Clinical Updates on
Low-Osmolar Contrast Media (LOCM)
V.S.
Iso-Osmolar Contrast Media (IOCM)

Latest ACR v12, 2021 guideline version

Ultravist®
Iopromide

Chemical Structures - Iodinated Contrast Media (ICM).

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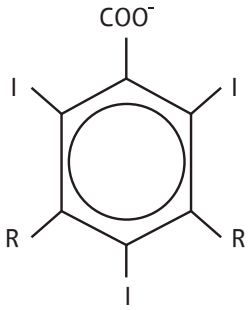
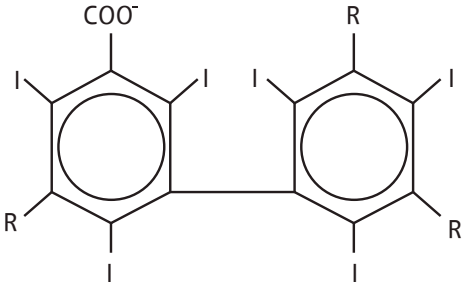
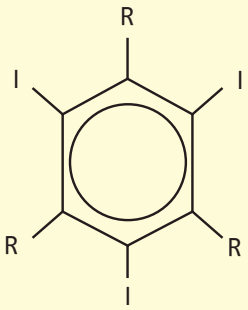
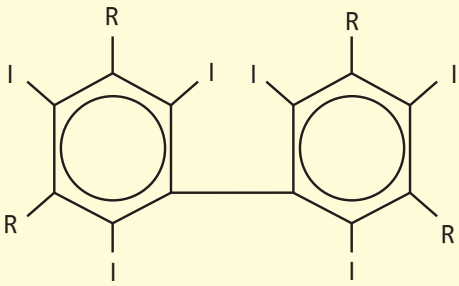
IONIC	 lothalamate Diatrizoate 'First generation' **HOCM** (1400-2016 m0sm/kg water)	 loxaglate **LOCM** (600 m0sm/kg water)
NON-IONIC	 Iopromide (Ultravist®) lopamidol lohexol loversol loxilan **LOCM** (659-796 m0sm/kg water)	 lodixanol **IOCM** (290 m0sm/kg water)

HOCM High-Osmolar Contrast Media

LOCM Low-Osmolar Contrast Media

IOCM Iso-Osmolar Contrast Media

Low-Osmolar Contrast Medias (LOCMs) like Ultravist® (Iopromide) are by far the leading class for over 20 years.

LOCMs have almost completely replaced first-generation contrast media agents (HOCMs) over time.

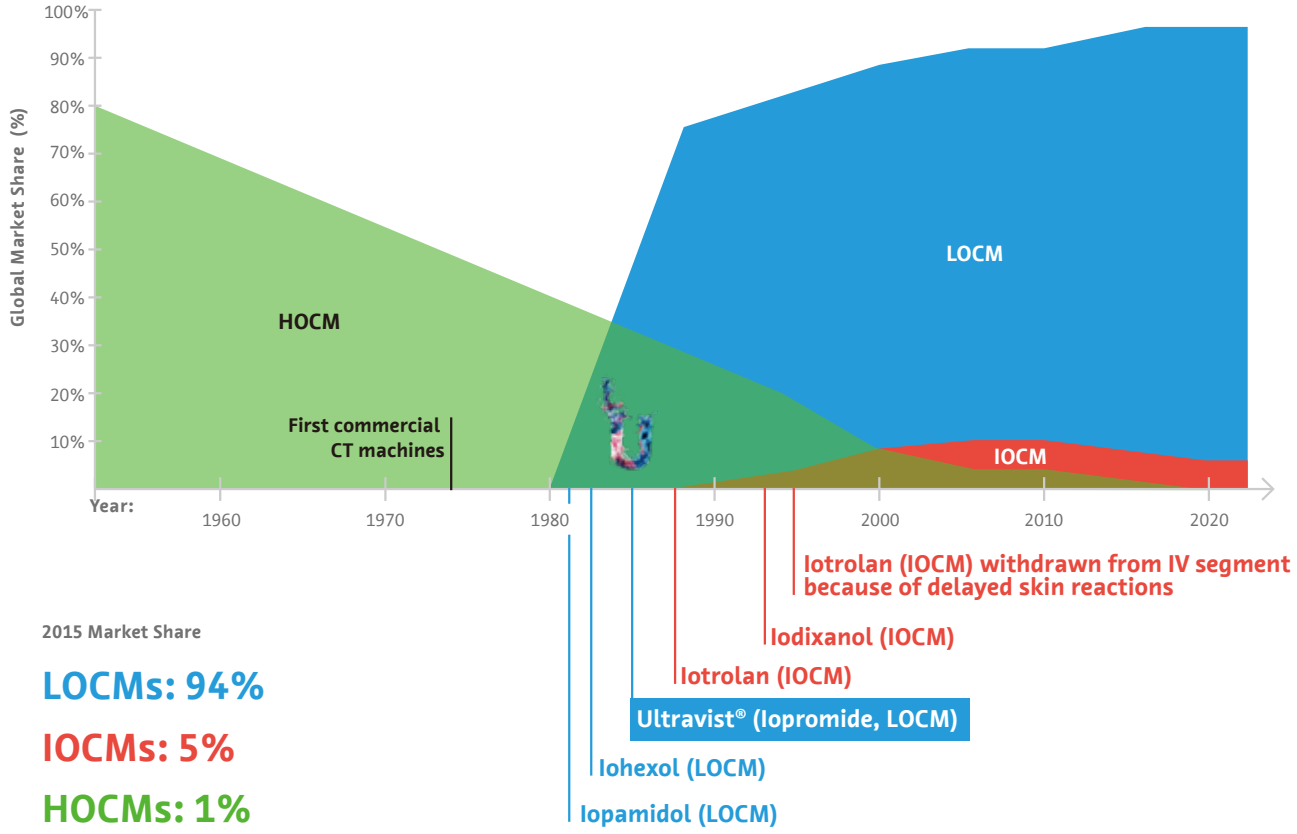


Figure: Schematic description of global CT/X-ray contrast media volumes in IV segment. IOCMs have been introduced only shortly after LOCMs and only account for a small portion of the global CT market

Feel confident delivering quality patient care using a well-established LOCM like Ultravist® (lopromide).

Literature

1. AMR Imaging Market Guide by Decision Resources Group 1995-2015. Coverage: USA, Germany, Italy, France. https://decisionresourcesgroup.com/solutions/medtech-solutions/what-is-amr-imaging/.

Iodine Delivery Rate (IDR) – a major determinant of image quality

The target IDR is achieved by flexibly adjusting contrast media concentrations and flow rates.[1]

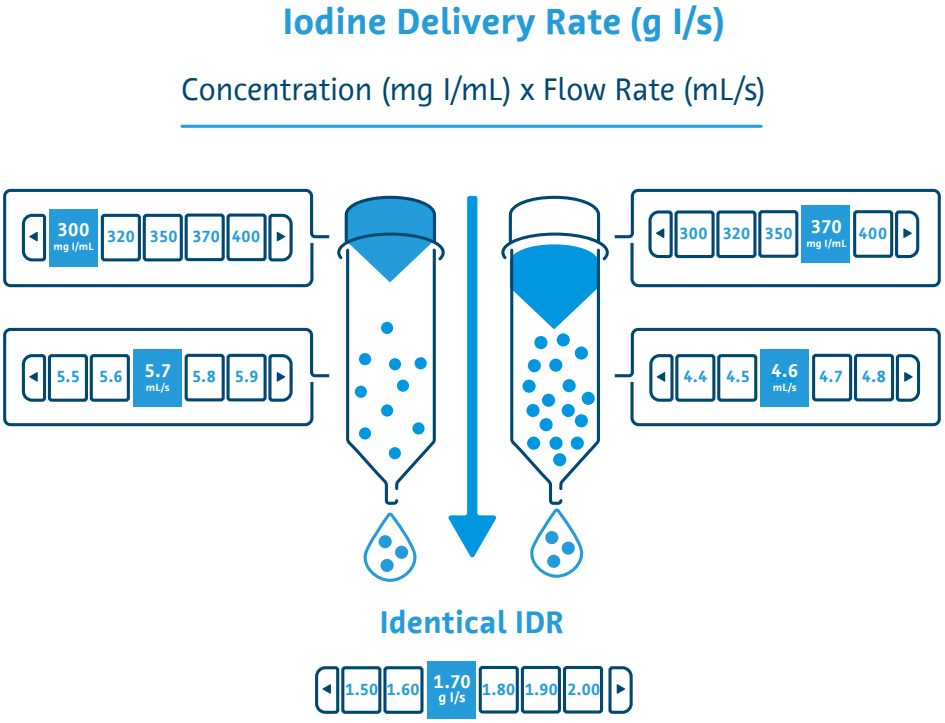


Figure 1 Examples of setting the identical target IDR by adjusting contrast medium concentration and flow rate.

- Image quality is especially important in CTA:
  - Overall diagnostic accuracy relies on sufficient intravascular attenuation,[2] which is important for the evaluation of the clinically relevant smaller vessels.[1,3]
- CT-CON confirmed that IDR is a major determinant of image quality and diagnostic efficiency in CTA.[1,]

Literature
1. Rengo M, Dharampal A, Lubbers M, et al. Impact of iodine concentration and iodine delivery rate on contrast enhancement in coronary CT angiography: a randomized multicenter trial (CT-CON). Eur Radiol. 2019 Nov;29(11):6109-6118.
2. Behrendt FF, Pietsch H, Jost G, et al. Identification of the iodine concentration that yields the highest intravascular enhancement in MDCT angiography. AJR Am J Roentgenol. 2013;200:1151–1156.
3. Faggioni L, Gabelloni M. Iodine Concentration and Optimization in Computed Tomography Angiography: Current Issues. Invest Radiol. 2016 Dec;51(12):816-822. Review.

