, CO_2 tends to rise to the nondependent portion of the vessel lumen. This property can improve visualization of anteriorly located structures but may reduce opacification of posterior or dependent vascular segments. Patient positioning, table tilt, catheter orientation, and repeated acquisition can therefore markedly influence image quality (6,10,11). In vessels with complex geometry or slow flow, gas fragmentation and incomplete lumen filling may impair interpretation. For these reasons, CO_2 angiography is highly operator-dependent and should be viewed as a technique requiring standardized procedural discipline rather than as a simple substitution of one contrast agent for another.

CO_2 is eliminated primarily through the lungs. After intravascular administration, CO_2 dissolves in blood, diffuses into red blood cells and plasma, is transported to the pulmonary circulation, and is exhaled through the alveoli (9,12). Most injected CO_2 is cleared during a single pulmonary pass, and small intravascular volumes dissolve rapidly. Despite this favorable metabolic profile, excessive volume, rapid repeated injections, impaired pulmonary reserve, or pulmonary hypertension may increase the risk of hypercapnia or transient hemodynamic effects. Accordingly, electrocardiography, pulse oximetry, blood pressure, respiratory rate, and clinical status should be monitored during CO_2-guided procedures.

Because CO_2 is non-nephrotoxic and non-allergenic, it is particularly useful in patients with advanced CKD, previous PC-AKI, severe ICM allergy, or a clinical need for repeated angiography. However, its gas properties make it inappropriate for arterial territories in which embolization to the cerebral or coronary circulation may occur. Supradiaphragmatic arterial injection is contraindicated, including use in the thoracic aorta, coronary arteries, and cerebral circulation (6,13,14).

3. Delivery systems, imaging technique, and quality optimization

Safe CO_2 angiography depends on controlled delivery. Historically, manually assembled or homemade systems were used, but such systems can be associated with inconsistent dose control and risk of air contamination. Contemporary practice favors closed or automated delivery systems that regulate injection pressure and volume, limit atmospheric air entry, and improve reproducibility (15-17). Automated injectors may also shorten the learning curve and reduce operator-dependent variation, although they require institutional investment and staff training.

Several technical measures improve image quality. Catheter placement should be as selective as possible, because

Table I. Recommended application levels of CO_2 angiography by anatomical site.

Application site/ procedure	Recommendation	Rationale	(Refs.)
Iliac artery	Recommended in selected patients	Evidence supports substantial reduction in ICM exposure during iliac interventions without compromising technical success in suitable anatomy.	(22)
Lower extremity arteries	Recommended in selected patients	The most consistent clinical evidence supports CO_2 use for PAD/CTLI interventions, especially in CKD or ICM contraindication.	(23-29,41)
Abdominal aorta/EVAR	Consideration for selected use	CO2 may reduce iodine exposure and renal injury, but endoleak detection and visualization of posterior or complex anatomy remain inconsistent.	(10,11,15,33-35)
Renal or transplant renal artery	Usage with caution	Selective use may reduce ICM volume, but complications, adjacent mesenteric circulation, and image-quality limitations require strict monitoring.	(36-38)
Superior mesenteric artery	Not recommended for routine use	Evidence is limited and clinically significant ischemic complications, including NOMI, have been reported.	(38,39)
Supradiaphragmatic arteries	Contraindicated	Arterial injection above the diaphragm can cause cerebral or coronary gas embolism, stroke, or death.	(6,13,14)

CO_2, carbon dioxide; ICM, iodinated contrast media; PAD, peripheral artery disease; CTLI, chronic limb-threatening ischemia; CKD, chronic kidney disease; EVAR, endovascular aneurysm repair; NOMI, non-occlusive mesenteric ischemia.

CO_2 image quality decreases when the gas bolus disperses before reaching the target vessel. Injection volumes and intervals should be adjusted according to vascular bed, catheter size, and patient tolerance. Repeated injections should allow sufficient time for pulmonary clearance. Table tilt and patient positioning may be used to exploit CO_2 buoyancy, especially when visualizing anterior or nondependent structures (6,10). Image stacking, subtraction refinement, and optimized acquisition angles can also enhance vascular delineation. Kakuta and Chida demonstrated that image acquisition parameters and stacking could improve CO_2-DSA signal-to-noise performance under defined experimental conditions (18).

