Considering the care of At Risk patients

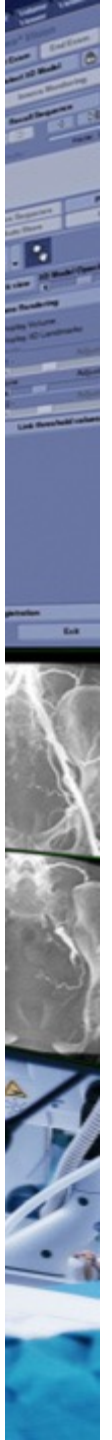
The role of isosmolar contrast media (IOCM)

Visipaque™ (iodixanol) injection, HCP Important Safety Information

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

Please see Boxed Warning, Important Safety Information, and full Prescribing Information starting on slide 59.



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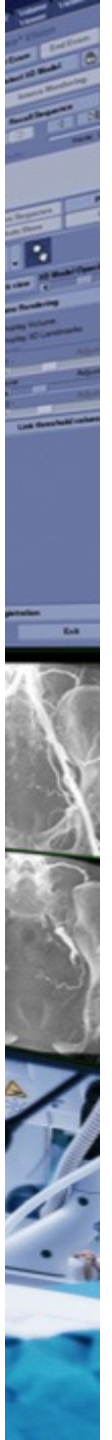

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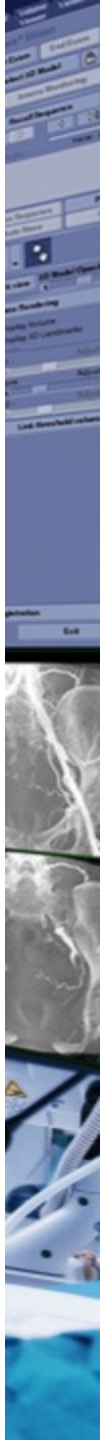
IOCM: isosmolar contrast medium

Contents



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CM: contrast media
IOCM: isosmolar CM

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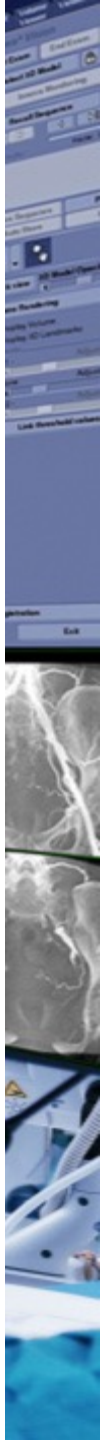

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CCTA: coronary CT angiography
CM: contrast media
CT: computed tomography
IA: intra-arterial
IOCM: isosmolar CM

Iodine-based contrast media

The evolution of iodinated CM

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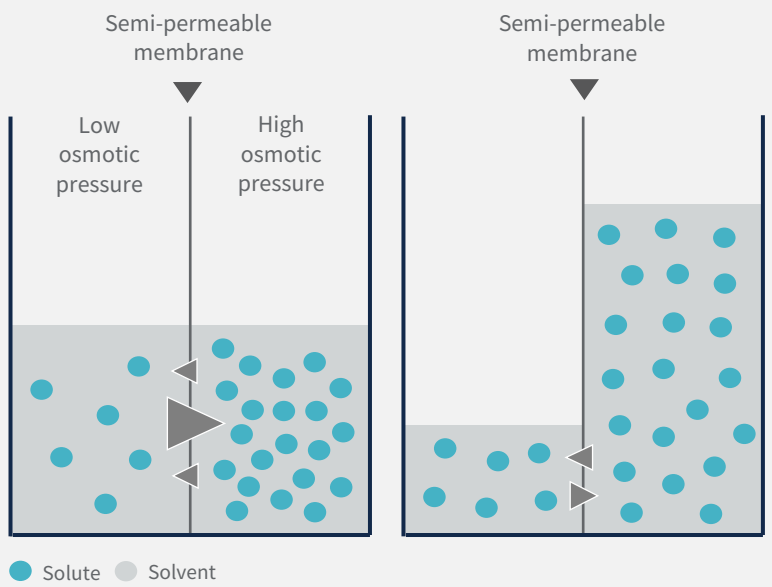
What is osmolality?