Taking the patient into account

- Often used “one size fits all” CT protocols with fixed contrast media volumes do not consider the patient’s body weight.[4]
- Because of this, standard protocols may result in different attenuation for different patients:
  - For heavier patients, the attenuation values may be below the diagnostic level[5]
  - For thin patients, on the other hand, attenuation may exceed required levels[5]

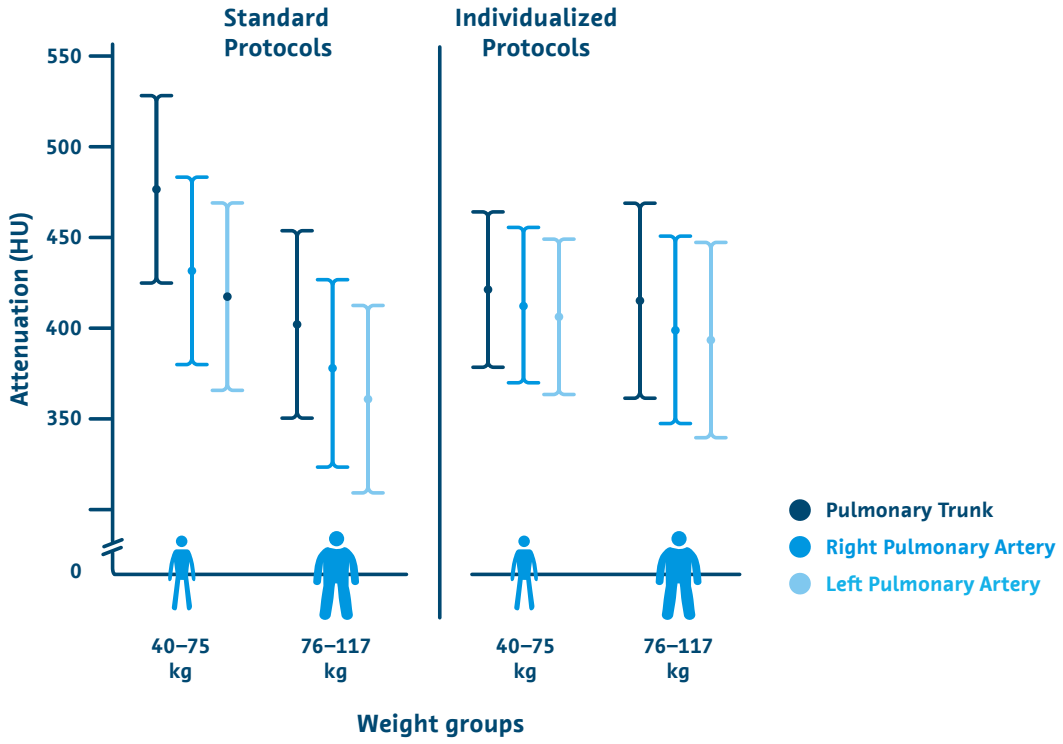


Figure 2 Comparison of attenuation between standard and individualized body weight adapted CT-protocols.[5]

Hendriks et al. showed that the use of individualized contrast media protocols provides diagnostic and robust enhancement in emergency CT pulmonary angiography, as well as substantial contrast media volume reduction in lower weight patients compared with a fixed protocol.[5]

The IDR concept and patient related factors provide a way for optimizing the contrast media application to achieve consistent image quality in CTA.[1,5]

Literature
1. Rengo M, Dharampal A, Lubbers M, et al. Impact of iodine concentration and iodine delivery rate on contrast enhancement in coronary CT angiography: a randomized multicenter trial (CT-CON). Eur Radiol. 2019 Nov;29(11):6109-6118.
4. Bae KT. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. Radiology. 2010;256:32–61.
5. Hendriks BMF, Kok M, Mihl C, Bekkers SCAM, Wildberger JE, Das M. Individually tailored contrast enhancement in CT pulmonary angiography. Br J Radiol 2016; 89: 20150850.

Ultravist® (Iopromide, LOCM) – a good choice to apply IDR

- Ultravist® (Iopromide, LOCM) allows for a high degree of flexibility in the implementation of optimal IDR protocols* with higher flow rates and without compromising patient comfort.[1,6]
- Both Ultravist® (Iopromide, LOCM) 300 and 370 have a relatively low viscosity in relation to their iodine concentration which allows for lower peak pressures at identical flow rates.[1]
- Despite having a lower iodine concentration, the viscosity of Iohexol 350 is higher than that of Ultravist® (Iopromide, LOCM) 370.**[1]

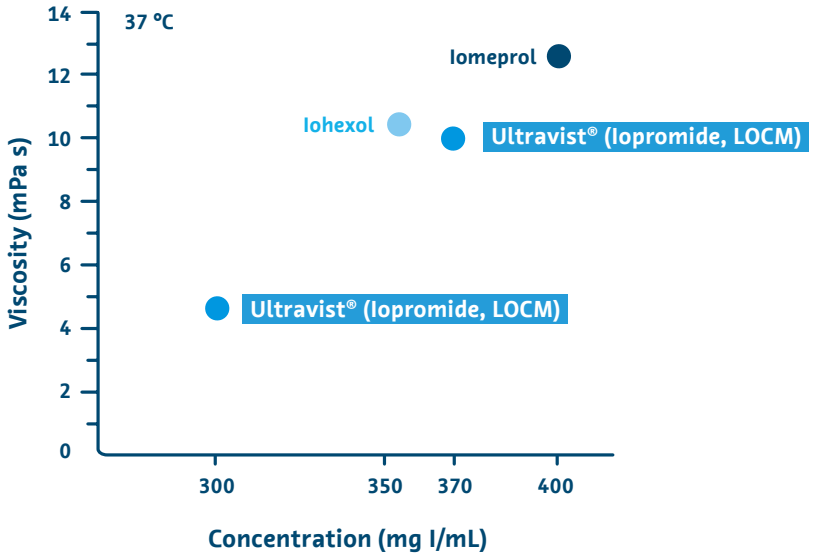


Figure 4 Relation of CT-CON investigated contrast media concentrations to their viscosity at 37° celsius as stated in the respective prescribing information.[7-9]

Ultravist® (Iopromide, LOCM) has low viscosity in relation to its iodine concentration.[9]

* A target IDR of approximately 1.2 to 1.6 gI/s and up to 2.0 gI/s is usually recommended for non-coronary and coronary CTA applications, respectively.[3]

** numerically, not statistically significant

Literature

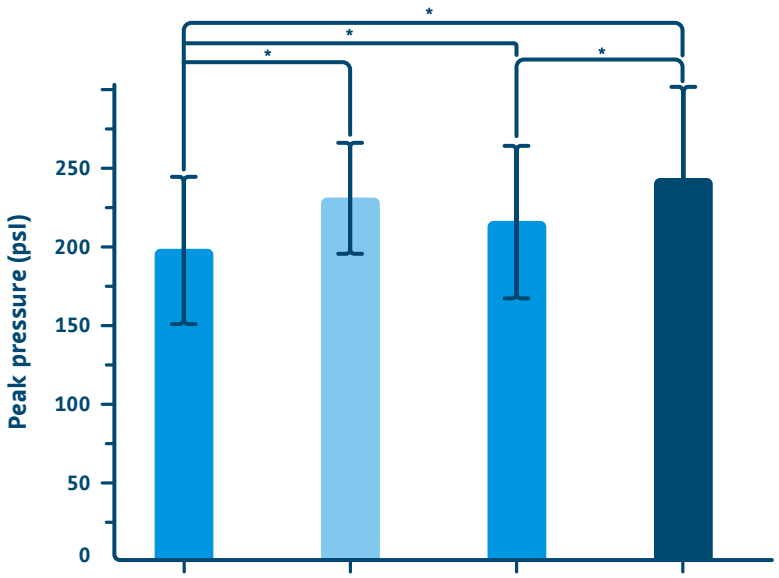
1. Rengo M, Dharampal A, Lubbers M, et al. Impact of iodine concentration and iodine delivery rate on contrast enhancement in coronary CT angiography: a randomized multicenter trial (CT-CON). Eur Radiol. 2019 Nov;29(11):6109-6118.
3. Faggioni L, Gabelloni M. Iodine Concentration and Optimization in Computed Tomography Angiography: Current Issues. Invest Radiol. 2016 Dec;51(12):816-822. Review.
6. Kok M, Mihl C, Hendriks BM, Altintas S, et al. Patient Comfort During Contrast Media Injection in Coronary Computed Tomographic Angiography Using Varying Contrast Media Concentrations and Flow Rates: Results From the EICAR Trial. Invest Radiol. 2016 Dec;51(12):810-815.
7. Iomeprol prescribing information. https://imaging.bracco.com/sites/braccoimaging.com/files/technica_sheet_pdf/de-de-2018-11-15-spc-Imeron.pdf. Date of access: December 2019.
8. Iohexol prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018956s101lbl.pdf. Date of access: December 2019.
9. Iopromide prescribing information. http://www.mhra.gov.uk/spc-pil/?subsName=IOPROMIDE&pageID=SecondLevel. Date of access: December 2019.

