health
Department:
Health
REPUBLIC OF SOUTH AFRICA

South African National Department of Health
Brief Report of NEMLC Limited Review[1]
Low Osmolar Contrast Media - Therapeutic Interchange
April 2026

Medicine details *(complete what is applicable):*

Medicine Class	Yes	*If applicable - Please consider therapeutic interchange policy*
Medicine/s name **-INN:** **- South African name (if differs from INN)**	Low-Ionic Contrast Media namely iohexol, iopamidol, iopromide, and ioversol	*http://www.whocc.no/atc_ddd_index/*
Medicine/s (ATC5):	Watersoluble, nephrotropic, low osmolar X-ray contrast media (V08AB)	*http://www.whocc.no/atc_ddd_index/*
SAHPRA Approved	Yes	SAHPRA registered health products database *https://medapps.sahpra.org.za:6006/*
Dosage form/s	Liquid, injection	
Route of administration/s	Dependent on imaging but Intravenous, intraventricular, intra-arterial, intrathecal, Intra-cisternal, intra-articular, oral	
Patient population	Individuals of all ages in need of diagnostic radiology	
Prevalence and/or incidence of condition	Unknown, dependent on condition	*May refer to estimates or routine data (DHIS, StatsSA), not necessarily published data.*
Level of Care	Paediatric and Adult Hospital Level	
Prescriber level	Specialist	

Current Standard of Care

Low-Ionic Contrast Media namely iohexol, iopamidol, iopromide, and ioversol and barium sulphate for diagnostic radiology listed in the Adult Hospital STGs. Currently iohexol and iopamidol are on contract, with iohexol the more widely utilised.

[1] This template was informed by examples of previous NEMLC limited reviews, input from the Essential Drug Programme Oversight Group and the NEMLC Medicine Review Template which was updated with support through the Evidence-to-Decision (E2D) project which is a collaboration between National Department of Health, the South African Medical Research Council and the University of Stellenbosch.

Executive Summary

- Low-Ionic Contrast Media namely iohexol, iopamidol, iopromide, and ioversol and barium sulphate for diagnostic radiology listed in the Adult Hospital STGs. Currently iohexol and iopamidol are on contract, with iohexol the more widely utilised.
- A limited review revealed no appropriate clinical practice guidelines, however three systematic reviews were found with one low quality review (AMSTAR 2) selected for inclusion (Suh 2019) after assessing against set criteria.
- Safety
  - Incidence of overall acute adverse reactions - no difference was found between agents however iohexol had the highest incidence.
  - Incidence of severe acute adverse reactions - no difference was reported between agents however iopromide had the highest incidence.
- Certainty of evidence for outcomes considered to be very low to low.
- Iohexol or iopamidol is often the most affordable option based on SEP across formulations and there is currently a good discount being achieved on iohexol for contract pricing.
- Feasibility and implementation issues were important consideration.
  - Only iohexol and iopromide can be utilised intrathecally and based on expert opinion iohexol is one of the few agents that can be utilised orally.
  - Iohexol is widely utilised across the country in multiple modalities and routes.
  - Introduction of a different agent may require implementation transition.

Key Recommendations *(if more appropriate, describe in narrative form)*

Type of ERC recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	☐	☐	X☐	☐
High level summary of conclusions	It is recommended that for intravascular administration, low osmolar contrast media agents (iohexol, ioversol, Iopamidol, Iopromide) be considered as a therapeutic class. For other routes of administration (intrathecal, oral, intraarticular, use within body cavities) iohexol is the preferred agent given its multimodal use across a range of labelled indications in both paediatric and adult patients. This is conditional recommendation subject to future changes in price or safety changes.			
NEMLC Ratification	**Date**	**Comments/Recommendation**		
	26 May 2026	ERC recommendation aproved		
EML Status	EML	Non-EML – contingent on stated reference price threshold in Rand Value	Non-EML	
	☐X	☐	☐	

Therapeutic Interchange Considerations (if applicable) *	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
		Iohexol Iopamidol Iopromide Ioversol	X	Injectable, via different routes of administration –	Injection protocols and volumes generally are the	☐

				Therapeutically interchnageable for intravascular route only	same, with adjustments made for procedures requiring precise contrast enhancement to account for differences in iodine concentration.	
Trigger for review	Safety, change in indications/contra-indications, cost					

*Depending on the review and number of products, an annexure may need to be included

REVIEW TEAM

Review contributors as detailed below:

Name & Affiliation	Declaration of Interests	Defining the PICO	Protocol development	Literature search	Study selection	Data extraction & characteristics of included studies	Quality appraisal	Data analysis	GRADE assessment	Write up and referencing	Clinical Expertise & interpretation	Quality assurance
Kim MacQuilkan, EDP Oversight Group, NDoH	None	X	X	X	X	X	X	n/a	n/a	X		
Maropeng Rapetsoa, EDP Oversight Group, NDoH	None	X	X		X	X	X	n/a	n/a	X		X
Andy Gray, UKZN	None	X						n/a	n/a		X	X
Dr Razaan Davis, Tygerberg Hospital, University of Stellenbosch	None	X						n/a	n/a		X	
Dr Ambrosius Swartbooi, Robert Mangaliso Sobukwe Hospital, Dept of Health, Northern Cape, Northern Cape. Affiliated Lecturer: Clinical Imaging Sciences, UFS	None	X						n/a	n/a		X	

Note: Leave box blank if did not contribute to that specific component and n/a if that component was not required at all for the review.

ACKNOWLEDGEMENTS

The members of the Expert Review Committee (ERC), Contrast Media Evidence Working group and National Essential Medicines List Committee.

Background and rationale

The Adult Hospital Level Standard Treatment Guidelines (STG) Chapter 22-section 22.1: Diagnostic contrast agents and related substances, currently recommends non-ionic contrast media (Low osmolar contrast media (LOCM) for use in diagnostic radiology. The STGs outlines four options namely iohexol, iopamidol, iopromide, and ioversol. This was a historic decision, largely influenced by provincial utilisation data; therefore, therapeutic equivalence and comparative safety between agents were not formally reviewed. Historically all four LOCM were included in the HP-05 (Contract for the supply and delivery of diagnostic agents and contract media) however, in the current contract (HP05-2024DI/01) only responsive bids were awarded for Iohexol and Iopamidol. The current bid specifications for tender are under review to ascertain if the agents could be formally declared as a therapeutic class. A therapeutic class allows potentially for economies of scale and procurement of the option for all relevant indications. A formal review by the NEMLC is thus required to determine if these agents can be considered interchangeable, if there are any potential differences for consideration based on imaging type or population. Due to the urgency of the topic, a limited review will be conducted.

Purpose/Objective i.e., PICO question (if relevant):

Population Subgroups	Individuals (all ages) with undergoing diagnostic imaging
Intervention(s)	Low-Ionic Contrast Media namely iohexol, iopamidol, iopromide, and ioversol Route of administration: intravenous, intraarterial, intrathecal, oral and others. Note not all agents can be administered through all routes particularly intrathecal and oral
Comparator(s)	*Each other*
Clinical Outcome(s)	*Safety (primary outcomes of interest) – majority of literature appears to be in this area - no concerns highlighted by experts regarding equivalent efficacy in imaging:* • *Contrast-induced nephropathy (CIN)* • *Cardiovascular events* • *Acute adverse reactions* • *Incidence of hypersensitivity reactions or serious adverse events e.g. anaphylaxis* *Efficacy (secondary outcomes of interest)* • *Diagnostic imaging quality*
Study types	*Clinical Practice Guidelines and SRs of randomised trials, SRs of multiple study types (for feasibility, acceptability expert opinion)*

Other outcomes of interest: Feasibility, acceptability, cost, patient preference

Exclusions:
Comparators: Iso-osmolar contrast media, ionic contrast media, barium sulphate

Methods

This review adopted a limited review approach and as such for the most part elements will be conducted one reviewer and checked with another and the Evidence Working Group (EWG). The focus of the search will be clinical practice guidelines and systematic reviews.