Digital variance angiography (DVA) has generated particular interest. DVA is a post-processing approach that enhances contrast dynamics and may improve image quality compared with conventional DSA. Pilot studies in lower extremity interventions reported higher signal-to-noise ratio (SNR) and improved image quality with DVA-processed CO_2 angiography (19,20). In selective lower extremity interventions, DVA also improved contrast-to-noise ratio and subjective image quality regardless of contrast agent, suggesting that the technique may reduce both iodine requirement and radiation burden in selected settings (21). These findings are promising, but wider adoption will require validation in larger cohorts, standardization across angiography platforms, and assessment of whether improved image metrics translate into better clinical decision-making.

4. Clinical applications by anatomical territory

The recommended clinical applications of CO_2 angiography across different anatomical territories are summarized in Table I.

Iliac and lower extremity arteries. The iliac and lower extremity arteries represent the most mature and clinically relevant clinical application of CO_2 angiography. The principal advantage is not that CO_2 is always superior to ICM, but that it can markedly reduce iodine exposure while maintaining procedural feasibility in patients at high renal risk. In iliac branched device implantation, predominant use of automated CO_2 angiography reduced ICM exposure without compromising technical success or radiation exposure (22). In femoropopliteal disease, automated CO_2-DSA achieved fair to excellent inter-rater agreement for image quality, vessel visibility, and stenosis or occlusion assessment compared with ICM-DSA (23). Automated CO_2 angiography has also been reported as feasible and safe in peripheral arterial interventions, with reductions in iodine use and radiation exposure (24).

Renal-risk reduction is the strongest clinical rationale for CO_2 in lower extremity interventions. In patients with chronic limb-threatening ischemia and renal impairment, CO_2-guided infrainguinal intervention was not associated with significant deterioration in postoperative serum creatinine (25). Diamantopoulos *et al* (26) reported that CO_2 angiography during peripheral angioplasty in patients with impaired renal function was associated with a lower incidence of contrast-induced nephropathy than a matched historical ICM cohort. A large Vascular Quality Initiative analysis by Lee *et al* (27) found that, among patients with advanced CKD undergoing peripheral vascular intervention, CO_2 use was associated with a 50% reduction in iodinated contrast volume and lower rates of PC-AKI and cardiac complications without a significant difference in technical failure or amputation outcomes. These data support CO_2 as a pragmatic renal-sparing strategy rather than a niche technology.

The evidence is not entirely uniform. A systematic review and meta-analysis by Wagner *et al* (28) found a lower CA-AKI event rate with CO_2 compared with ICM for peripheral angiography, although the confidence interval crossed unity in the overall analysis and data for radiation dose, procedure duration, and CO_2-related adverse events were limited. More recent data also indicate that AKI may still occur after CO_2-guided peripheral intervention, particularly in patients with severe cardiovascular comorbidity or residual bailout ICM exposure (29). Thus, CO_2 reduces but does not eliminate renal risk. Renal protection should be combined with hydration when appropriate, avoidance of nephrotoxic drugs when clinically feasible, hemodynamic optimization, and careful post-procedure surveillance in high-risk patients.

Cost and patient tolerance also influence implementation. CO_2 itself is inexpensive, and femoropopliteal revascularization data suggest that contrast-agent cost can be lower with CO_2 than with ICM when other intravascular material costs are similar (30). However, true cost-effectiveness depends on equipment amortization, procedure duration, staff training, rescue ICM use, repeat imaging, and the economic consequences of AKI. Pain is another important practical limitation. Lower extremity CO_2 angiography may cause transient leg, abdominal, or pelvic discomfort, but most patients tolerate the procedure, and pain can be mitigated by reducing injection volume, avoiding excessive injection pressure, spacing injections, and using intra-arterial lidocaine when necessary (31,32). Overall, lower extremity CO_2 angiography is most appropriate when the expected renal-sparing benefit outweighs the disadvantages of variable image quality and transient discomfort.