Peak pressure and image quality

High peak pressures should be avoided to achieve optimal image quality.[1]

- CT-CON demonstrated that higher iodine concentrated contrast media with simultaneously increased viscosity result in higher peak pressures.[1]
- Lower viscosity is known to be beneficial in terms of injection pressure.[4,6]
- High viscosity complicates the contrast administration at higher flow rates.[3]

CT-CON investigated the relationship between viscosity and peak pressure for the different contrast media used.[1]



	Ultravist® (Iopromide, LOCM) 300 mg I/mL	Iohexol 350 mg I/mL	Ultravist® (Iopromide, LOCM) 370 mg I/mL	Iomeprol 400 mg I/mL
Peak pressure (psi)**	197.4 ± 47.7	229.8 ± 35.7	216.1 ± 46.1	243.7 ± 58.7

Figure 3 Influence of viscosity on peak pressures for different contrast media.[1]

* p<0.05

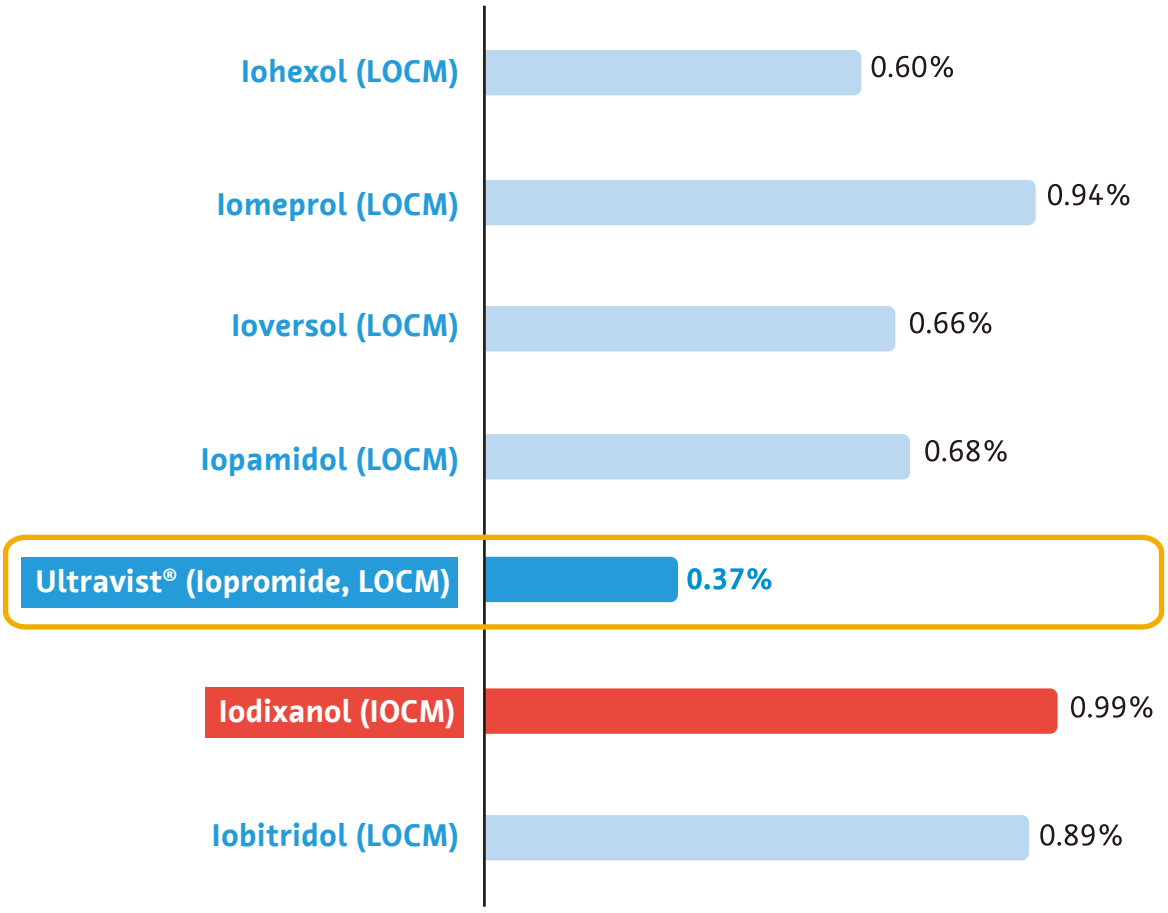
** extract from table 2 from Rengo et al.[1]

Literature

1. Rengo M, Dharampal A, Lubbers M, et al. Impact of iodine concentration and iodine delivery rate on contrast enhancement in coronary CT angiography: a randomized multicenter trial (CT-CON). Eur Radiol. 2019 Nov;29(11):6109-6118.
3. Faggioni L, Gabelloni M. Iodine Concentration and Optimization in Computed Tomography Angiography: Current Issues. Invest Radiol. 2016 Dec;51(12):816-822. Review.
4. Bae KT. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. Radiology. 2010;256:32–61.
6. Kok M, Mihl C, Hendriks BM, Altintas S, et al. Patient Comfort During Contrast Media Injection in Coronary Computed Tomographic Angiography Using Varying Contrast Media Concentrations and Flow Rates: Results From the EICAR Trial. Invest Radiol. 2016 Dec;51(12):810-815.

Proven Safety profile of Ultravist® (Iopromide, LOCM)

Ultravist® (Iopromide, LOCM) demonstrated the lowest acute adverse reactions occurrence rate from a recent Korean multi-center study conducted among 7 national public hospitals to evaluate acute adverse reactions occurrence rate of low-osmolar contrast medias (LOCMs)[1].



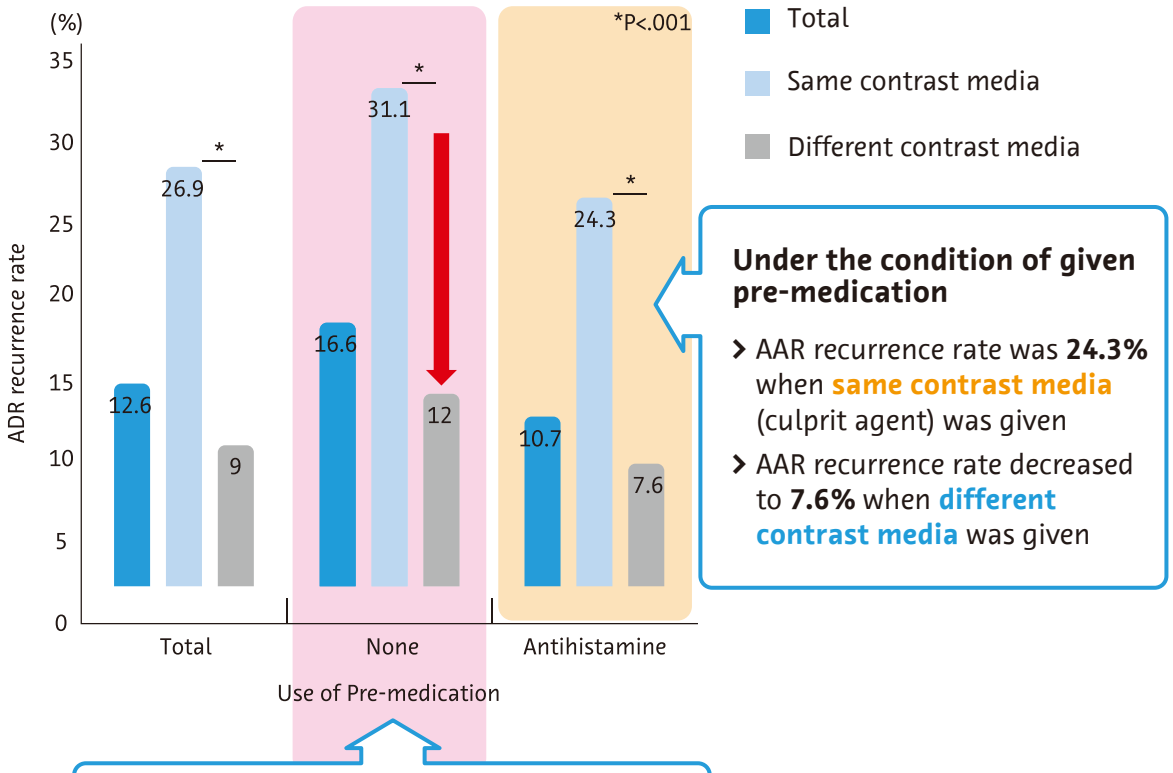
*This study is sponsored by Ministry of Food and Drug Safety (MFDS)

Literature
1. MJ Cha et al. Hypersensitivity Reactions to Iodinated Contrast Media: A Multicenter study of 196081 Patients. Radiology 2019;293:117-124

New paradigm of patient safety management

Allergy specialists and radiologists collaborated at Seoul National University Hospital to learn more about patient safety management with the results published in Radiology 2018.
This study evaluated the effectiveness of premedication protocol, the most commonly used actue adverse reaction recurrence prevention method, for patient with previous history of mild acute adverse reaction[2].