1. Data Sources

Search was conducted on three databases namely PUBMED, Cochrane and epistemonikos for effectiveness. Information regarding feasibility, acceptability and current practice was sourced by Members of the Evidence Working Group (EWG) shared perspectives based on usage and clinical practice in the Western Cape and Northern Cape, while additional information from other provinces could not be obtained.

2. Search Strategy

See Appendix 1 for the full search strategy. Records were limited to systematic reviews. Language was not restricted however if full text was not accessible, the record was excluded due to time constraints.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

Screening was conducted by one reviewer (KM), and full text review independently by two reviewers (KM and MR). Final selection of studies was undertaken by one reviewer (KM) and checked by a second reviewer (MR). Eligible systematic reviews were assessed by according to the following criteria to determine final selection: directness of matching this review PICO, comprehensive of included studies, and appraisal results with AMSTAR II. One reviewer did data extraction and results were discussed with second reviewer (MR) and reviewed by the EWG.

4. Assessment of methodological quality

AMSTAR II assessment (Shea, et al., 2017) was conducted on systematic reviewers by one reviewer (KM) and results discussed with second reviewer (MR). Quality appraisal of underlying studies within the included systematic reviewers were extracted directly from the publications.

Results

1. Result of the search

The search resulted in 70 publications and 15 duplicates were removed. After screening, a further 37 articles were excluded. Full text review of 18 remaining articles resulted in the exclusion of 15 studies. Three records matched the eligibility criteria and were evaluated based on the criteria outlined in the methods above (See Table 1 below). No appropriate clinical practice guidelines were identified. One systematic review was selected for final inclusion (See Figure 1 for PRISMA diagram). See Appendix 2 for excluded studies.

Table 1: Comparison of four eligible systematic reviews to determine final inclusion

Publication	AMSTAR 2 rating	Number of critical domain flaws	Industry COI	PICO directness	Comprehensive & up to date
(Solomon & DuMouchel, 2006)	Critically Low	4	Bracco-funded statistician	**Agents:** LOCM (iopromide grouped) **Population:** patients with pre-existing renal impairment **Outcomes:** contrast induced nephropathy	22 prospective controlled studies (3112 patients); + FDA adverse event database, oldest study (up to Aug 2005)

Suh 2019 (Suh, et al., 2019)	Low	1 (no protocol)	None	**Agents:** All agents included **Outcomes:** acute reactions	30 studies (1,360,488 exposures), up to Nov 2017 Multiple study types
Wei 2025 (Wei, Jiang, Hibberd, & et al, 2025)	Critically Low	2	All authors GE Healthcare	**Agents:** All agents included **Outcomes:** acute reactions	32 studies, most recent study, up to Mar 2024, multiple study types

One systematic review reported on contrast induced nephropathy as a primary outcome (Solomon & DuMouchel, 2006) and two reviews reported on acute adverse reactions (Suh, et al., 2019) (Wei, Jiang, Hibberd, & et al, 2025). Solomon 2006 and Wei 2025 were evaluated to be critically low with AMSTAR II (See Appendix 3 for full AMSTAR II results) with flaws in two and four critical domains respectively. Furthermore, Solomon 2006 and Wei 2026 included authors funded by industry. Suh 2019 had a critical flaw in one domain (due to not reporting a protocol being predefined), however fulfilled or partially fulfilled majority of domains thus considered low. Although Wei 2025 was more recent than Suh 2019, the articles included therein, that were not possible to include in the Suh 2019 study, were retrospective or pharmacovigilance studies. There were studies also not included in Wei 2025 that were included in Suh 2019 however both articles did not include a table outlining specific reasons for exclusion. Suh 2019 importantly included analyses to ascertain heterogeneity due to study design and pre-medication. One systematic was ultimately selected (Suh 2019 for acute adverse reactions). There were no eligible studies exploring efficacy specifically.

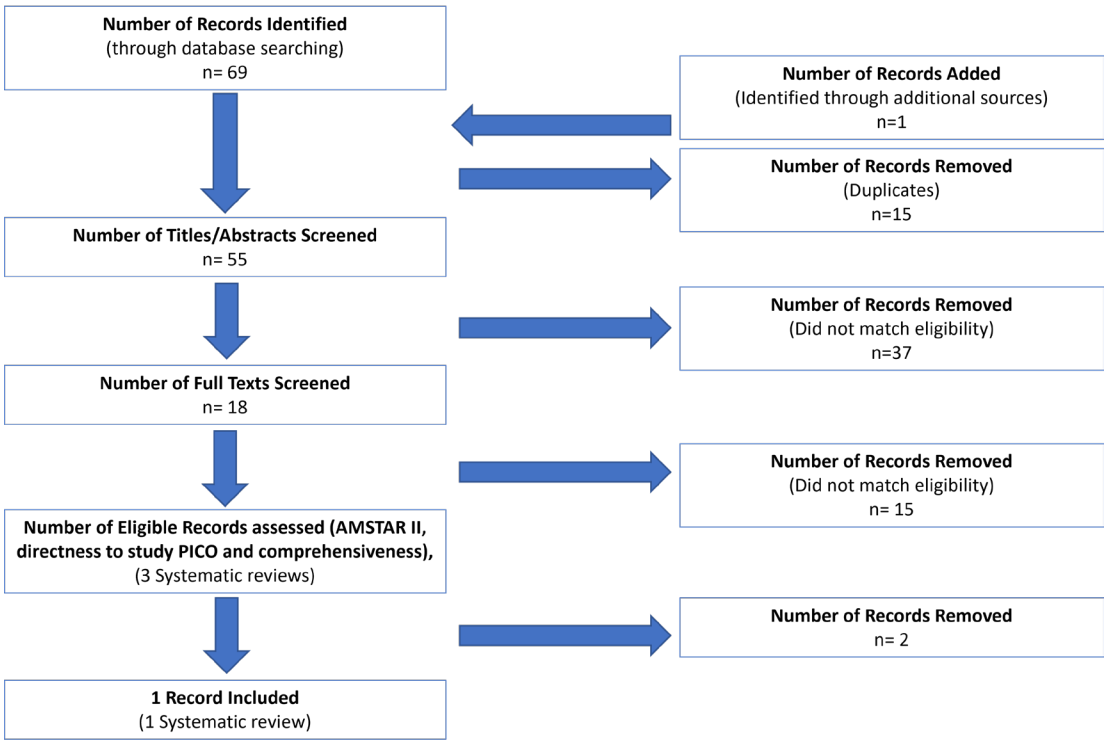

Figure 1: PRISMA Diagram for limited review on non-ionic contrast media

2. Description of included studies

See Table 2 for characteristics of the included study and Appendix 4 for individual studies included within the selected systematic review (Suh 2019).

Table 2: Characteristics of included systematic review.

	Suh 2019 (Suh, et al., 2019)
Population	Patients who underwent radiologic examinations with administration of ICM via intravascular route. study subject population comprising 100 adults or more (age >18 years), administration of non-ionic ICM via the peripheral intravenous and intra-arterial routes for modalities other than coronary angiography
Interventions	Iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioversol, iodixanol
Comparators	Iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioversol, iodixanol
Outcomes	Incidence of overall AAR to ICM and incidence of severe severe AAR to ICM
Study Design and number	SR of multiple study types 30 studies (1,360,488 exposures)

3. Methodological quality of included studies

As discussed above, the included systematic review (Suh 2019) was evaluated to be low based on AMSTAR II assessment results (See Appendix 3).

Suh 2019 included multiple study designs and utilised the Newcastle-Ottawa Quality Scale. It was reported that all but eight of the studies were high quality. The supplementary material comprising the specific scores for each study was not available.

4. Effectiveness and/or safety

Results are reported narratively below and extracted directly from the articles, comparisons will be discussed together under each relevant outcome.