Abdominal aorta and aneurysm repair. CO_2 angiography has been applied during standard endovascular aneurysm repair (EVAR), ruptured abdominal aortic aneurysm (rAAA) repair, and selected complex aortic procedures. The potential benefit is reduction in ICM exposure in patients who often have CKD and require repeated imaging. However, evidence is less consistent than in lower extremity interventions. Aortic imaging is technically challenging because aneurysm sac volume, branch orientation, posterior anatomy, respiratory motion, and endoleak flow dynamics may limit CO_2 opacification (10,11).

A narrative review of CO_2 angiography in standard and complex abdominal aortic repair reported that factors such as aneurysm diameter >70 mm and certain renal artery positions predicted the need for supplementary ICM (10). Lesions or target vessels located on the anterior wall may be more readily visualized than posterior structures because of CO_2 buoyancy. Mascoli *et al* (11) also reported difficulty identifying the lowest renal artery in patients with larger aneurysm sac volumes when using CO_2-DSA (11). These findings indicate that CO_2 is sensitive to anatomy and should not be expected to provide uniform aortic visualization.

Endoleak detection remains controversial. Some studies report no major difference between CO_2-based and ICM-based EVAR for endoleak detection, whereas others suggest that low-flow type II endoleaks may be missed or detected inconsistently with intraoperative CO_2-DSA (33-35). Conversely, CO_2 may occasionally detect subtle low-flow leaks because gas is less diluted than iodinated contrast in certain settings. These conflicting data suggest that CO_2 can be useful as part of an aortic imaging strategy but should be supplemented by ICM, intravascular ultrasound, fusion imaging, or postoperative cross-sectional surveillance when critical anatomical information is uncertain. In patients with rAAAs, pilot data suggest technical feasibility of CO_2-only repair and a potentially lower AKI rate than historical iodine-based reports, but the evidence remains preliminary (15).

Renal and transplant renal arteries. Renal and transplant renal artery interventions are conceptually attractive targets for CO_2 because the patients often have compromised kidney function. In transplant renal artery stenosis, selective CO_2 angiography has been reported to reduce ICM use while preserving technical success in selected patients (36). CO_2-DSA may also provide adequate visualization of renal arteries during specific procedures and may reduce postoperative renal function worsening compared with ICM in some cohorts (37).

However, renal artery use requires caution. The renal artery territory is close to the mesenteric circulation, and inadvertent or excessive CO_2 delivery may be associated with abdominal pain, bowel ischemia, or non-occlusive mesenteric ischemia (NOMI) in susceptible patients (37-39). Severe atherosclerosis, occlusive mesenteric disease, impaired collateral perfusion, low-flow states, and repeated high-volume injections may increase risk. Therefore, CO_2 should be considered selectively rather than routinely for renal interventions. When used, it should be delivered through selective catheter placement with controlled volume, adequate injection intervals, continuous monitoring, and a low threshold for alternative imaging if image quality is inadequate or symptoms occur.

Mesenteric arteries and gastrointestinal bleeding. The mesenteric circulation is one of the most sensitive territories for CO_2 use. CO_2 angiography can theoretically identify bleeding because gas is less viscous and may escape through small vascular defects. It has been described in hemorrhage detection and trauma-related angioembolization, and some studies suggest improved localization of active bleeding in selected scenarios (30). Nevertheless, routine superior mesenteric artery CO_2 angiography is not recommended because NOMI and bowel ischemia have been reported (38,39).

The clinical concern is not simply image quality but tissue viability. CO_2 can transiently displace blood, and in patients with severe atherosclerosis, compromised mesenteric collateralization, or inferior mesenteric artery occlusion, this displacement may contribute to ischemia. A reported case of total bowel ischemia after CO_2 angiography in a patient with inferior mesenteric artery occlusion underscores this hazard (39). Conversely, selected cases have demonstrated technically successful use of CO_2 combined with intravascular ultrasound in complex mesenteric aneurysm repair (40). These reports should be interpreted as examples of specialized, carefully selected applications rather than support for routine mesenteric CO_2 angiography.