Acute Adverse Reactions (AAR) recurrence rate according to choice of iodinated contrast media



Under the condition of given pre-medication

- AAR recurrence rate was **24.3%** when **same contrast media** (culprit agent) was given
- AAR recurrence rate decreased to **7.6%** when **different contrast media** was given

Under the condition of no pre-medication:

- AAR recurrence rate was **31.1%** when **same contrast media** (culprit agent) was given
- AAR recurrence rate decreased to **12%** when **different contrast media** was given

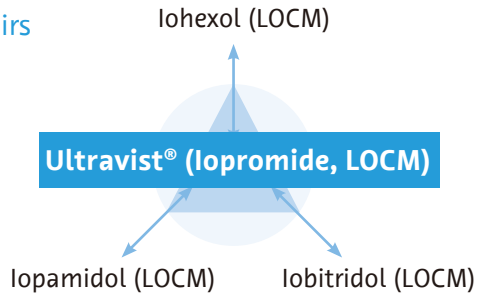
Literature
2. SJ Park et al. Immediate Mild Reactions to CT with Iodinated Contrast Media: Strategy of Contrast Readministration without Corticosteroids. Radiology; 2018

New paradigm of patient safety management

Choose the right 'pair' of iodinge contrast media

Ultravist® (Iopromide, LOCM) is included in 3 out of 5 pairs that showed effective decrease in acute adverse reactions recuurence rate

Iohexol (LOCM) ‹› **Ultravist® (Iopromide, LOCM)**
Iopamidol (LOCM) ‹› **Ultravist® (Iopromide, LOCM)**
Iobitridol (LOCM) ‹› **Ultravist® (Iopromide, LOCM)**



Recurrence Rates accordingly to Combination of Contrast Media in Absence of Pre-medication[2]

Combination of Contrast Media	Recurrence	Odds ratio*	95% Confidence Interval	P Value	Odds Ratio+	95% Confidence Interval	P Value
Iohexol (LOCM) / Iopamidol (LOCM)	24/110 (21.8)	0.470	0.247, 0.892	.021	1.863	0.995, 3.487	.052
Iopamidol (LOCM) / **Ultravist® (Iopromide, LOCM)**	11/58 (19.0)	0.366	0.163, 0.820	.015	1.466	0.654, 3.289	.353
Iohexol (LOCM) / **Ultravist® (Iopromide, LOCM)**	37/268 (13.8)	0.402	0.227, 0.712	.002	1.353	0.788, 2.321	.273
Iobitridol (LOCM) / Iohexol (LOCM)	32/261 (12.3)	0.245	0.127, 0.474	<.0001	0.887	0.468, 1.680	.713
Iobitridol (LOCM) / **Ultravist® (Iopromide, LOCM)**	18/169 (10.7)	0.296	0.129, 0.682	.004	1.048	0.462, 2.374	.911
Iobitridol (LOCM) / Iopamidol (LOCM)	7/17 (41.2)	0.942	0.340, 2.608	.909	4.175	1.545, 11.281	.005
Iobitridol (LOCM) / Ioversol (LOCM)	7/21 (33.3)	0.890	0.321, 2.466	.823	3.310	1.210, 9.056	.020
Ultravist® (Iopromide, LOCM) / Ioversol (LOCM)	1/2 (50.0)	1.344	0.083, 21.898	.835	5.961	0.369, 96.259	.208
Iohexol (LOCM) / Ioversol (LOCM)	5/12 (41.7)	0.876	0.237, 3.232	.842	3.585	0.978, 13.137	.054
Iohexol (LOCM) / Iomeprol (LOCM)	3/13 (23.1)	0.709	0.163, 3.084	.647	1.937	0.437, 8.591	.384
Iomeprol (LOCM) / Iopamidol (LOCM)	4/19 (21.1)	0.472	0.144, 1.551	.216	1.804	0.551, 5.913	.330
Iopamidol (LOCM) / Ioversol (LOCM)	2/10 (20.0)	0.188	0.023, 1.569	.123	0.779	0.094, 6.454	.817
Iomeprol (LOCM) / Ultravist® (Iopromide)	2/11 (18.2)	0.612	0.108, 3.451	.578	1.877	0.321, 10.980	.485
Iobitridol (LOCM) / Iomeprol (LOCM)	0/8 (0)	...	NA	...	...	NA	...
Iomeprol (LOCM) / Ioversol (LOCM)	0/1 (0)	...	NA	...	...	NA	...

Note: Except where indicated, data are the numerator/denominator of patients, with percentages in parentheses. NA = not assessable.
*Compared with exposure to same contrast media.
+Compared with exposure to different contrast media.

Literature
2. SJ Park et al. Immediate Mild Reactions to CT with Iodinated Contrast Media: Strategy of Contrast Readministration without Corticosteroids. Radiology; 2018

New paradigm of patient safety management

This study outcome is reflected on recent clinical practice guidelines[1]
(ESUR v10.0, 2018 and ACR v12, 2021)

ESUR (v10.0, 2018)[2]

ESUR Guideline 10.0, revised in 2018, states
"For previous contrast agent reactors: **Use a different contrast agent,** preferably after consultation with a specialist in drug allergy."

Premedication:

› **Premedication is not recommended** because there is not good evidence of its effectiveness.

ACR (v.12, 2021)[3]

ACR Manual version 12, revised in 2021, states
"In patients with a prior allergic-like or unknown-type contrast reaction to a known contrast medium, **changing contrast media within the same class** (e.g. one iodinated medium for another) may help reduce the likelihood of a subsequent contrast reaction."

Premedication:

› Nonetheless, many experts believe that **premedication does reduce the likelihood of a reaction in high-risk patients** receiving low-osmolality iodinated contrast medium, although the number needed to treat to prevent a reaction is high.

Literature

1. MJ Cha et al. Hypersensitivity Reactions to Iodinated Contrast Media: A Multicenter study of 196081 Patients,Radiology 2019;293:117-124
2. ESUR Guidelines on Contrast Agents V.10.0 (www.esur-cm.org)
3. ACR Manual on Contrast Media Version 12; 2021 ACR Committee on Drugs and Contrast Media (and references therein) (https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf)

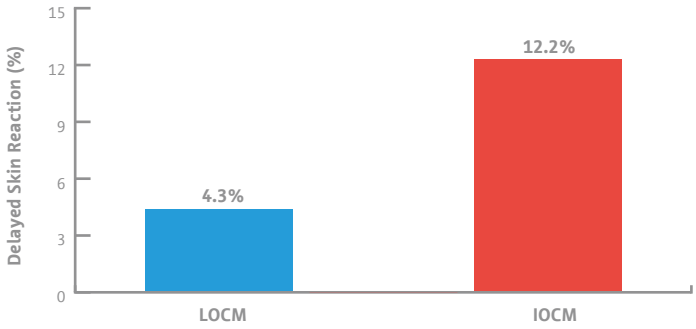
Low-Osmolar Contrast Medias (LOCMs) like Ultravist® (Iopromide) cause significantly fewer delayed skin reactions than Iso-Osmolar Contrast Medias (IOCMs) like Iodixanol.

Impact on patient safety

Iodixanol (IOCM)

caused 2.5 times higher rates of delayed skin reactions compared to LOCMs Iopamidol and Ioxaglate.

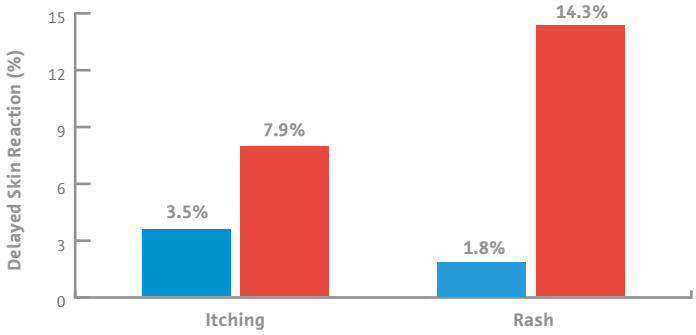
Source: Sutton AG, et al. 2001.



Iodixanol (IOCM)

caused 2 times higher rates of itching and 7 times higher rates of rashes than the LOCM Ultravist® (Iopromide).

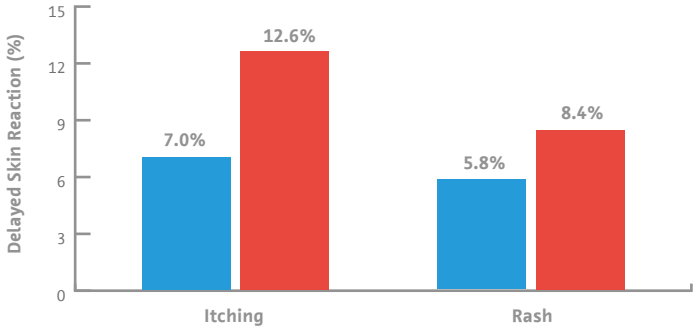
Source: Gharekhanloo F, et al. 2012.



Iotrolan (IOCM)

caused significantly higher rates of delayed skin reactions than the LOCM Ultravist® (Iopromide).

Source: Schild, et al. 2006.



LOCMs: Ultravist®(Iopromide), Ioxagate

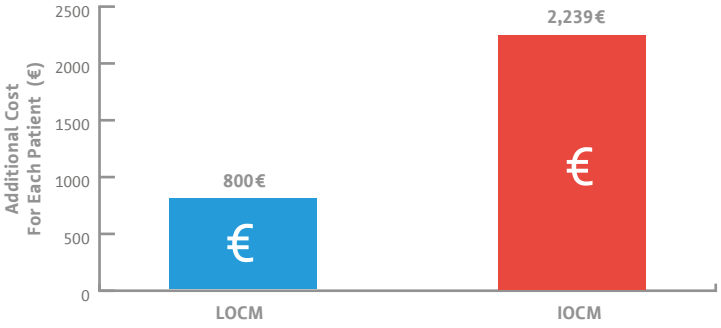
IOCMs: Iodixanol, Iotrolan

LOCMs like Ultravist® (Iopromide) have a lower rate of delayed skin reactions than IOCMs.

The ESUR Guidelines list IOCMs as a risk factor for delayed skin reactions.

Impact on costs

Additional costs caused by delayed skin reactions when using the IOCM Iodixanol are 2.5 times higher than when using LOCMs like Ultravist® (Iopromide),Iomeprol or Iobitridol.



Source: Arana E, et al 2012.