Acute Adverse Events – all data extracted from *(Suh, et al., 2019)*

Overall acute adverse events

The pooled incidence of overall acute adverse events from lowest to highest was reported to as 0.82% [CI 0.43%–1.55%] i^2=99.6% for iopromide, 0.88% [CI 0.43%–1.83%] i^2=96.1% for ioversol, 1.10% [CI 0.60%–2.03%] i^2=98.9% for Iopamidol and 1.21% [CI 0.67%–2.17%] i^2=99.2% for iohexol (see figure 2 below). In univariable and multivariable meta-regression analysis the type of contrast media was not associated with an increased incidence (P=0.5369 and P=0.1453 respectively). However, the type of study design (prospective) was associated with an increase in overall AAR and reported use of pre-medication a decrease (See table 3 below) (Suh, et al., 2019).

Severe acute adverse events

The pooled incidence of severe acute adverse events from lowest to highest was reported to be 0.0082% [CI 0.0010%–0.0677%] i^2=55.1% for ioversol, 0.0119% [CI 0.0024%–0.0584%] i^2=87.2% for iohexol, 0.0148% [CI 0.0083%–0.0266%] i^2=21.9% for Iopamidol, and 0.0182% [CI 0.0111%–0.0298%] i^2=57.3% for iopromide (see figure 3 below). In univariable meta-regression analysis the type of contrast media was not associated with an increased incidence (P=0.4265) - See table 4 below (Suh, et al., 2019).

Table 3: Results of meta-regression for overall AARs – extracted from Suh 2019

	Univariable Meta-Regression Analysis				Multivariable Meta-Regression Analysis			
	OR [95% CI]	*P*	H0: Tests of Homogeneity for AAR Rate Across Different ICM	Test for Residual Heterogeneity	OR [95%CI]	*P*	H0: Tests of Homogeneity for AAR Rate Across Different ICM	Test for Residual Heterogeneity:
ICM								
Iobitridol	1		0.5369	<0.0001	1		0.1453	<0.0001
Iohexol	1.59 [0.63, 4.04]	0.3183			1.04 [0.46, 2.38]	0.9164		
Iomeprol	2.29 [0.86, 6.15]	0.0969			1.94 [0.83, 4.57]	0.1256		
Iopamidol	1.45 [0.57, 3.68]	0.4294			0.85 [0.37, 1.96]	0.6973		
Iopromide	1.07 [0.43, 2.68]	0.8762			0.90 [0.40, 1.99]	0.7889		
Ioversol	1.17 [0.40, 3.44]	0.7735			0.68 [0.26, 1.78]	0.4205		
Iodixanol	1.10 [0.41, 2.99]	0.8442			0.60 [0.24, 1.51]	0.2726		
Country								
Asian only	1			<0.0001				
Western	0.98 [0.58, 1.63]	0.9300						
Study design								
Retrospective	1			<0.0001	1			
Prospective	2.04 [1.30, 3.20]	0.0025			2.13 [1.36, 3.33]	0.0014		
Patients at risk for AAR								
<1%	1			<0.0001				
≥1% or unknown	0.73 [0.44, 1.20]	0.2118						
Premedication								
Yes	1			<0.0001	1			
No or unknown	1.88 [1.19, 2.97]	0.0077			1.66 [1.08, 2.56]	0.0230		
Injection route								
Intravenous only	1			<0.0001				
Other studies	2.00 [0.91, 4.43]	0.0849						
Type of examinations								
CT scan only	1			<.0001				
Other studies	1.15 [0.66, 1.99]	0.6230						

AAR indicates acute adverse reaction; OR, odds ratio; CI, confidence interval; ICM, iodinated contrast media; CT, computed tomography.

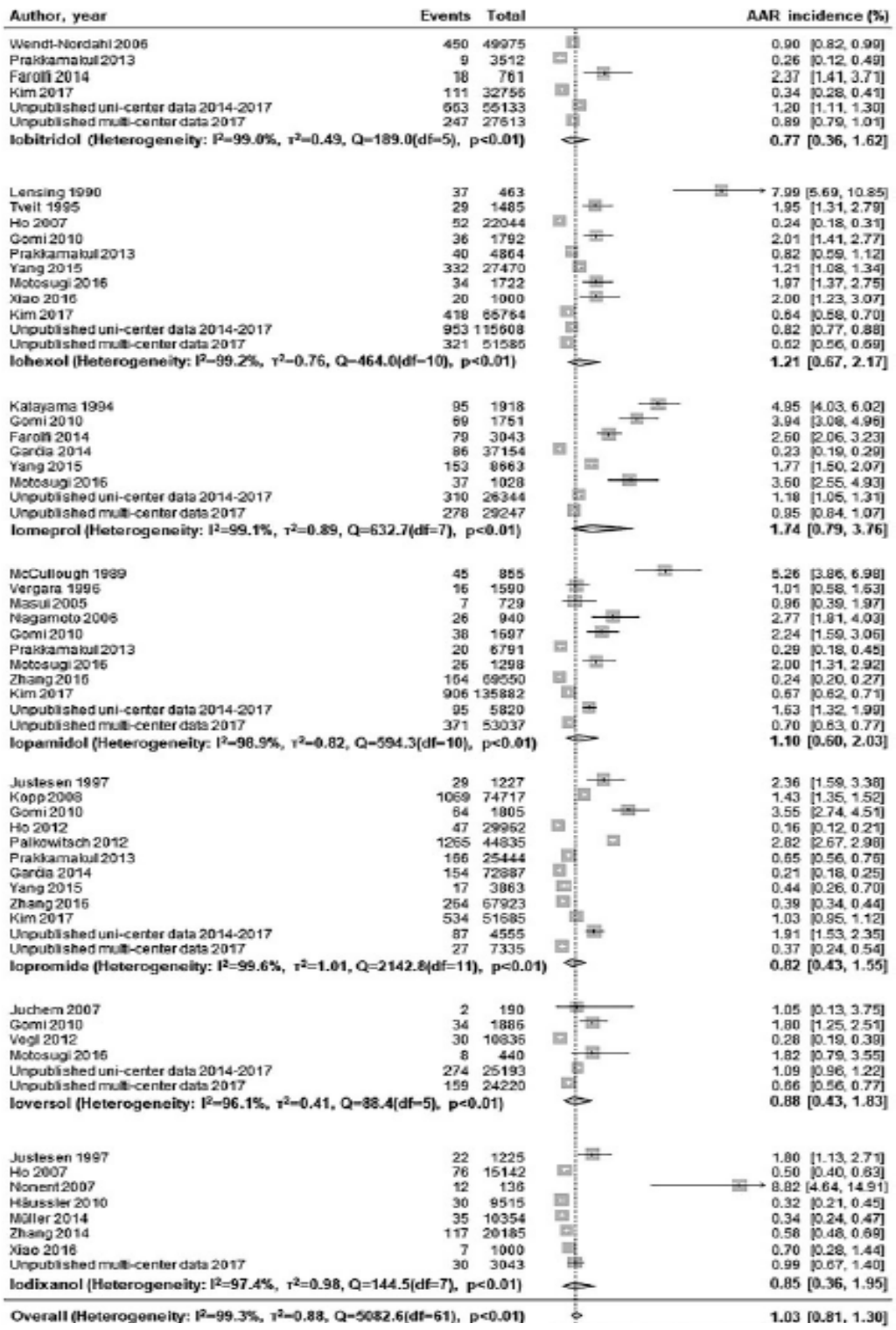

FIGURE 2. Pooled incidence of overall AARs according to the type of ICM. The estimated overall rate of AARs to nonionic ICM is 1.03% (95% confidence interval, 0.81%–1.30%). AAR indicates acute adverse reaction; ICM, iodinated contrast media.