Osmolality describes the concentration of solute/kg of water[1]



- Water will pass across a membrane from a solution with fewer dissolved particles (lower osmotic pressure) to one with a greater concentration of dissolved particles (higher osmotic pressure) until equilibrium is obtained
- Osmolality increases with concentration of iodine
- Different CM can have very different osmolalities at the same iodine concentration because of the salt (ion) concentration

CM: contrast media

Rx

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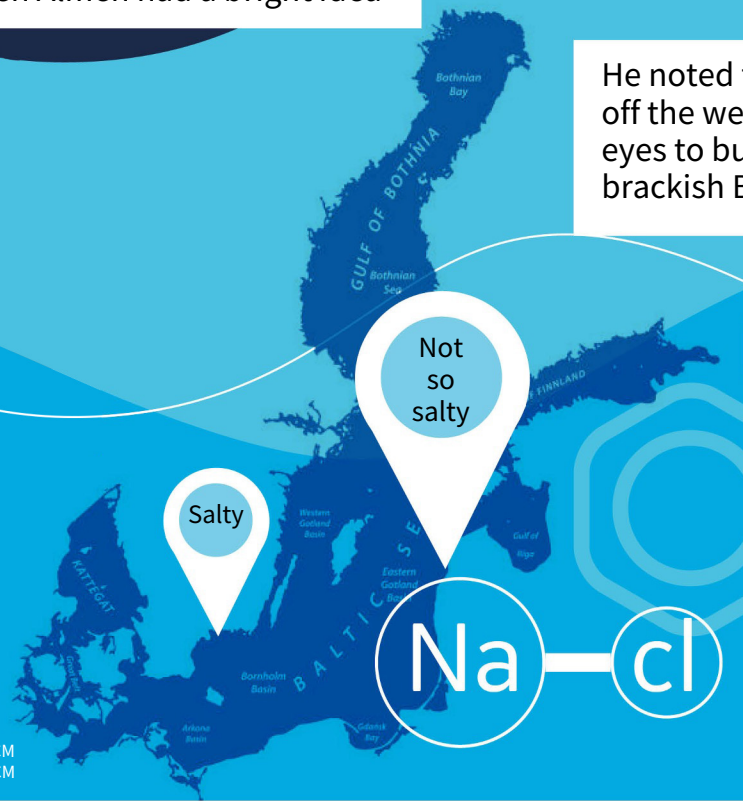
How did a swim in the sea inspire a focus on osmolality in the evolution of iodinated CM?

In the early days, pain, nausea, and vomiting were common after injection of CM; the view at the time was that these side effects mainly resulted from the chemotoxicity of agents[1]

But, the Swedish radiologist Torsten Almén had a bright idea

He noted that swimming in the salty water off the west coast of Sweden caused his eyes to burn, yet swimming in the more brackish Baltic Sea was painless[1]



Almén had a theory.

Was it the high osmolality of CM solutions that was responsible for their side effects?[1]

Inspired, he championed an osmolality evolution for iodinated CM, from HOCM, to LOCM (e.g. iohexol), to isosmolar iodixanol[1]

CM: contrast media
HOCM: high osmolar CM
LOCM: 'low' osmolar CM

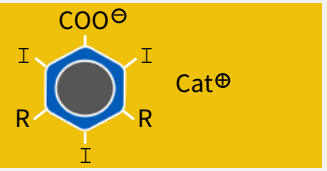
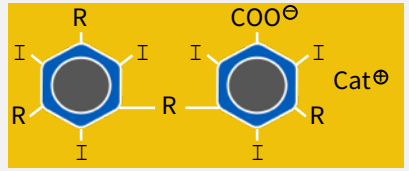
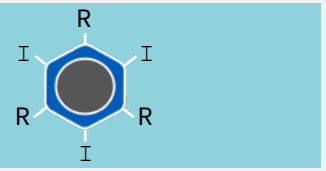
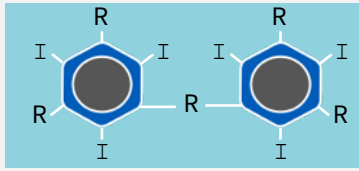
Rx