LOCMs: Ultravist®(Iopromide), Ioxagate

IOCMs: Iodixanol, Iotrolan

Delayed skin reactions are a patient safety concern. Higher incidences of reactions with IOCMs cause the healthcare system additional costs.

Literature
Arana E and Catalá-López F, Imaging Med. 2012 4(2), 193–99.
Gharekhanloo F and Torabian S, Iran J Radiol. 2012 Jun;9(2):63-6.
Hosoya T et al., Radiat Med. 2000 Jan-Feb;18(1):39-45.
Schild HH et al., Radiology. 2006 Jul;240(1):56-64.
Sutton AG et al., Am Heart J. 2001 Apr;141(4):677-83.

Renal Safety - Clinical Trials Low-Osmolar Contrast Media (LOCM) vs Iso-Osmolar Contrast Media (IOCM)

Post-contrast acute kidney injury (PC-AKI) may be a severe complication to the administration of iodine-based contrast media for diagnostic or interventional procedures. A difference in nephrotoxic potential between iso-and low-osmolar contrast media has been investigated in a variety of studies.

Ultravist® (Iopromide, LOCM) shows no clinically relevant difference to IOCM[1-7]

Individual Comparison Ultravist® (Iopromide, LOCM) VS Iodixanol (IOCM)

Chen et al. (2012)	Iodixanol 320 (N=284) Iopromide 370 (N=278)	SCr of ≥ 50 % from baseline at 72 h p.a.	**NON-inferior** (p<0.001)
Bolognese et al. (2012)	Iodixanol 320 (N=236) Iopromide 370 (N=239)	SCr ≥ 25 % from baseline till 72 h p.a.	**NON-inferior** (p<0.0002)
Shin et al. (2011)	Iodixanol 320 (N=215) Iopromide 300 (N=205)	≥ 25 % or 0.5 mg/dl from baseline at 24 h or 48 h	**NO Significant Difference** (p=0.394)
Juergens et al. (2009)	Iodixanol 320 (N=91) Iopromide 370 (N=100)	≥ 25 % or 0.5 mg/dl from baseline at 48 h	**NO Significant Difference** (p=0.56)

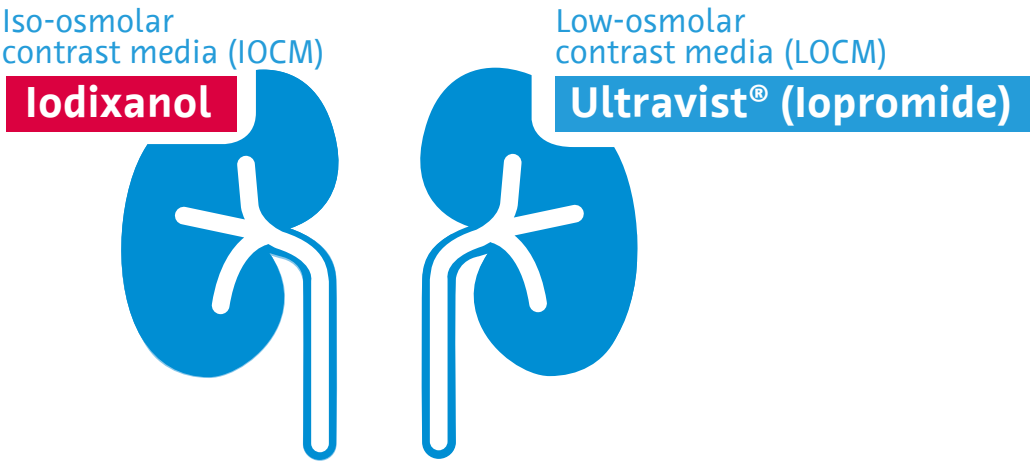
Meta-analyses All LOCM group VS Iodixanol (IOCM)

Han et al. (2018)	Iodixanol 320 (N=575) LOCM (N=525)	12 trials Diabetic patients	**NO Signficant Difference** Subgroup analysis: **Significant difference between Iohexol (LOCM) vs Iodixanol (IOCM)**
From et al. (2010)	Iodixanol 320 (N=3,672) LOCM (N=3,494)	36 trials	**NO Significant Difference** Subgroup analysis: **Significant difference between Iohexol (LOCM) vs Iodixanol (IOCM)**
Heinrich et al. (2009)	Iodixanol (N=1,701) LOCM (N=1,569)	25 trials	**NO Significant Difference** Subgroup analysis: **Significant difference between Iohexol (LOCM) vs Iodixanol (IOCM)**

Table 1: PC-AKI: Direct comparison studies and meta-analyses
SCr: Serum Creatinine; p.a.: post administration

Literature
1. Chen Y et al. Renal tolerability of iopromide and iodixanol in 562 renally impaired patients undergoing cardiac catheterisation: the DIRECT study. EuroIntervention 2012;8:830-838.
2. Bolognese L, Falsini G, Schwenke C et al. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.
3. Shin DH, Choi DJ, Youn TJ et. al. Comparison of contrast-induced nephrotoxicity of iodixanol and iopromide in patients with renal insufficiency undergoing coronary angiography. Am J Cardiol. 2011 Jul 15;108(2):189-94.
4. Juergens CP, Winter JP, Nguyen-Do P et al. Nephrotoxic effects of iodixanol and iopromide in patients with abnormal renal function receiving N-acetylcysteine and hydration before coronary angiography and intervention: a randomized trial. Intern Med J. 2009 Jan;39(1):25-31.
5. Han XF, Zhang XX et al. Contrast-induced nephropathy in patients with diabetes mellitus between iso- and low-osmolar contrast media: A meta-analysis of full-text prospective, randomized controlled trials. PLoS One. 2018 Mar 20;13(3)
6. From AM, Al Badarin FJ, McDonald FS et al. 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.
7. Heinrich MC, Häberle L, Müller V, Bautz W, Uder M. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. Radiology. 2009; 250(1):68-86.

Update Guideline (ESUR v. 10.0, 2018 and ACR v.12, 2021) see no preference for Iso-Osmolar Contrast Media (IOCM) over Low-Osmolar Contrast Media (LOCM)



ESUR (v10.0, 2018)[4]

- **Use low- OR iso-osmolar contrast media.**

Risk-factors for PC-AKI:

- Intra-arterial contrast medium administration with first pass renal exposure.
- Large doses of contrast medium given intra-arterially with first pass renal exposure.
- High-osmolality contrast media.
- Multiple contrast medium injections within 48-72 hours.

ACR (v.12, 2021)[5]

- (...)Studies [83-86] have **failed to establish a clear advantage** of IV iso-osmolality iodixanol over IV LOCM with regard to CA-AKI or CI-AKI.

- A 2009 meta-analysis using data pooled from 25 trials found **no difference** in the rate of CA-AKI between iodixanol and low osmolality agents after intravenous administration [87]. (...)

Literature
4. ESUR Guidelines on Contrast Agents V. 10.0 (www.esur-cm.org)
5. ACR Manual on Contrast Media Version 12; 2021 ACR Committee on Drugs and Contrast Media (and references therein). (https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf)

Incidence of Post Contrast-Acute Kidney Injury (PC-AKI)

ESUR assessment on PC-AKI incidence

"The risk of PC-AKI after intravenous (IV) CM has probably been overestimated. Two meta-analyses of [...] showed PC-AKI incidences of 6.4 % [...] and 5.0 % [...] [11,12]".[1 and references therein]

Ultravist® (Iopromide, LOCM) data on PC-AKI:

AMACING trial[2]

The Lancet 2017

In a landmark investigation the AMACING trial showed a rate of 2.7 % of PC-AKI in patients with an eGFR between 30–60 mL per min/1.73m^2 undergoing CE-CT (IV) or coronary angiography (IA) examinations irrespective of prophylactic i.v. hydration.

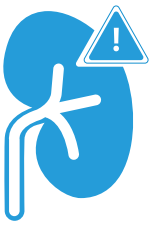
Endpoint definition PC-AKI	Increase in serum creatinine by more than 25% or 44 µmol/L within 2-6 days of contrast exposure		
Study population	IA	IV	Sum
Group size n	289	314	603
Incidence of PC-AKI	4.2 %	1.3 %	**2.7 %**

DIRECT study[3]

EuroIntervention 2012

562 patients with with an eGFR between 30–60 mL per min/1.73m^2 undergoing coronary angiography showed a rate of PC-AKI in a multicenter, single country (China) study showed a rate of 0,4% PC-AKI in a multicenter, single country (China) study.

Endpoint definition PC-AKI	Relative increase in serum creatinine of ≥50% from baseline to 72 hours after CM administration
Study population	IA (coronary angiography with or without PCI)
Group size n	278 (Iopromide)
Incidence of PC-AKI	**0.4%**



ESUR and ACR recommendations reduced the risk threshold for renal safety to eGFR < 30 mL/min/1.73m^2 for IV contrast application

ESUR (v10.0, 2018)[4]

Risk-factors for PC-AKI:

- eGFR less than 30 mL/min/1.73 m^2 before intravenous contrast medium or intra-arterial contrast medium administration with second pass renal exposure.
- eGFR less than 45 mL/min/1.73 m^2 before intra-arterial contrast medium administration with first pass renal exposure or in ICU patients.
- Known or suspected acute renal failure.