Figure 2: Extracted from Suh 2019 – pooled incidence of overall AARs according to type of contrast media

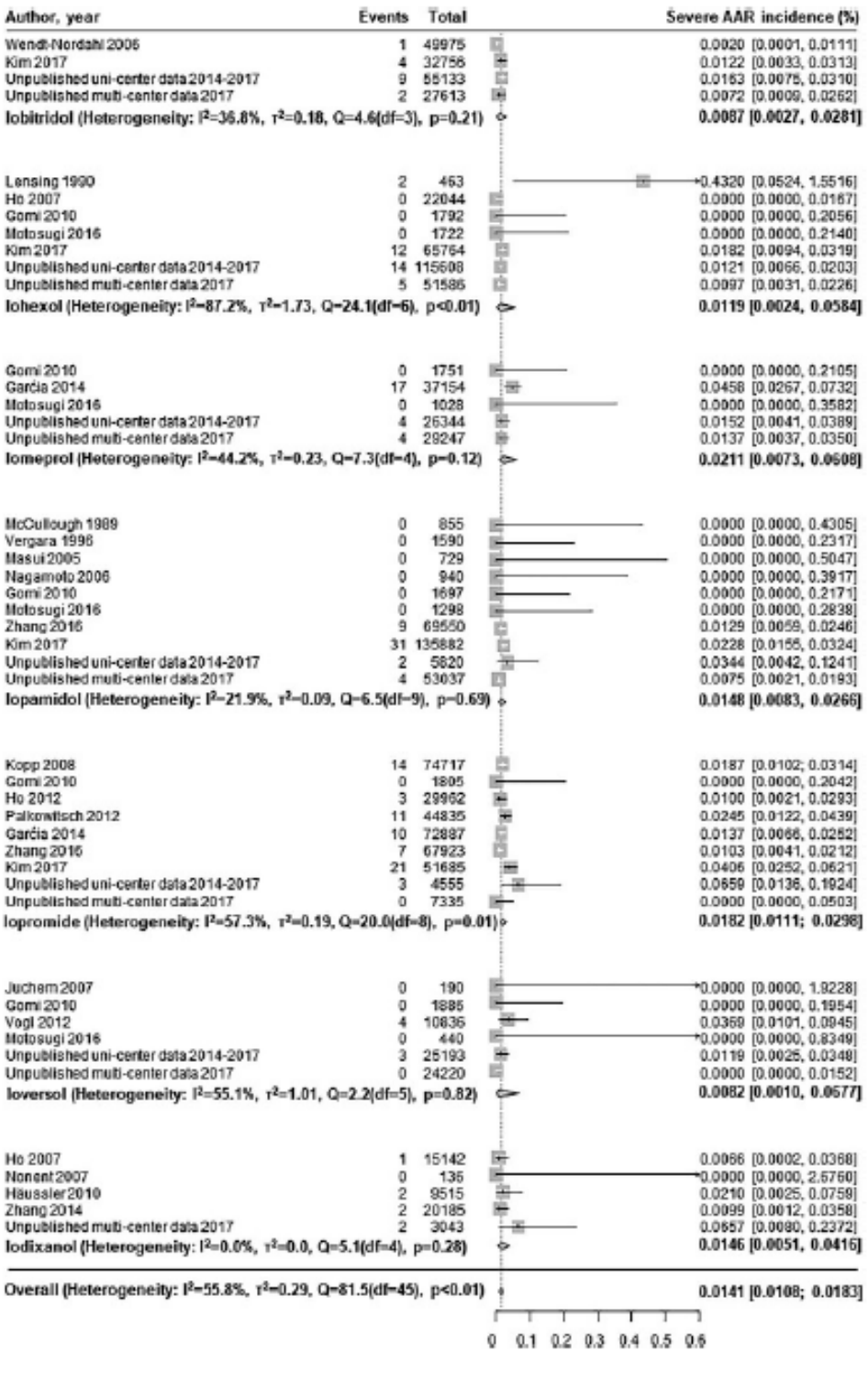

FIGURE 3. Pooled incidence of severe AARs according to the type of ICM. The estimated pooled incidence of severe AARs to 7 ICM is 0.0141% (95% confidence interval, 0.0108%–0.0183%). AAR indicates acute adverse reaction; ICM, iodinated contrast media.

Figure 3: Extracted from Suh 2019 – pooled incidence of severe AARs according to type of contrast media

Table 4: Results of meta-regression for severe AARs (extracted from Suh 2019)

	Univariable Meta-Regression Analysis			
	OR [95% CI]	*P*	H0: Tests of Homogeneity for AAR Rate Across Different ICM	Test for Residual Heterogeneity
ICM				
Iobitridol	1		0.4265	<0.0001
Iohexol	1.39 [0.57, 3.36]	0.4581		
Iomeprol	2.50 [0.99, 6.33]	0.0530		
Iopamidol	1.61 [0.67, 3.86]	0.2799		
Iopromide	2.09 [0.95, 4.60]	0.0675		
Ioversol	1.23 [0.40, 3.80]	0.7126		
Iodixanol	1.68 [0.55, 5.16]	0.3573		
Country				
Asian only	1			<0.0001
Western	1.20 [0.69, 2.07]	0.5106		
Study design				
Prospective	1			<0.0001
Retrospective	0.83 [0.48, 1.42]	0.4770		
Patients at risk for AAR				
<1%	1			<0.0001
≥1% or unknown	1.45 [0.87, 2.40]	0.1458		
Premedication				
Yes	1			<0.0001
No or unknown	0.92 [0.53, 1.59]	0.7686		
Injection route				
Intravenous only	1			<0.0001
Other studies	1.41 [0.77, 2.57]	0.2626		
Type of examinations				
CT scan only	1			<0.0001
Other studies	1.27 [0.57, 2.86]	0.5486		

AAR indicates acute adverse reaction; OR, odds ratio; CI, confidence interval; ICM, iodinated contrast media; CT, computed tomography.

Contrast induced nephropathy

No SRS matched the eligibility criteria of this outcome

Effectiveness

No SRS matched the eligibility criteria for clinical effectiveness

Certainty of evidence

A formal GRADE assessment was not conducted however elements were explored and will be discussed narratively. For Suh 2019, majority of the studies were retrospective or prospective cohort designs (only three RCTs). The Newcastle-Ottawa Scale scores were generally acceptable (all but 8 rated high quality), but this tool did not assess certain aspects that may influence overall certainty and the supplementary material was not accessible. A very high statistical heterogeneity was observed (over 90%) for all comparisons. There was a large sample for the overall acute adverse reactions however only a few studies reported severe events resulting in wider estimates. There are no concerns with directness or publication bias. For both outcomes (overall and severe acute adverse reactions) certainty of evidence is considered very low to low.

Provincial usage of Low osmolar contrast media

Product	Provincial usage (for the current 3 year contract)									
	EC	FS	KZN	LP	MP	NC	NW	WC	GP	SAMH
Iohexol	On contract									
Iohexol; 300mg/ml; injection; 20 ml	6500	0	0	0	0	0	1350	100	540	0
Iohexol; 300mg/ml; injection; 50 ml	9000	7280	30000	2000	12600	990	8530	65000	0	0
Iohexol; 300mg/ml; injection; 100 ml	3700	27130	60000	1400	18720	9900	10310	90000	0	0
Iohexol; 350mg/ml; injection; 50 ml	0	19300	20000	0	18720	400	600	7000	41400	0
Iohexol; 350mg/ml; injection; 100 ml	32000	18210	60000	0	0	4500	16970	60000	163800	0
Iopamidol	On contract									
Iopamidol; 300mg/ml; injection;50ml	0	0	0	0	0	0	0	0	0	750
Iopamidol; 300mg/ml; injection;100ml	0	0	0	0	0	0	0	0	0	1500
Iopamidol; 370mg/ml; injection;50ml	0	0	0	0	0	0	0	2500	0	0
Iopamidol; 370mg/ml; injection;100ml	0	0	0	0	0	0	0	6500	216	0
Iopromide	Not on contract (Previously awarded)									
Iopromide; 300mg/ml; injection; 50 ml	0	0	0	0	0	0	0	21000	0	0
Iopramide;300mg iodine/ml injection, 100m	0	0	0	0	0	0	0	2000	0	188
Iopromide; 370mg/ml; injection; 100 ml	0	0	0	0	0	0	0	4500	1620	57
Ioversol	Not on contract									
Ioversol 300mg/ml; injection ;50ml	0	0	0	0	0	0	0	0	0	0
Ioversol 300mg/ml; injection ;100ml	0	0	0	0	0	0	0	0	0	0
Ioversol 350mg/ml; Injection;50ml	0	0	0	0	0	0	0	0	0	0
Ioversol 350mg/ml; injection;100ml	0	0	0	0	0	0	0	0	0	0

Costs

See table x below and attached excel© document with full costing of different available strengths in SEP.