Venous, portal, and other infra-diaphragmatic applications. Although this review focuses on arterial interventions, CO_2

has a longer history in venous and portal applications. It has been used for venography, arteriovenous access interventions, wedge hepatic venography for portal vein visualization, and assessment of vascular anatomy below the diaphragm (6,8,9). In venous applications, the consequences of gas migration differ from those of arterial injection, but pulmonary hypertension, right-to-left shunt, and impaired pulmonary reserve remain important considerations. The general principles of closed-system delivery, avoidance of air contamination, controlled injection, and careful monitoring remain applicable across vascular territories.

5. Contraindications and patient selection

Appropriate patient selection is the most important determinant of safe CO_2 angiography. The strongest indications include advanced CKD, previous PC-AKI, severe ICM allergy, the need to minimize cumulative iodine exposure, and lower extremity or iliac interventions where CO_2 image quality is expected to be adequate. Relative contraindications include severe chronic obstructive pulmonary disease (COPD), pulmonary hypertension, right-to-left intracardiac or intrapulmonary shunt, severe cardiopulmonary instability, and situations requiring rapid repeated high-volume injections (6,9). In such patients, the risk of hypercapnia, pulmonary artery pressure elevation, or systemic gas embolization must be weighed carefully against the renal benefit.

Absolute or practical contraindications include arterial injection above the diaphragm, including the thoracic aorta, coronary arteries, and cerebral circulation (6,13,14). Fatal neurological injury after CO_2 angiography has been reported, reinforcing the importance of strict anatomical discipline (14). Mesenteric arterial use should be avoided as a routine strategy because of NOMI risk, and renal artery use should be reserved for selected cases with appropriate expertise. CO_2 should also not be used when the operator cannot obtain adequate images with safe injection volumes; in such cases, hybrid CO_2-low-dose ICM angiography, intravascular ultrasound, duplex guidance, fusion imaging, or alternative cross-sectional imaging may be safer.

6. Complications and management

Most CO_2-related adverse events are mild and transient when the gas is administered below the diaphragm through an appropriate system. Common symptoms include limb pain, abdominal discomfort, nausea, diarrhea, and transient hypotension or bradycardia (37,38). Pain is thought to result from vessel wall distension, transient ischemia, or perivascular nociceptor activation. Practical management includes reducing injection volume and pressure, allowing longer intervals between injections, ensuring selective catheter placement, and using intra-arterial lidocaine when discomfort compromises image acquisition (32).

Serious complications are uncommon but clinically important. Air contamination can produce true air embolism and must be prevented by closed delivery systems and careful line preparation. Gas trapping or excessive repeated injection may cause transient ischemia or hemodynamic effects. Mesenteric ischemia, including NOMI, has been reported and requires immediate recognition. New abdominal pain, lactic acidosis, livedo-like skin changes, hypotension, or persistent gastrointestinal symptoms after CO_2 angiography should prompt urgent evaluation and supportive management (37-39).

Hypercapnia is theoretically possible if CO_2 delivery exceeds pulmonary clearance. Although most intravascular CO_2 dissolves and is exhaled rapidly, patients with severe pulmonary disease or pulmonary hypertension may tolerate large or repeated injections poorly (6,9,12). Continuous cardiopulmonary monitoring is recommended, and operators should avoid rapid repetitive injections. When symptoms occur, injections should be stopped, the patient should be stabilized, oxygenation and ventilation assessed, and alternative imaging considered.

7. Practical clinical workflow

A practical workflow for CO_2 angiography, including common problems and corresponding management strategies, is summarized in Table II. For centers intending to implement CO_2 angiography, a structured workflow is essential. Before the procedure, the operator should document the indication for CO_2 use, baseline renal function, allergy history, cardiopulmonary status, and anatomical target. Patients with severe pulmonary hypertension, significant right-to-left shunt, unstable respiratory status, or planned supradiaphragmatic arterial injection should be excluded or managed with alternative imaging. The procedural plan should specify whether CO_2 is intended to reduce ICM exposure completely or to serve as the primary contrast agent with low-dose ICM available for confirmation.

During the procedure, the safest approach is selective catheterization with small, controlled injections and sufficient time between injections for pulmonary clearance. Images should be acquired with attention to table position, projection angle, and breath-hold instructions. Operators should review each acquisition for diagnostic adequacy rather than assuming that repeated gas injection will solve poor opacification. If target visualization remains inadequate, early use of adjunctive imaging may be safer than repeated high-volume CO_2 injections. Intravascular ultrasound, duplex guidance, fusion roadmapping, or carefully limited ICM can be used to confirm device position, branch patency, endoleak, or residual stenosis.