Prescribing information is available at the end of this presentation

1. Nyman U *et al.* Acta Radiol 2016; 57(9): 1072-8.

How did the structure of iodine-based CM evolve?

While the basic form of x-ray CM is an iodinated benzene ring, agents differ in the structure of their side chains[1,2]

			Molecule	Osmolality*[3]	Iodine/ molecule
Ionic	1950s HOCM	**Monomer** diatrizoate iothalamate metrizoate		High (5-8 times higher vs blood)	3/2
	1980s LOCM	**Dimer** ioxaglate		Low (2-3 times higher vs blood)	6/2
Non-ionic	1980s LOCM	**Monomer** iohexol iopamidol ioversol		Low (2-3 times higher vs blood)	3/1
	1990s IOCM	**Dimer** iodixanol		Equal to blood	6/1

- If a contrast molecule contains only one benzene ring it is called a monomer
- To deliver more iodine with each molecule of contrast, two benzene rings may be combined to produce a dimer
- However, only non-ionic dimers increase the number of iodine atoms per molecule (6/1) whereas ionic dimers dissociate in solution, resulting in two non-ionic monomers (6/2)

CM: contrast media
HOCM: high osmolar CM
IOCM: isosmolar CM
LOCM: 'low' osmolar CM

Rx

Prescribing information is available at the end of this presentation

1. Jakobsen JA. Eur J Radiol 2007; 62(Suppl.): s14-25.
2. Aspelin P. Eur Radiol Suppl 2006; 16(Suppl.4): D22-27.

The IOCM iodixanol

The science of protection

Visipaque™ (iodixanol) injection, HCP Important Safety Information

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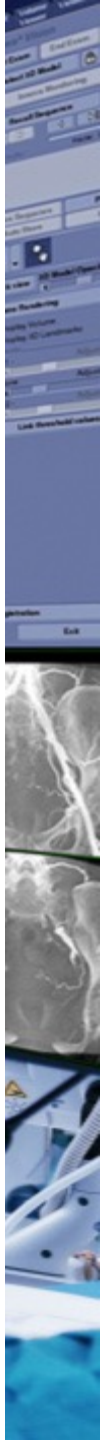