Drug Cost

Drug	Strength	Cost per vial – contract	SEP
Iohexol	300mg/ml 20ml	Discontinued	Discontinued
	300mg/ml 50ml	R189.65 (On contract)	R341.15
	300mg/ml 100ml	R379.30 (On contract)	R682.35
	350mg/ml 50ml	R221.26 (On contract)	R468.05
	350mg/ml 100ml	R442.51 (On contract)	R790.96
Iopamidol	300mg/ml 50ml	R254.18 (On contract)	R281.80
	300mg/ml 100ml	R492.6 (On contract)	R563.55
	370mg/ml 50ml	R342.17 (On contract)	R379.31
	370mg/ml 100ml	R663.12 (On contract)	R758.63
Iopromide	300mg/ml 50ml	NA	R353.38 (SEP)
	300mg/ml 100ml		R706.62 (SEP)
	300mg/ml 75ml		R529.97 (SEP)
	370mg/ml 50ml		R460.22 (SEP)
	370mg/ml 100ml		R920.44 (SEP)
Ioversol	300mg/ml 30ml	NA	R228.69 (SEP)
	300mg/ml 50ml		R401.17 (SEP)
	300mg/ml 100ml		R802.36 (SEP)
	350mg/ml 50ml		R468.05 (SEP)
	350mg/ml 125ml		R1635.23 (SEP)

Iohexol or iopamidol is often the most affordable option based on SEP across formulations.

Feasibility and acceptability considerations

User experience from WC & NC technical working group members at tertiary Hospitals

- Patient safety regarding contrast reactions including hypersensitivity to iodinated contrast, anaphalaxis, nausea and vomiting are the primary considerations for the choice of LOCM selected. It was noted that patients prefer the taste of oral Iohexol over other options.
- If a patient is unable to have an MRI spine, a CT myelogram which requires intrathecal injection of LOCM is required. According to the Professional information of the 4 LOCMs, only Iohexol and Iopamidol are registered for use intrathecally.
- Practical considerations, including injection rates, are important. The less dense contrast (iohexol) 300 mg /mL) is easier to inject by hand and pump injector. It is the preferred density used during invasive digital subtraction angiography in the radiology theatre by the vascular surgeons and radiologists.
- Iohexol 300 mg/Ml 50ml is currently used for interventional radiology and Urology (after Urografin was withdrawn)
- Iohexol 350 mg/ml 100ml is currently used for CT Angiography. The denser contrast is required for optimum contrast enhancement and image quality
- In clinical practice, the subject matter experts felt that the same low-osmolar contrast medium (LOCM) could be used across all patient groups, provided that varying volumes are supplied to suit different procedures, thereby minimizing waste and promoting cost efficiency.

Paediatric populations

- At Red Cross War Memorial Children's Hospital, iohexol 300 mg/mL 50ml is currently used for all the indications required. The Bid specification Committee has confirmed that the iohexal 300mg/ml 20ml has been discontinued by the supplier.

An example Professional Information Leaflet for each agent was examined and data extracted in the table below (Table 5). An important consideration is the administration options as only certain agents can be administered intrathecally (iohexol and Iopamidol). Oral formulations are not registered with SAHPRA however iohexol is used orally in practice. Iohexol and Iopamidol are currently on contract and iohexol is widely utilised across all modalities and all provinces. Table 6 compares the route of administration options for each agent.

Table 5: Summary of PIs (example of each) in terms of imaging options

Agent	Example product PI	Indications for use	Contraindications	Notes
Iohexol	Omnipaque (Omnipaque [Professional Information]. SAHPRA - 2008])	OMNIPAQUE (iohexol) injection is a radiographic contrast agent indicated for intrathecal (only the 300mg) , intravascular, oral, rectal, intraarticular and body cavity use. OMNIPAQUE oral solution is indicated for oral use only in conjunction with OMNIPAQUE injection administered intravenously for computed tomography (CT) of the abdomen	• History of serious reaction Iohexol • Manifest thyrotoxicosis	• Adults and Paediatrics • Utilised across difference techniques and modalities
Ioversol	Optiray (example from SAPHRA) (Optiray. [Professional information], 2026)	Optiray 300 is indicated in adults for cerebral, peripheral and visceral angiography, intravenous urography, intravenous digital subtraction angiography and venography. Optiray 300 is also indicated for contrast enhanced computed tomography of the head and body. Optiray 300 is indicated in children for cerebral, peripheral and visceral angiography, and for intravenous urography. Optiray 320 is indicated in adults for angiography throughout the cardiovascular system. The uses include cerebral, coronary, peripheral, visceral and renal angiography, in aortography, left ventriculography and intravenous urography. Optiray 320 is also indicated for contrast enhanced computed tomography of the head and body. Optiray 320 is indicated in children for angiocardiography, contrast enhanced computed tomography of the head and body, and intravenous urography. Optiray 350 is indicated in adults for angiography throughout the cardiovascular system. The uses include coronary, peripheral, visceral and renal angiography, aortography and left ventriculography. Optiray 350 is also indicated for contrast enhanced computed tomography of the head and body, intravenous urography, intravenous digital subtraction angiography and venography.	• Hypersensitivity to ioversol or to any of the ingredients, including excipients. • Proven hypersensitivity to iodine-containing contrast media. • Manifest hyperthyroidism. • Pregnancy and lactation (see section 4.6 Fertility, Pregnancy and Lactation). • Not indicated for intrathecal use.	• Adults and Paediatrics • Utilised across difference techniques and modalities
Iopamidol	Jopamiron (example from SAHPRA)	JOPAMIRON is indicated for myelography, cisternography and ventriculography, for all angiographic and urographic examinations and for contrast enhancement in	Hypersensitivity to iopamidol, iodine or to any of the excipients of JOPAMIRON (see section 6.1).	• Adults and Paediatrics

	(Jopamiron. [Professional Information], 2022)	computerised tomography. Its properties also permit the visualisation of body cavities (e.g. arthrography, fistulography, vesiculography, endoscopic-retrograde cholangio-pancreaticography).	• Intrathecal administration: the concomitant intrathecal administration of corticosteroids with JOPAMIRON. • Intrathecal administration: immediate repeat myelography in the event of technical failure, to avoid overdosage. • Cerebral fits are a relative contraindication for myelography. When the examination is carried out, all facilities to counter any convulsions which may occur must first of all be made readily available (see section 4.8). • Manifest hyperthyroidism. • Waldenströms macroglobulinemia. • Multiple myeloma. • Severe kidney disease. • JOPAMIRON should not be used during pregnancy (see section 4.6).	• Adults and paediatrics • Utilised across difference techniques and modalities
Iopromide	Ultravist) (Ultravist. [Professional Information]., 2015)	ULTRAVIST® (iopromide) Injection is a nonionic, water soluble x-ray contrast agent for intravascular administration. INTRA-ARTERIAL: ULTRAVIST® Injection (300 mgI/mL) is indicated for cerebral arteriography and peripheral arteriography. ULTRAVIST® Injection (370 mgI/mL)∗ is indicated for coronary arteriography and left ventriculography, visceral angiography, and aortography INTRAVENOUS: ULTRAVIST® Injection (240 mgI/ mL) is indicated for peripheral venography. ULTRAVIST® Injection (300 mgI/mL)∗ is indicated for contrast enhanced computed tomographic (CECT) imaging of the head and body, and excretory urography.	ULTRAVIST® Injection is not indicated for intrathecal use. In the pediatric population prolonged fasting and the administration of a laxative before ULTRAVIST® Injection are contraindicated.	• Adults and Paediatrics (with warnings) • Utilised across difference techniques and modalities

Table 6: Different route of administrations for each agent

LOCM	Route of Admin				
	Intravascular	Intrathecal	Intraarticular	Use in body cavities	Oral use for GI-studies
Iohexol	✓	✓	✓	✓	✓
Iopamidol	✓	✓	✓	✓	X
Iopromide	✓	X	✓	✓	X
Ioversol	✓	X	X	X	X

Discussion

A limited review was conducted to explore whether four non-ionic low osmolar contrast media agents namely iohexol, iopamidol, iopromide and ioversol could be considered in a therapeutic class for diagnostic radiology. An evidence working group was formed with specialists in the field. A limited review revealed no appropriate clinical practice guidelines, however three systematic reviews were found with one low quality review (AMSTAR 2) selected for inclusion (Suh 2019) after assessing against set criteria.