After the procedure, documentation should include total CO_2 volume when available, total ICM volume, reason for bailout iodine if used, patient tolerance, and any adverse symptoms. High-risk patients should undergo serum creatinine or eGFR follow-up according to institutional protocol and contemporary PC-AKI guidance. When AKI occurs despite CO_2 use, the assessment should not stop at contrast volume; hemodynamics, embolic complications, infection, heart failure, medications, and baseline renal reserve should also be reviewed.

This workflow emphasizes that CO_2 angiography is a technique rather than merely a contrast agent. Its value depends on appropriate case selection, equipment, operator training, and integration with other imaging tools. A standardized protocol can reduce variability, improve safety, and make outcomes more comparable across institutions.

Table II. Common issues and management strategies in CO_2 angiography.

Issue	Mechanism or concern	Prevention/management
Air contamination	Atmospheric air may enter non-closed systems and cause true air embolism.	Use closed or automated delivery systems; purge lines carefully; avoid syringe disconnection.
Gas embolism above diaphragm	CO_2 may enter cerebral or coronary circulation during supradiaphragmatic arterial injection.	Avoid thoracic aorta, coronary arteries, and cerebral circulation; follow strict anatomical contraindications.
Variable image quality	Buoyancy, gas fragmentation, posterior lesions, and slow flow may reduce opacification.	Use selective catheterization, table tilt, image stacking, DVA/post-processing, or low-dose bailout ICM.
Pain or discomfort	Transient vascular distension or ischemia during gas injection.	Reduce volume/pressure, increase injection interval, monitor VAS, consider intra-arterial lidocaine.
Hypercapnia or cardiopulmonary stress	Large or repeated injections may exceed pulmonary clearance in vulnerable patients.	Monitor ECG, oxygen saturation, blood pressure, respiratory rate; use cautious dosing in COPD or pulmonary hypertension.
Mesenteric ischemia/NOMI	Transient blood displacement or impaired collateral perfusion in susceptible mesenteric circulation.	Avoid routine mesenteric use; stop injection and evaluate urgently if abdominal pain, lactic acidosis, or ischemic signs occur.

CO_2, carbon dioxide; DVA, digital variance angiography; ICM, iodinated contrast media; VAS, visual analog scale; ECG, electrocardiogram; COPD, chronic obstructive pulmonary disease; NOMI, non-occlusive mesenteric ischemia.

8. Discussion

The available literature supports an anatomy-specific, risk-adapted role for CO_2 angiography. Its strongest evidence base is in iliac and lower extremity interventions, where it can substantially reduce ICM exposure while maintaining acceptable technical success in numerous patients (22-28,30,31,41). This is clinically meaningful because peripheral artery disease and CKD frequently coexist, and endovascular revascularization may be necessary precisely in patients most vulnerable to renal complications. For these patients, CO_2 may facilitate limb-salvage procedures in high-risk patients while reducing a modifiable procedural risk factor.

At the same time, the renal benefit of CO_2 should not be overstated. Contemporary guidelines emphasize that not all post-procedure AKI is caused by contrast media, and the causal risk of ICM may be lower than previously assumed in some settings (3-5). In endovascular practice, however, procedures often involve intra-arterial contrast, atherosclerotic embolic risk, hemodynamic shifts, and high baseline comorbidity. Therefore, the appropriate conclusion is balanced: CO_2 is not a guarantee against AKI, but it is a valuable component of a renal-protection strategy when used in high-risk patients and suitable anatomy. Residual AKI after CO_2-guided procedures should prompt attention to systemic risk factors such as heart failure, hypertension, coronary artery disease, baseline eGFR, and bailout ICM volume (27,29).

The principal limitation of CO_2 is image quality variability. ICM provides more predictable visualization of the vascular lumen, calcified segments, small branches, and posterior structures. CO_2 visualization is affected by buoyancy, respiratory motion, vascular orientation, catheter position, and flow state (6,10,11). In lower extremity disease, these limitations can often be mitigated by selective injection, repeated acquisition, table tilt, image stacking, and limited supplemental ICM. In complex aortic, renal, or mesenteric applications, however, inadequate visualization may have greater consequences, including missed endoleak, uncertain branch catheterization, or ischemic complications. Hybrid imaging strategies are therefore often more clinically practical than complete replacement of ICM.