ACR (v.12, 2021)[5] & NKF Consensus Statements 2020[6]

- (...)At the current time, there is **very little evidence that IV iodinated contrast material is an independent risk factor for AKI in patients with eGFR ≥30 mL/min/1.73m^2.** Therefore, if a threshold for CI-AKI risk is used at all, 30 mL / min/1.73m^2, seems to be the one with the greatest level of evidence [Davenport 2013]. (...)[5]

- In patients at high risk of CI-AKI, including those with recent AKI, eGFR < 30 mL/min/1.73m^2, and nonanuric patients undergoing maintenance dialysis. **Ad hoc lowering of contrast media dose below a known diagnostic threshold should be avoided**. Rather, the minimum routine clinical diagnostic dose should be used.[6]

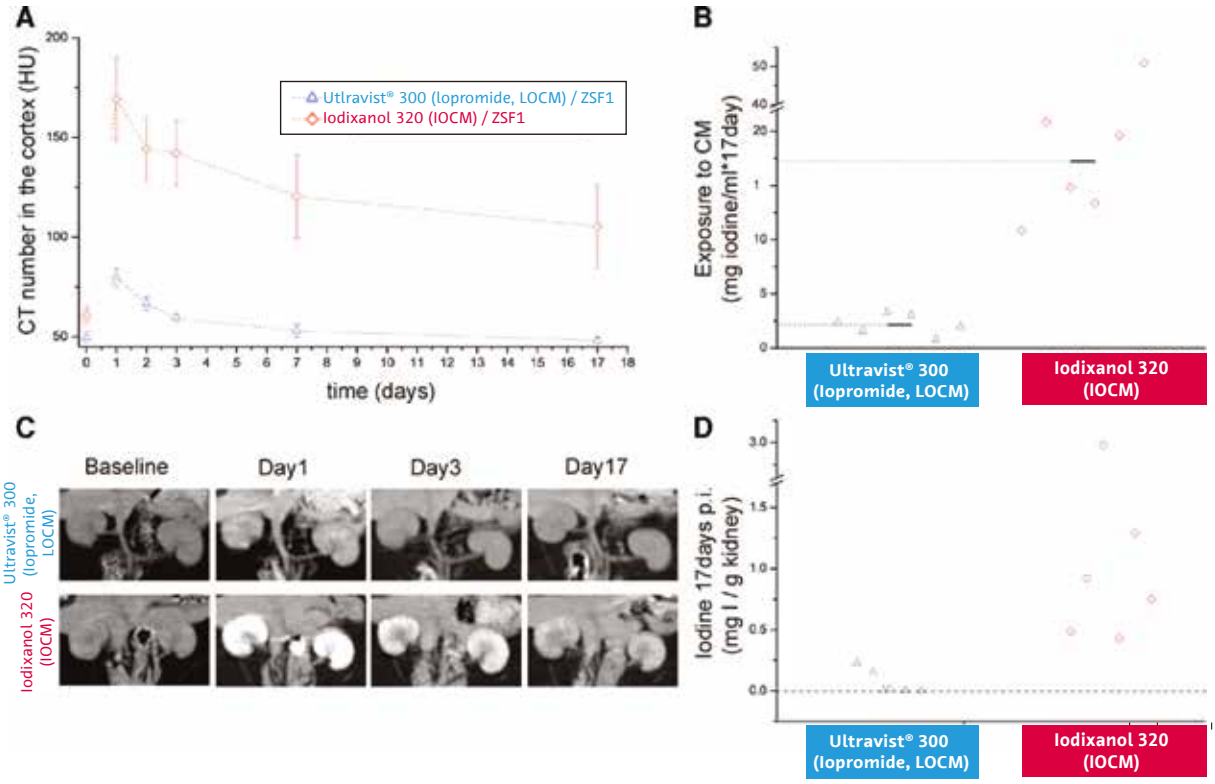
Literature

1. van der Molen AJ, Reimer P, Dekkers IA, et al. Post-contrast acute kidney injury - Part 1: Definition, clinical features, inci dence, role of contrast medium and risk factors : Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol. 2018 Jul;28(7):2845-2855.
2. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017 Apr 1;389(10076):1312-1322.
3. Chen Y, Hu S, Liu Y, et al. Renal tolerability of iopromide and iodixanol in 562 renally impaired patients undergoing cardiac catheterisation: the DIRECT study. EuroIntervention. 2012 Nov 22;8(7):830-8.
4. ESUR Guidelines on Contrast Agents V. 10.0 (www.esur-cm.org)
5. ACR Manual on Contrast Media Version 12; 2021 ACR Committee on Drugs and Contrast Media (and references therein). (https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf)
6. Davenport et al.Radiology.2020 Mar;294(3):660-668.

Preclinical data showed that there is significant contrast media retention inthe kidneys with Iso-Osmolar Contrast Media (IOCM) more than Low-Osmolar Contrast Media (LOCM)

This prolonged retention is possibly associated with higher renal toxicity as elevated by the biomarkers of hypoxia and renal injury.[1,2]

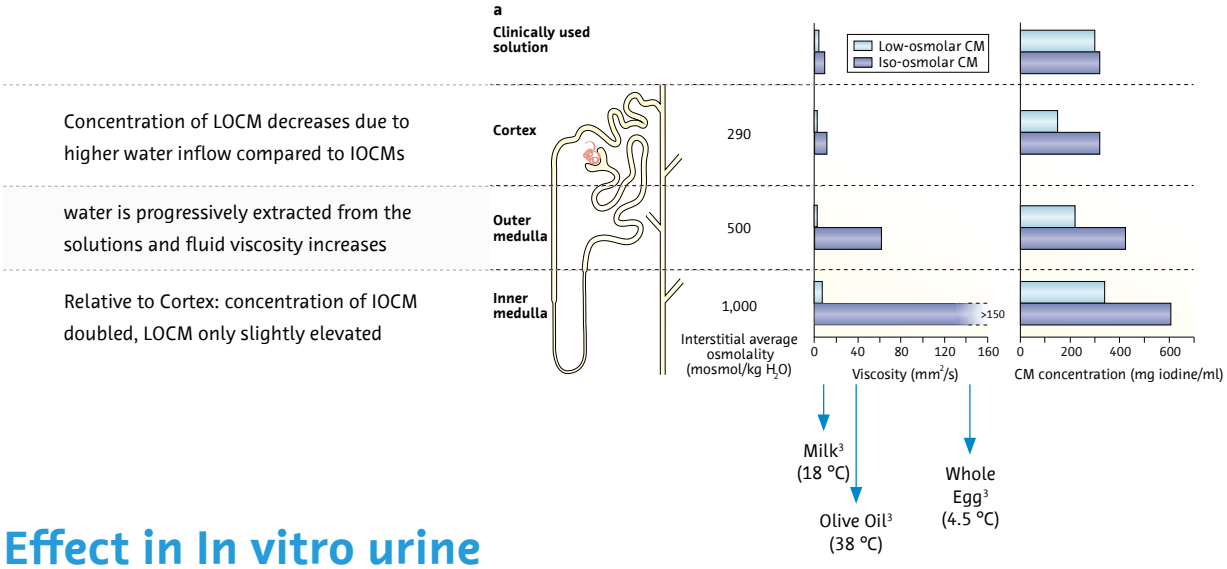
Transit time through kidney in rats are much longer for Iodixanol (IOCM) than for Ultravist® (Iopromide, LOCM)[2]



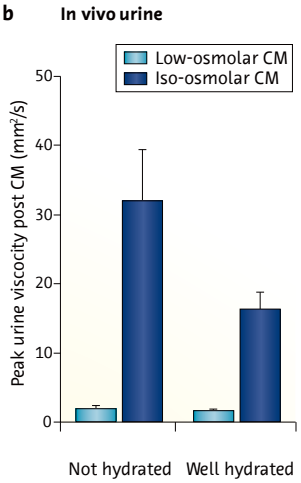
Contrast media retention in renally impaired ZSF1 rats. (A), Attenuation (HU) in the cortex in the kidney of rats injected with 1 gI/kg b.w. of Ultravist® 300 (Iopromide, LOCM) (blue line) and Iodixanol 320 (red line) at before, 1-day, 2-day, 3-day, 7-day, and 17-day p.i. (B) in addition the area under the curve is given. The respective median of the exposure is given as black line. (C), Representative CT scans of the kidney at baseline, 1-day, 3-day, and 17-day p.i., after application of Ultravist® 300 (Iopromide, LOCM) (upper row) and Iodixanol 320 (lower row). (D), Iodine concentration in the kidney of rats injected with 1 gI/kg b.w. of Ultravist® 300 (Iopromide, LOCM) (blue triangles) and Iodixanol 320 (red diamonds) 17 hours p.i. determined by RFA analysis. Over time significantly higher iodine concentrations were observed after application of the high-viscous CM compared with the low-viscous CM.