In terms of safety, for the outcome of incidence of overall acute adverse reactions, no difference was found between agents however iohexol had the highest incidence. Likewise for severe acute adverse reactions no difference was reported between agents however iopromide had the highest incidence. Quality of systematic review was evaluated to be low on AMSTAR 2. The studies included were not RCTs and high heterogeneity was observed. There were no issues with directness or publication bias. Certainty of evidence for the outcomes was considered to be very low to low (not a formal GRADE assessment but consideration of certain elements).

Feasibility and implementation issues were important consideration. Only iohexol and iopromide can be utilised intrathecally and based on expert opinion iohexol is one of the few agents that can be utilised orally. Iohexol is widely utilised across the country in multiple modalities and routes. Introduction of a different agent may require implementation transition. Iohexol or iopamidol is often the most affordable option based on SEP across formulations and there is currently a good discount being achieved on iohexol for contract pricing.

Conclusion and Recommendation

It is recommended that for intravascular administration, low osmolar contrast media agents (iohexol, ioversol, Iopamidol, Iopromide) be considered as a therapeutic class. For other routes of administration (intrathecal, oral, intraarticular, use within body cavities) iohexol is the preferred agent given its multimodal use across a range of labelled indications in both paediatric and adult patients. This is conditional recommendation subject to future changes in price or safety changes.

References

Jopamiron. [Professional Information]. (2022). South Africa.

Omnipaque [Professional Information]. [FDA version]. (n.d.). Marlborough, MA 01752 U.S.A.2017 .

Optiray. [Professional information]. (2026). South Africa.

Shea, B. J., Reeves, B. C., Wells, G., Thuku, M., Hamel, C., Moran, J., & et al. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. doi:doi:10.1136/bmj.j4008

Solomon, R., & DuMouchel, W. (2006). Contrast Media and Nephropathy: Findings From Systematic Analysis and Food and Drug Administration Reports of Adverse Effects. *Investigative Radiology, 41*(8), 651-660. doi:10.1097/01.rli.0000229742.54589.7b

Suh, Y. J., Yoon, S. H., Hyunsook, H., Hahn, S., Kang, D.-Y., Kang, H.-R., . . . Lee, W. (2019). Acute Adverse Reactions to Nonionic Iodinated Contrast Media: A Meta-Analysis. *Investigative Radiology, 54*(9), 589-599. doi:10.1097/RLI.0000000000000568

Ultravist. [Professional Information]. . (2021). Montville, Berlin, Germany.

Wei, Y., Jiang, X., Hibberd, M., & et al. (2025). Estimating the rate of acute adverse reactions to non-ionic low-osmolar contrast media: a systematic review and meta-analysis. *35*, 6240-6249. doi:10.1007/s00330-025-11526-z

Appendices

APPENDIX 1 -SEARCH STRATEGY

PUBMED – Search Date 9th April 2026

#	Query	Search Details	Results
7	#6 AND filter for systematic review and meta-analyses	(("radiography"[MeSH Terms] OR "radiography"[MeSH Terms] OR "diagnostic imaging"[MeSH Terms] OR "diagnostic techniques and procedures"[MeSH Terms]) AND ("iohexol"[Title/Abstract] OR "iopamidol"[Title/Abstract] OR "iopromide"[Title/Abstract] OR "ioversol"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract])) AND (meta-analysis[Filter] OR systematicreview[Filter])	14
6	#6 AND #4	("radiography"[MeSH Terms] OR "radiography"[MeSH Terms] OR "diagnostic imaging"[MeSH Terms] OR "diagnostic techniques and procedures"[MeSH Terms]) AND ("iohexol"[Title/Abstract] OR "iopamidol"[Title/Abstract] OR "iopromide"[Title/Abstract] OR "ioversol"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract])	21
7	#6 AND #5	("clinical practice guideline"[Title/Abstract] OR "practice guideline"[Title/Abstract]) AND "practice guideline"[Publication Type] AND (("radiography"[MeSH Terms] OR "radiography"[MeSH Terms] OR "diagnostic imaging"[MeSH Terms] OR "diagnostic techniques and procedures"[MeSH Terms]) AND ("iohexol"[Title/Abstract] OR "iopamidol"[Title/Abstract] OR "iopromide"[Title/Abstract] OR "ioversol"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract]))	0
6	#1 AND #2	("radiography"[MeSH Terms] OR "radiography"[MeSH Terms] OR "diagnostic imaging"[MeSH Terms] OR "diagnostic techniques and procedures"[MeSH Terms]) AND ("iohexol"[Title/Abstract] OR "iopamidol"[Title/Abstract] OR "iopromide"[Title/Abstract] OR "ioversol"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract])	3 449
5	Clinical Practice Guidelines	("clinical practice guideline"[Title/Abstract] OR "practice guideline"[Title/Abstract]) AND (practiceguideline[Filter])	2602
4	Systematic reviews	"systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]	584 607
3	RCTs	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	5 902 632
2	Low osmolar contrast media	"iohexol"[Title/Abstract] OR "iopamidol"[Title/Abstract] OR "iopromide"[Title/Abstract] OR "ioversol"[Title/Abstract] OR "low-osmolar	5 245

	(intervention & comparator)	*contrast media"[Title/Abstract] OR "low-osmolar contrast media"[Title/Abstract]*	
1	*Diagnostic imaging (population)*	*(((radiology[MeSH Terms]) OR (diagnostic x ray radiology[MeSH Terms])) OR (diagnostic imaging[MeSH Terms])) OR (diagnostic techniques and procedures[MeSH Terms])*	*8 420 588*

COCHRANE – Search 9th April

search	***Query***	***Results***
#1	*MeSH descriptor: [diagnostic imaging] explode all trees*	***71837***
#2	*MeSH descriptor: [diagnostic techniques and procedures] explode all trees*	***329 183***
#3	*MeSH descriptor: [iohexol explode all trees*	***673***
#4	*iopamidol*	***560***
#5	*iopromide*	***267***
#6	*ioversol*	***101***
#7	*Low-osmolar contrast media*	***222***
#8	*Low osmolar contrast media*	***296***
#9	*#3 OR #4 OR #5 OR #6 OR #7 or #8*	***1412***
#10	*#9 AND #2*	***1109***
#11	*Limit – Cochrane review in #*	***1***

Epistemonikos
(title:("iohexol"OR "iopamidol" OR "iopromide" OR "ioversol" OR "low-osmolar contrast media" OR "low-osmolar contrast media") OR abstract:("iohexol"OR "iopamidol" OR "iopromide" OR "ioversol" OR "low-osmolar contrast media" OR "low-osmolar contrast media"))