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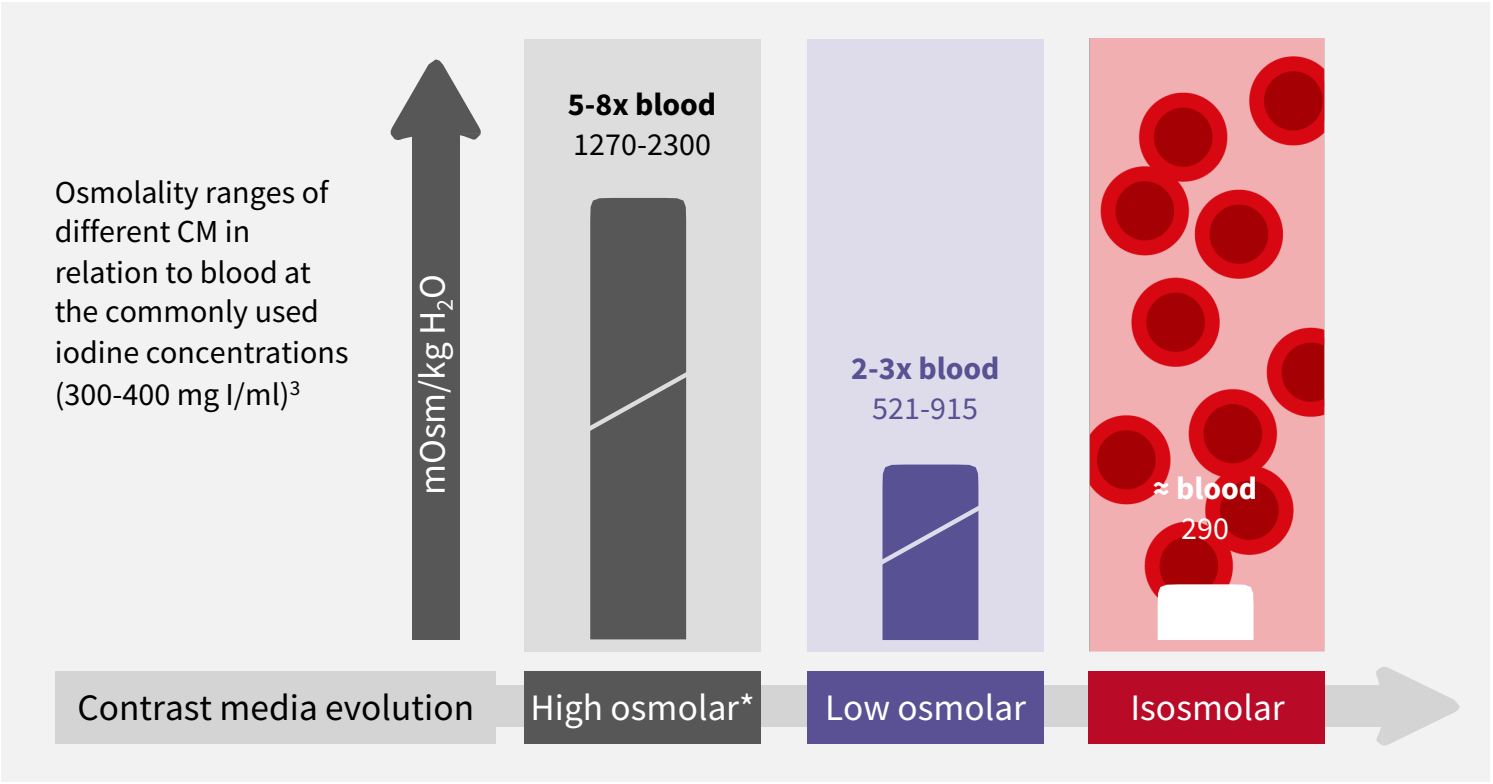
How does osmolality compare across generations of CM?

Because the osmolality of a CM is commonly associated with clinical adverse outcomes, a major driving force in the evolution of CM has been the reduction of osmolality[1,2]

Osmolality ranges of different CM in relation to blood at the commonly used iodine concentrations (300-400 mg I/ml)[3]



Iodixanol is the only CM available for intravascular use that is isosmolar to blood at all concentrations[3]