Implementation requires institutional standardization. A CO_2 program should define indications, contraindications, injection volumes, minimum intervals, equipment setup, monitoring requirements, pain-management protocols, bailout criteria, and documentation of residual ICM exposure. Operators and technologists must understand that CO_2 behaves as a gas rather than a liquid contrast agent. Automated injectors and closed delivery systems may reduce variability and contamination risk, but they should not replace anatomical judgment or careful monitoring (15-17).

Future research should move beyond direct comparisons between CO_2 and ICM. Important outcomes include image interpretability by arterial segment, device-specific technical success, procedure duration, fluoroscopy time, radiation dose, patient-reported pain, residual ICM volume, AKI adjudicated by contemporary definitions, ischemic complications, and cost-effectiveness. Randomized trials or well-designed prospective registries should stratify patients by CKD stage, lesion location, intervention type, pulmonary comorbidity, and delivery system. Ongoing randomized and prospective studies should address the current evidence gaps. Emerging technologies such as DVA, fusion imaging, intravascular ultrasound, and optimized acquisition algorithms may expand the safe use of CO_2, but they require clinical validation before broad recommendations can be made.

9. Future research priorities

Several research priorities should guide the next phase of CO_2 angiography studies. First, standardized definitions of renal outcomes are needed. Older studies often used CI-AKI or contrast-induced nephropathy, whereas contemporary literature increasingly uses PC-AKI or CA-AKI (3-5). Future studies should report baseline eGFR, AKI stage, timing of serum creatinine measurement, residual ICM volume, hemodynamic instability, and competing renal insults so that the independent contribution of contrast strategy can be more accurately assessed.

Second, image-quality endpoints should be clinically meaningful. Numerous studies report subjective image scores, SNR, or inter-rater agreement (18-21,23). These metrics are useful but should be linked to procedural decisions, such as whether a stenosis was crossed, whether distal runoff was adequately assessed, whether device sizing changed, whether a branch vessel was missed, or whether additional ICM was required. Segment-specific reporting is also important because the diagnostic value of CO_2 differs between iliac, femoropopliteal, tibial, aortic, renal, and mesenteric territories.

Third, patient-centered outcomes should be incorporated. Pain during injection, anxiety related to repeated acquisitions, procedure duration, limb salvage, reintervention, hospital length of stay, dialysis requirement, and mortality are more clinically relevant than technical image metrics alone. Cost-effectiveness analyses should include injector acquisition, disposable tubing, staff training, fluoroscopy time, potential reduction in AKI-related hospitalization, and the cost of repeat imaging.

Finally, technology-focused studies should evaluate whether DVA, artificial intelligence-based subtraction, fusion imaging, and intravascular ultrasound can expand safe CO_2 use while reducing both ICM and radiation. Such studies should be prospective, ideally multicenter, and should include predefined bailout criteria to avoid excessive gas injection when image quality is inadequate.

10. Conclusions

CO_2 angiography is a clinically useful alternative or adjunct to ICM in selected arterial endovascular procedures. Its most established role is in iliac and lower extremity interventions, particularly for patients with CKD, previous PC-AKI, or ICM hypersensitivity. The main advantages are minimal renal toxicity, absence of iodine allergy risk, low material cost, and the ability to reduce total ICM exposure. However, CO_2 should not be considered a universal replacement for ICM. Abdominal aortic, renal, and mesenteric applications require careful patient selection, strict monitoring, and readiness to use adjunctive imaging. Supradiaphragmatic arterial injection remains contraindicated. Future work should prioritize standardized protocols, improved image-processing strategies, prospective comparative studies, and clinically meaningful renal and safety endpoints.

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Authors' contributions

XL and YZ designed the scope and structure of the review, performed literature searches, and drafted the manuscript. PL contributed to literature analysis and interpretation of the findings. CZ supervised the study, critically revised the manuscript, and finalized the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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