All studies – 1283 results
Filtered for systematic reviews = 58 results

GIN
No results for low osmolar or individual agents

APPENDIX 2 - Table of excluded studies

No.	Study	Reason for exclusion
1	Floriani I, Ciceri M, Torri V, Tinazzi A, Jahn H, Noseda A. Clinical Profile of Ioversol: A Metaanalysis of 57 Randomized, Double-Blind Clinical Trials. Investigative Radiology 31(8):p 479-491, August 1996.	Study design, incorrect comparator
2	Zhang J, Jiang Y, Rui Q, Chen M, Zhang N, Yang H, Zhou Y. Iodixanol versus iopromide in patients with renal insufficiency undergoing coronary angiography with or without PCI. Medicine 97(18):p e0617, May 2018. | DOI: 10.1097/MD.0000000000010617	Incorrect intervention
3	Alhelaly M, Abdelhakim A, Ellotf H et al. Comparative effect of iso-osmolar versus low-osmolar contrast media on vascular attenuation, image quality, and heart rate changes in coronary CT angiography: A systematic review and meta-analysis Clinical Imaging, 2020; 61, 69-79	Incorrect intervention
4	Reed M, Meier P, Tamhane UU, Welch KB, Moscucci M, Gurm HS. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2009 Jul;2(7):645-54. doi: 10.1016/j.jcin.2009.05.002. Erratum in: JACC Cardiovasc Interv. 2009 Nov;2(11):1167. PMID: 19628188.	Incorrect intervention
5	Goldfarb S, Spinler S, Berns JS, Rudnick MR. Low-osmolality contrast media and the risk of contrast-associated nephrotoxicity. Invest Radiol. 1993 Nov;28 Suppl 5:S7-10; discussion S11-2. doi: 10.1097/00004424-199311001-00003. PMID: 8282507.	Incorrect population, full text unavailable
6	Tardioli MO, Pejcic AV. Iodinated Contrast-Induced AGEP and ALEP: Recognition, Diagnosis, and Management. Int J Dermatol. 2026 Feb 22. doi: 10.1111/ijd.70353. Epub ahead of print. PMID: 41724881.	Incorrect study design
7	Pandya B, Chalhoub JM, Parikh V, Gaddam S, Spagnola J, El-Sayegh S, Bogin M, Kandov R, Lafferty J, Bangalore S. Contrast media use in patients with chronic kidney disease undergoing coronary angiography: A systematic review and meta-analysis of randomized trials. Int J Cardiol. 2017 Feb 1;228:137-144. doi: 10.1016/j.ijcard.2016.11.170. Epub 2016 Nov 9. Erratum in: Int J Cardiol. 2017 May 15;235:205. doi: 10.1016/j.ijcard.2017.03.021.. Chaloub, Jean [corrected to Chalhoub, Jean M]. PMID: 27863354.	Incorrect intervention
8	Eng J, Wilson RF, Subramaniam RM, Zhang A, Suarez-Cuervo C, Turban S, Choi MJ, Sherrod C, Hutfless S, Iyoha EE, Bass EB. Comparative Effect of Contrast Media Type on the Incidence of Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. Ann Intern Med. 2016 Mar 15;164(6):417-24. doi: 10.7326/M15-1402. Epub 2016 Feb 2. PMID: 26830055.	Incorrect intervention
9	van der Molen AJ, Dekkers IA, Bedioune I, Darmon-Kern E. A systematic review of the incidence of hypersensitivity reactions and post-contrast acute kidney injury after ioversol: part 2-intra-arterial administration. Eur Radiol. 2022 Aug;32(8):5546-5558. doi: 10.1007/s00330-022-08637-2. Epub 2022 Mar 21. PMID: 35312791; PMCID: PMC9279267.	Incorrect comparator
10	Solomon R. The role of osmolality in the incidence of contrast-induced nephropathy: a systematic review of angiographic contrast media in high	Incorrect study design

	risk patients. Kidney Int. 2005 Nov;68(5):2256-63. doi: 10.1111/j.1523-1755.2005.00684.x. PMID: 16221227.	
11	Sharma SK, Kini A. Effect of nonionic radiocontrast agents on the occurrence of contrast-induced nephropathy in patients with mild-moderate chronic renal insufficiency: pooled analysis of the randomized trials. Catheter Cardiovasc Interv. 2005 Jul;65(3):386-93. doi: 10.1002/ccd.20404. PMID: 15926184.	Cannot access full text
12	Arana E, Catalá-López F. Nefropatía inducida por contraste en pacientes de riesgo con insuficiencia renal explorados con tomografía computarizada: revisión sistemática y metaanálisis de ensayos clínicos aleatorizados [Contrast-induced nephropathy in patients at risk of renal failure undergoing computed tomography: systematic review and meta-analysis of randomized controlled trials]. Med Clin (Barc). 2010 Sep 11;135(8):343-50. Spanish. doi: 10.1016/j.medcli.2010.01.035. Epub 2010 Jun 17. PMID: 20594563.	Cannot access full text, incorrect intervention
13	From AM, Al Badarin FJ, McDonald FS, Bartholmai BJ, Cha SS, Rihal CS. Iodixanol versus low-osmolar contrast media for prevention of contrast induced nephropathy: meta-analysis of randomized, controlled trials. Circ Cardiovasc Interv. 2010 Aug;3(4):351-8. doi: 10.1161/CIRCINTERVENTIONS.109.917070. Epub 2010 Jul 20. PMID: 20647563.	Incorrect intervention
14	The Royal Australian and New Zealand College of Radiologists. Iodinated Contrast Media Guideline. Sydney: RANZCR; 2018.	Insufficient specific information relevant to PICO
15	Biondi-Zoccai G, Lotrionte M, Thomsen H et al. Nephropathy after administration of iso-osmolar and low-osmolar contrast media: Evidence from a network meta-analysis. International Journal of Cardiology, 2014; 172, 375-380	Incorrect intervention
16	Solomon, Richard MD*; DuMouchel, William PhD†. Contrast Media and Nephropathy: Findings From Systematic Analysis and Food and Drug Administration Reports of Adverse Effects. Investigative Radiology 41(8):p 651-660, August 2006. | DOI: 10.1097/01.rli.0000229742.54589.7b	After assessment against criteria – See Table 1 under Results
17	Wei, Y., Jiang, X., Hibberd, M. et al. Estimating the rate of acute adverse reactions to non-ionic low-osmolar contrast media: a systematic review and meta-analysis. Eur Radiol 35, 6240–6249 (2025). https://doi.org/10.1007/s00330-025-11526-z	After assessment against criteria – See Table 1 under Results

Appendix 3 – AMSTAR 2 Assessments

Item	AMSTAR 2 Domain	Critical?	Suh et al. 2019	Wei et al. 2025 Rating	Solomon 2006 Rating
1	Did the research questions and inclusion criteria include PICO components?	No	Yes	Partial Yes	Partial Yes
2	**Was the protocol registered before commencement and did it deviate from the protocol?**	**Yes (CRITICAL)**	No	No	No
3	Did the authors explain their selection of study designs for inclusion?	No	Yes	Yes	Yes
4	**Did the authors use a comprehensive literature search strategy?**	**Yes (CRITICAL)**	Yes	Partial Yes	Yes
5	Was study selection performed in duplicate?	No	Yes	Yes	No
6	Was data extraction performed in duplicate?	No	Yes	No	No
7	**Did the authors provide a list of excluded studies and justify exclusions?**	**Yes (CRITICAL)**	Partial Yes	Partial Yes	No
8	Did the authors describe the included studies in adequate detail?	No	Yes	Yes	Yes
9	**Did the authors use a satisfactory technique to assess risk of bias (RoB)?**	**Yes (CRITICAL)**	Partial Yes	Yes	No
10	Did the authors report sources of funding for included studies?	No	No	No	No
11	**If meta-analysis was performed, did the authors use appropriate methods?**	**Yes (CRITICAL)**	Yes	Yes	Partial Yes
12	Did the authors assess the potential impact of RoB on the results?	No	Partial Yes	Partial Yes	No
13	**Did the authors account for RoB when interpreting/discussing results?**	**Yes (CRITICAL)**	Yes	Partial Yes	Partial Yes
14	Did the authors provide a satisfactory explanation for heterogeneity?	No	Partial Yes	Partial Yes	Partial Yes
15	**Did the authors investigate publication bias and discuss its impact?**	**Yes (CRITICAL)**	Yes	Yes	No
16	**Did the authors report any potential sources of conflict of interest, including funding?**	**Yes (CRITICAL)**	Yes	No	No