Mode of Action:

"Contrast media (CM) are not reabsorbed so they become concentrated en route through the tubules [in the kidney]. Conversely, interstitial osmolality drives tubular water reabsorption. The effects of these osmotic forces on CM concentration and viscosity were modelled by in vitro dialysis of CM solutions.[57] At the ambient osmolality of 290 mosmol/kg H_2O, the concentration of CMs with high osmolality (that is low-osmolar CMs when compared to iso-osmolar CMs) decreased owing to water inflow. With increasing ambient osmolalities, water is progressively extracted from the solutions and fluid viscosity increases."[1]



Effect in In vitro urine



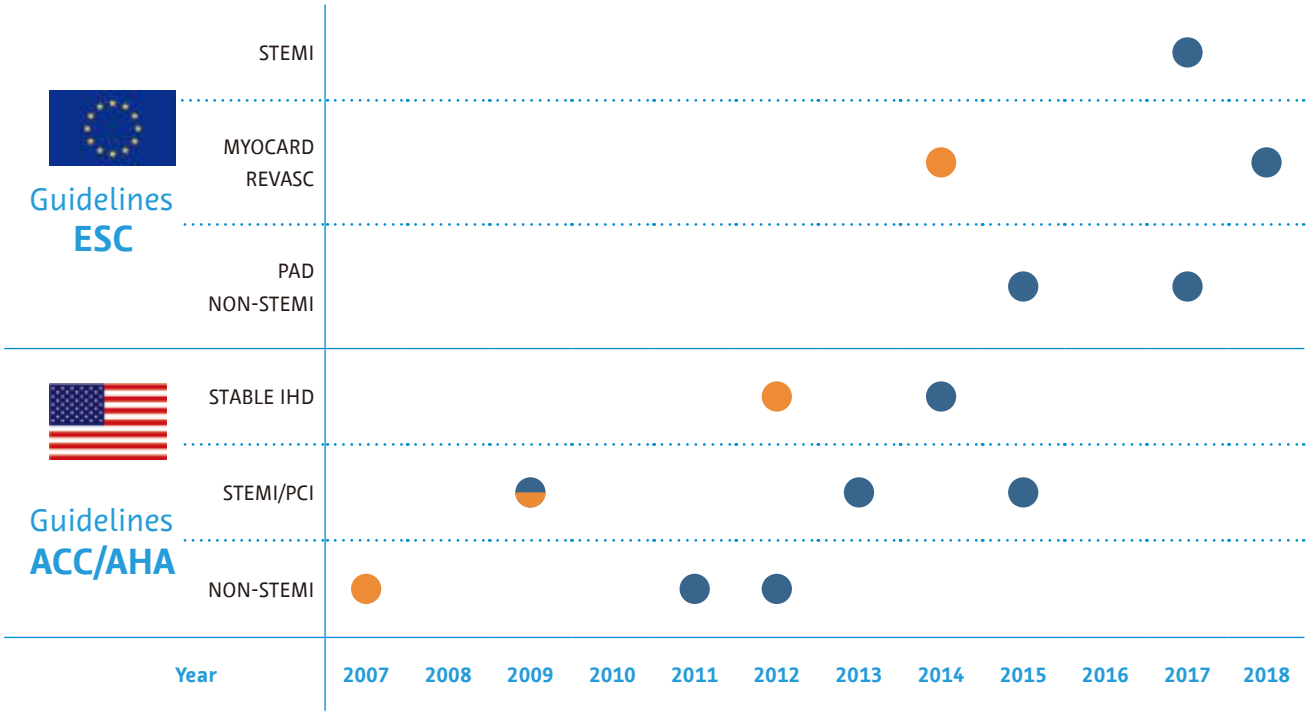
"In vivo, all contrast agents induce osmodiuresis to the degree of their osmolality. Consequently, in a rat model, tubular CM enrichment is higher, and urine viscosity much higher, following iso-osmolar versus low-osmolar CM administration.[84]

These differences in the magnitude of tubular CM concentration and viscosity are inversely related to the hydration status." [1]

Literature
1. Fähling et al. Nat Rev Nephrol 2017
2. Jost et al. Inv Rad 2009
3. https://www.michael-smith-engineers.co.uk/resources/useful-info/approximate-viscosities-of-common-liquids-by-type (Nov 05, 2019)

No distinction between Low-Osmolar Contrast Media (LOCM) and Iso-Osmolar Contrast Media (IOCM) regarding renal safety in updated cardiac guidelines

Cardiac guidelines changed over time from recommending IOCM to not recommending IOCM over LOCM



ESC: European Society of Cardiology
ACC: Amercian College of Cardiology **AHA:** Amercian Heart Association

ACC/AHA guidelines

NON-STEMI

2007 **Guideline:**[1]
"In chronic kidney diease (CKD) patients undergoing angiography, ***IOCM are indicated and are preferred***."

2011 **Focused Update:**[2] DELETED
"In chronic kidney disease (CKD) patients undergoing angiography, ***IOCM are indicated and are preferred.***"

2012 **Focused Update (replacement of 2011):**[3]
"... that strength and consistency [...] between specific IOCM and CIN or renal failure are ***not sufficient to enable a guideline statement on selection among commonly used LOCM and IOCM.***"

STEMI/PCI

2009 **Focused Update:**[4]
"Thus, the updated evidence base suggest that the recommended choices of contrast media during coronary angiography be expanded to ***either IOCM or LOCM other than ioxaglate or iohexol.***"

2013 **Guideline:**[5]
"Contrast-induced nephropathy after angiography and intervention for STEMI is always a risk, and ***attention to minimization of contrast volume and optimal hydration is required***."

2015 **Focused Update:**[6]
No contrast media mentioned

STABLE IHD

2012 **Guideline:**[7]
"To avoid worsening underlying kidney disease, physicians should consider creatinine clearance in pharmacotherapy and should apply risk scores for predicting the likelihood of contrast-induced nephropathy in conjunction with the use of renal protective strategies such as IOCM during angiography."

2014 **Focused Update:**[8]
No contrast recommendation. Instead risk-benefit/informed consent.

ESC guidelines

MYOCARD REVASC

2014 **Guideline:**[9]
› Use of LOCM or IOCM is recommended (Class I, Level A)
› IOCM should be considered over LOCM (Class IIa, Level A)

2018 **Guideline (replaced 2014 recommendations)**[10]
"Adequate hydration remains the mainstay of CIN prevention. (...) All other strategies for the prevention of CIN do not have sufficient evidence to justify a recommendation in favour or against."

PAD

2017 **Guideline:**[11]
"Nephrotoxicity can be limited by minimizing contrast agent volume and ensuring adequate hydration before and after imaging."

NON-STEMI

2015 **Focused Update:**[12]
"In patients undergoing an invasive strategy, hydration with isotonic saline and IOCM or LOCM (at lowest possible volume) is recommended."(Class I, Level A)

STEMI

2017 **Guideline:**[13]
"Consequently, ***in pataients with known or anticipated reduction of renal function***, [...]Ensuring proper hydration during and after primary PCI and limiting the dose of contrast agents ,***preferentially low-osmolality contrast agents, are important steps in minimizing the risk of contrast-induced nephropathy"***

IOCM preferred

No recommendation/no distinction between IOCM or LOCM

Literature

1. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction. Circulation 2007;116:e148–e304.
2. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction. J Am Coll Cardiol 2011;57:e215–367.
3. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update). J Am Coll Cardiol 2012;60:645– 81.
4. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update). Circulation. 2009;120:2271–2306.
5. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll
6. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/CAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol 2016;67:1235–50.
7. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol 2012;60:e44 –164.
8. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol 2014;64:1929–49.
9. 014 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2014 Oct;46(4):517-92. doi: 10.1093/ejcts/ezu366. Epub 2014 Aug 29.
10. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019 Jan 7;40(2):87-165.
11. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018 Mar 1;39(9):763-816.
12. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016 Jan 14;37(3):267-315.
13. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2018 Jan 7;39(2):119-177.

Renal Safety : FAQs on recommended Iodine-based Contrast Media (ICM) and Gadolinium-Based Contrast Media (GBCA) contrast media injection interval

(ESUR Guidelines on Contrast Media Version 10.0; 2018)

	Patients with normal or moderately reduced renal function (GFR > 30 ml/min/1.73 m²)	**Patients with severely reduced renal function (GFR < 30 ml/min/1.73 m²)**
Can ICM & GBCAs safely be given on the same day for routine exam?	75% of both ICM & GBCAs are excreted by 4 h after administration. › 4 h between injections of ICM &GBCAs.	› 7 days between injections of ICM & GBCAs.
How long should there be between two ICM injections for routine exam?	75% of both ICM & GBCAs are excreted by 4 h after administration. › 4 h between injections of ICM.	› 48 h between injections of ICM.
How long should there be between two GBCAs injections for routine exam?	75% of extracellular GBCAs are excreted by 4 h after administration. › 4 h between injections of GBCAs.	› 7 days between injections of GBCAs.

ICM: Iodine-based Contrast Media (X-ray, CT Exams)
GBCA: Gadolinium-Based Contrast Agent (MRI Exams)
CM: Contrast Medium

Patients on dialysis	Note
Same as patients with GFR < 30 ml/min/1.73 m^2.	GBCAs attenuate X-rays well and may be misinterpreted on CT when they have been excreted into the urinary tract. For abdominal examinations, enhanced CT should be done before enhanced MR. For chest and brain examinations, either CT or MR may be done first.
If there is remnant renal function › at least 48 h between injections of ICM.	
Same as patients with GFR < 30 ml/min/1.73 m^2.	

American College of Radiology (ACR) 2021 Guidelines Update Summary on Contrast Safety

Changes	Details
Addition of Chapter 5 **Fasting Prior to Intravascular Contrast Media Administration**	• Given the potential for negative consequences due to fasting and a lack of evidence that supports the need for fasting, **fasting is not required prior to routine intravascular contrast material administration.** • However, for patients receiving conscious sedation, anesthesia guidelines should be consulted.
Chapter 10 **Change in terminologies**	Post-contrast acute kidney injury (PC-AKI) **IS NOW** **Contrast-associated acute kidney injury (CA-AKI)** Contrast-induced nephropathy (CIN) **IS NOW** **Contrast-induced acute kidney injury (CI-AKI)**
Chapter 10 **Volume Expansion protocol recommendations to prevent CA-AKI made more concrete**	• Isotonic fluid such as **0.9% normal saline (NS) is preferred.** • Typical prophylaxis regiments begin **1 hour prior to the exam and continue 3-12 hours after.** Typical doses may be fixed volume (e.g., 500 mL NS) before and after or weight-based volumes (1-3mL/kg per hour) • The ideal infusion rate and volume is unknown
Chapter 10 **Addition of Indications & Contraindications for volume expansion to prevent CA-AKI**	**Indications** • Patients who have **AKI or severe CKD with an eGFR less than 30 mL/min/1.73m²**, although the risks of volume expansion (i.e., heart failure or other hypervolemic conditions) should be considered before initiation. • Considered on an individual basis for **high-risk circumstances (e.g., numerous risk factors, recent AKI, borderline eGFR)** in patients with an eGFR of 30-44 mL/min./1.73m² at the discretion of the ordering provider. **Contraindication** • General population of patients with stable eGFR greater than or equal to 30 mL/min 1.73 m² or patients on chronic dialysis.