Appendix 4 – Individual studies included in Suh 2019

TABLE 1. Study Characteristics

Source	Study Site (Countries)	Study Design	Study Period	Injection Route	Type of Examinations	Age, y	Male Sex	Patients at Risk for AAR	Premedication	Specific Type of ICM	Total No. Patients	Incidence of overall AAR (%)	Incidence of Severe AAR (%)
Lensing et al, 1990[21]	Netherlands	Prospective, single-center	1985–1988	IV	Non-CT	Mean, 58 (range, 17–89)	46%	<1%	Unknown	Iohexol	463	7.99	0.43
Katayama et al, 1994[22]	Japan	Retrospective, multicenter	1990–1992	IV, IA	Various	Unknown (range, 50–59)	61%	<1%	Unknown	Iomeprol	1918	4.95	Not reported
Tveit et al, 1995[23]	Europe (4 countries)	Prospective, multicenter	Unknown	IV	Non-CT	Mean, 51.6	60.6%	<1%	Unknown	Iohexol	1485	1.95	Not reported
Vergara and Seguel, 1996[24]	Chile	Prospective, single-center	Unknown	IV	CT	Median 33.5 (IQR, 18.4–52.8)	43.4–48%	≥1% or unknown	No	Iopamidol	1590	1.01	0.00
Justesen et al, 1997[25]	Europe (12 countries)	Prospective, multicenter	1994	IA	Non-CT	65.3 ± 11.4	72.1%	≥1% or unknown	Unknown	Iopromide	1227	2.36	Not reported
										Iodixanol	1225	1.80	Not reported
Masui et al, 2005[26]	Japan	Prospective, single-center	2002	IV	CT	Mean, 60.8	60.1%	≥1% or unknown	Unknown	Iopamidol	729	0.96	0.00
Nagamoto et al, 2006[27]	Japan	Prospective, single-center	2003–2003	IV	CT	Mean, 64.1	60.2%	≥1% or unknown	Unknown	Iopamidol	940	2.77	0.00
Wendt-Nordahl et al, 2006[28]	Germany	Post-marketing surveillance, multicenter	Unknown	IV	Non-CT	56.6 (range, 3–101)	56.7%	<1%	Unknown	Iobitridol	49,975	0.90	0.00
Ho et al, 2007[29]	Canada	Retrospective, single-center	2002–2004	IV	CT	Unknown	52.9%	≥1% or unknown	Unknown	Iohexol	22,044	0.24	0.00
										Iodixanol	15,142	0.50	0.01
Juchem and Dall'Agnol, 2007[30]	Brazil	Retrospective, single-center	2004	IV	CT	Unknown	Unknown	≥1% or unknown	Unknown	Ioversol	190	1.05	0.00
Nonent et al, 2007[31]	Europe (7 countries)	Prospective, multicenter	Unknown	IV	CT	66.7 ± 10.1	156:17	<1%	Unknown	Iodixanol	136	8.82	2.21
Kopp et al, 2008[32]	United States	Prospective, multicenter	1999–2003	IV, IA	CT and non-CT	56.1 ± 16.66	52.9%	≥1% or unknown	Yes	Iopromide	74,717	1.43	0.02
Häussler, 2010[33]	Germany	Prospective, multicenter	2008	IV	CT	Mean, 61.8 (range, 18–100)	51.3%	≥1% or unknown	Yes	Iodixanol	9515	0.32	0.02
Ho et al, 2012[34]	Australia	Retrospective, single-center	2004–2008	IV	CT	Mean, 56.7, (range, 12–106)	54.9%	≥1% or unknown	Yes	Iopromide	29,962	0.16	0.01
Palkowitsch et al, 2012[35]	Europe and Asia (21 countries)	Prospective, multicenter	2008–2009	IV, IA	CT and non-CT	Median, 55 (IQR, 44–66)	57.7%	≥1% or unknown	Yes	Iopromide	44,835	2.82	0.02
Vogl et al, 2012[36]	Germany	Prospective, multicenter	2006–2007	IV	CT	60.8 ± 15.1	48.7%	≥1% or unknown	Unknown	Ioversol	10,836	0.28	0.04
Farolfi et al, 2014[37]	Italy	Retrospective, single-center	2010–2012	IV	CT	63.9 ± 13.01	50.2%	≥1% or unknown	Yes	Iobitrol	761	2.37	Not reported
										Iomeprol	3043	2.60	Not reported
García et al, 2014[38]	Spain	Retrospective, single-center	2009–2013	IV	CT and non-CT	55.4 ± 17.5	Unknown	≥1% or unknown	Yes	Iomeprol	37,154	0.23	0.05
						50.9 ± 17.9	Unknown			Iopromide	72,887	0.21	0.01
Müller, 2014[39]	Germany	Prospective, multicenter	2009–2010	IV	CT	61.3 ± 14.88	50.8%	≥1% or unknown	Yes	Iodixanol	10,354	0.34	Not reported
Zhang et al, 2014[40]	China	Prospective, multicenter	2011–2012	IV, IA	CT and non-CT	Mean, 60.4 (range, 5–100)		<1%	Yes	Iodixanol	20,185	0.58	0.01
Xiao et al, 2016[41]	China	Prospective, single-center	2014–2015	IV	CT	53.5 ± 13.4		<1%	Unknown	Iohexol	1000	2.00	Not reported
										Iodixanol	1000	0.70	Not reported
Zhang et al, 2016[42]	China	Retrospective, single-center	2006–2012	IV	CT	54.4 ± 18.8	61.0%	≥1% or unknown	No	Iopamidol	69,550	0.24	0.01
										Iopromide	67,923	0.38	0.01
McCullough et al, 1989[43]	England	Prospective, randomized controlled trial, single-center	1988	IV	Urography	Unknown	Unknown	≥1% or unknown	Unknown	Iopamidol	855	5.26	0.00
Gomi et al, 2010[3]	Japan	Prospective, single-center	2004–2007	IV	CT	Mean, 65	Unknown	≥1% or unknown	Unknown	Iomeprol	1751	3.94	0.00
							Unknown			Iopamidol	1697	2.24	0.00
							Unknown			Iohexol	1792	2.01	0.00
							Unknown			Iopromide	1805	3.55	0.00
							Unknown			Ioversol	1886	1.80	0.00
Prakkamakul and Lerdlum, 2013[7]	Thailand	Retrospective, single-center	2006–2009	IV	CT and non-CT	Unknown	Unknown	≥1% or unknown	Yes	Iohexol	4864	0.82	Not reported
										Iopamidol	6791	0.29	Not reported
										Iopromide	25,444	0.65	Not reported
										Iobitridol	3512	0.26	Not reported
Yang et al, 2015[9]	Korea	Retrospective, single-center	2011–2012	IV	CT	56.8 ± 16.3	54.8%	≥1% or unknown	Yes	Iomeprol	8663	1.77	Not reported
										Iohexol	27,470	1.21	Not reported
										Iopromide	3863	0.44	Not reported
Motosugi et al, 2016[8]	Japan	Prospective, single-center	2012–2013	IV	CT	65.2	61.4%	≥1% or unknown	No	Iohexol	1722	1.97	0.00
										Iopamidol	1298	2.00	0.00
										Iomeprol	1028	3.60	0.00
										Ioversol	440	1.82	0.00
Kim et al, 2017[6]	Korea	Retrospective, single-center	2006–2010	IV	CT	51.6 ± 18.5	54.6%	≥1% or unknown	Unknown	Iobitridol	32,756	0.34	0.01
										Iohexol	65,764	0.64	0.02
										Iopamidol	135,882	0.67	0.02
										Iopromide	51,685	1.03	0.04
Unpublished unicenter data, 2014–2017	Korea	Retrospective, single-center	2014–2017	IV	CT	59.8 ± 14.5	50.4%	<1%	Yes	Iobitridol	55,133	1.20	0.02
										Iohexol	115,608	0.82	0.01
										Iomeprol	26,344	1.18	0.02
										Iopamidol	5820	1.63	0.03
										Iopromide	4555	1.91	0.07
										Ioversol	25,193	1.09	0.01
Unpublished multicenter data, 2017	Korea	Retrospective, multicenter	March to October 2017	IV	CT	60.3 ± 14.7	50.6%	<1%	Yes	Iobitridol	27,613	0.89	0.01
										Iodixanol	3043	0.99	0.07
										Iohexol	51,586	0.62	0.01
										Iomeprol	29,247	0.95	0.01
										Iopamidol	53,037	0.70	0.01
										Iopromide	7335	0.37	0.00
										Ioversol	24,220	0.66	0.00