AKI: Acute kidney injury CKD: Chronic kidney disease eGFR: Estimated glomerular filtration rate

Reference: ACR Manual on Contrast Media Version 2020 & 2021

American College of Radiology (ACR) 2021 Guidelines Update Summary on Contrast Safety

Changes	Details
Changes in Chapter 10 **Use of N-acetylcysteine & Sodium Bicarbonate for prevention of CA-AKI**	• Recent randomized trial showed that **N-acetylcysteine** was no more effective than placebo at preventing CA-AKI for intra-arterial iodinated contrast media administration and is therefore **not recommended** for intravenous contrast media prophylaxis • **Bicarbonate** is likely similar to normal saline for the prevention of CA-AKI, but it is **not preferred** due to the additional requirement for pharmacist compounding.
Renal Dialysis Patients and the Use of Iodinated Contrast Medium	• Patients undergoing dialysis who make more than 1-2 cups of urine/day (100 mL) should be considered **nonanuric and treated as high-risk patients** similar to patients with AKI or eGFR less than 30 mL/min/1.73m^2 who are not undergoing hemodialysis. • Patients **should not have acute dialysis nor continuous renal replace ment therapy initiated or alter their schedule solely based on iodinat ed contrast media administration.**
Chapter 16 **Identifying patients at-risk of NSF**	• **Addition of -** History of **CKD** or prior history of AKI to the list • **Removal of -** History of **hypertension** requiring medical therapy from the list • **Changed to Optional -** History of **diabetes mellitus**
Chapter 16 **Calculating eGFR**	• Methods of calculating eGFR are in flux as efforts are underway to **remove race from clinical calculators.**
Chapter 16 **Changes made to Additional Specific Recommendations for Specific Groups of Patients-**	• The ACR & NKF recommend that in patients who are already receiving dialysis, if feasible, **elective GBCA-enhanced MRI examinations be performed before regularly scheduled dialysis.** • Due to the risks of catheter placement and infection, the possibility of worsening kidney function in patients with AKI and CKD, and the perceived very low risk of NSF from group II and III GBCM agents, **dialy sis should not be initiated or altered in patients receiving a group II GBCM.**

CA-AKI: Contrast-associated acute kidney injury GBCA/GBCM: Gadolinium based contrast media NSF : Nephrogenic systemic fibrosis

Reference: ACR Manual on Contrast Media Version 2020 & 2021

Notes

Ultravist® (iopromide) Prescribing Information (Refer to package insert before prescribing) **Presentation:** Intravascular injections of nonionic iopromide in strengths of 300mg and 370mg of iodine/ml. Intravascular injections of nonionic iopromide in strengths of 300mg and 370mg of iodine/ml. **Indications:** For diagnostic use only. Delineation of the vascular and renal systems and of body cavities **Posology and administration:** ***Adults Intravenous urography:*** minimum doses: Ultravist 370: 0.8ml/kg body weight; Ultravist 300: 1ml/kg body weight. ***Children Intravenous urography:*** see package insert. ***Adults Computed tomography:*** Cranial CT: Ultravist 300: 1-max, 2ml/kg body weight; Ultravist 370:1-max, 1.5ml/kg body weight. Whole-body CT: Dosage and administration rate depend on investigation and scanner. ***Adults Angiography:*** depends on age, weight, cardiac output, general condition, clinical problem, examination technique and the nature and volume of the vascular region to be investigated. (see package insert). ***Paediatric population:*** young infants (age < 1 year) and especially newborns are susceptible to electrolyte imbalance and haemodynamic alterations. Care should be taken regarding the dose of contrast medium to be given, the technical performanc of the radiologicalprocedure and the patient status. ***Renal impairment:*** to reduce the risk of additional contrast media-induced renal impairment in patients with pre-existing renal impairment, the minimum possible dose should be used (see package insert). ***Hepatic impairment:*** no dosage adjustment is necessary. ***Elderly:*** possibility of reduced renal function should be considered. **Contra-indications:** Uncontrolled thyrotoxicosis. **Warnings and precautions:** Can be associated with anaphylactoid/hypersensitivity reactions, ensure preparedness for institution of emergency measures. Allergy-like reactions from mild to severe possible, mostly within 30 min, but delayed reactions (hours to days) may occur. Particularly careful risk/benefit judgement required for patients with: known hypersensitivity to Ultravist or its excipients; previous reaction to any contrast medium or; history of bronchial asthma or allergic disorders (increased risk). Pre-medicate with corticosteroids if necessary. To minimise risk: administer Ultravist to recumbent patients; observe patients closely for 15 minutes and keep them in hospital for at least one hour after the last injection. Patients on beta-blockers may be resistant to the effects of beta agonists. If severe reaction occurs, patients withcardiovascular disease are more susceptible to serious or fatal outcomes. Caution in patients with: known/suspected hyperthyroidism or goitre, monitor thyroid function in neonates exposed via mother or during neonatal period. Caution in patients with cerebral arteriosclerosis, pulmonary emphysema, poor general health, renal insufficiency, dehydration, diabetes mellitus, multiple myeloma/ paraproteinaemia, repetitive and/ or large doses of Ultravist. Nephrotoxicity may occur or rarely acute renal failure. Ensure adequate hydration of patients; correct water or electrolyte imbalances before administration. With cardiac or severe coronary artery disease, increased risk of haemodynamic changes or arrhythmia. Intravascular injection may precipitate pulmonary oedema in patients with heart failure. Increased risk of neurological complications in patients with seizure historyor CNS disorders. Caution in patients with reduced seizure threshold. May aggravate the symptoms of myasthenia gravis. Flush intravascular catheters frequently with physiological saline (if possible with addition of heparin) and minimise procedure length to minimise procedure-related thromboembolism risk. Patients with phaeochromocytoma may be at increased risk of developing a hypertensive crisis. Minimise excitement, anxiety and pain. Do not use in myelography. Sensitivity testing is not recommended. **Interactions:** Consider interruption of biguanides treatment prior to Ultravist administration as a precaution against development of lactic acidosis. Prevalence of delayed reactions higher in patients who have received interleukin-2. Diagnosis and treatment of thyroid disorders with thyrotropic radioisotopes may be impeded for up to several weeks due to reduced radioisotope uptake. **Pregnancy and lactation:** Adequate and well-controlled studies in pregnant women have not been conducted. Safety for nursed infants has not been investigated. **Effects on ability to drive and use machines:** Driving or operating machinery is not advisable for 30 minutes after the last injection. **Undesirable effects:** Common: dizziness, headache, dysgeusia, blurred/disturbed vision, chest pain/ discomfort, hypertension, vasodilatation, vomiting, nausea, pain, injection site reactions (e.g. oedema, soft tissue injury post extravasation), feeling hot. Uncommon: Hypersensitivity/anaphylactoid reactions (anaphylactoid shock, respiratory arrest, bronchospasm, laryngeal/ pharyngeal/face oedema, tongue oedema, laryngeal/pharyngeal spasm, asthma, conjunctivitis, lacrimation, sneezing, cough, mucosal oedema, rhinitis, hoarseness, throat irritation, urticaria, pruritus, angioedema), vasovagal reactions, confusional state, restlessness, paraesthesia/ hypoaesthesia, somnolence, arrhythmia, hypotension, dyspnea, abdominal pain,oedema. Rare: Anxiety, cardiac arrest, myocardial ischemia, palpitations. Frequency not known: Thyrotoxic crisis, thyroid disorder, coma, cerebral ischaemia/infarction, stroke, brain oedemaa, convulsion, transient cortical blindness, loss of consciousness, agitation, amnesia, tremor, speech disorders, paresis/paralysis, hearing disorders, myocardial infarction, cardiac failure, bradycardia, tachycardia, cyanosis, shock, thromboembolic events,vasospasm, pulmonary edema, respiratory insufficiency, aspiration, dysphagia, salivary gland enlargement, diarrhoea, bullous conditions (e.g. Stevens-Johnson's or Lyell syndrome), rash, erythema, hyperhydrosis, compartment syndrome in case of extravasation, renal impairment, acute renal failure, malaise, chills, pallor, body temperature fluctuation. *These adverse reactions may have a fatal or life-threatening outcome and are considered the most serious adverse drug reactions. Prescribers should consult the SmPC in relation to other side effects. **Overdose:** Symptoms may include fluid and electrolyte imbalance, renal failure, cardivascular and pulmonary complications. Monitoring of fluids, electrolytes and renal function recommended in case of intravascular overdosage. Treatment of overdose should be directed towards the support of vital functions. Ultravist is dialysable. **Incompatibilities:** Because of possible precipitation, X-ray contrast media and prophylactic agents must not be injected as mixed solutions. **Special Precautions for Storage:** Protect from light and X-rays. **Date of revision of text:** April 2017. **Please note:** for current prescribing information refer to the package insert and/or contact your local Bayer HealthCare organization. **Bayer HealthCare Ltd.**14th Floor, Oxford House, Taikoo Place, 979 King's Road, Quarry Bay, Hong Kong.

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For further information, please refer to the product's full prescribing information.

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