CM: contrast media
mOsm: milliosmole

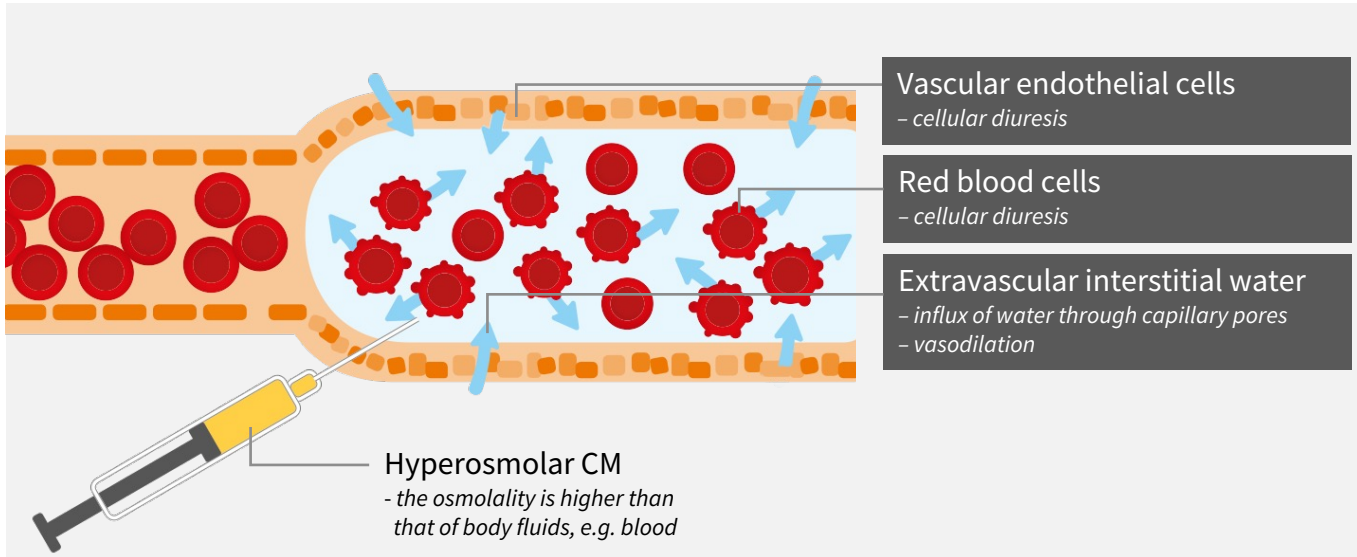
*High osmolar CM is no longer used in clinical practice

Rx

Prescribing information is available at the end of this presentation

1. Jakobsen JA. Eur J Radiol 2007; 62(Suppl.): s14–25.
2. Pedersen HK. Acta Radiol Suppl 1996; 37(Suppl.405): 1–31.
3. Davidson C *et al.* Am J Cardiol 2006; 98(Suppl.): 42–58k.

What are the physiological effects of hyperosmolar CM injection?



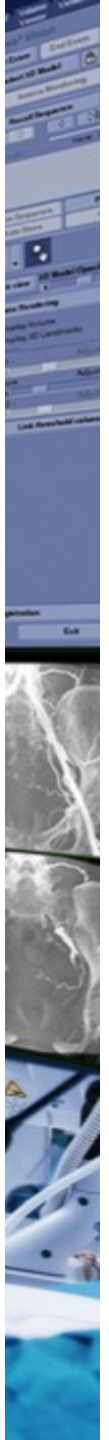
Adapted from Swanson 1990[1]

Water moves out of cells (cellular diuresis) into the vasculature to equalize the difference in osmotic pressure between cells and blood containing CM[2,3]

Water is also pulled from the space between cells (the interstitium) into the vasculature[4]

- This fluid shift following infusion of hyperosmolar CM results in expansion of blood volume[2]
  - this may cause sensations of warmth and pain[2]
  - this may cause the patient to move, resulting in suboptimal images[5,6]

CM: contrast media



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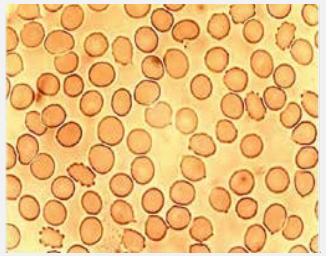
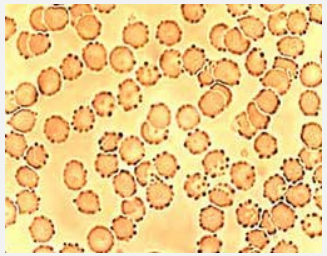
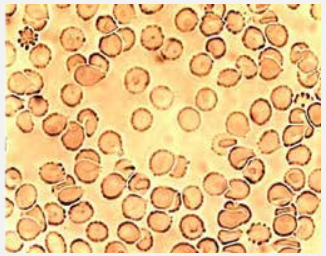
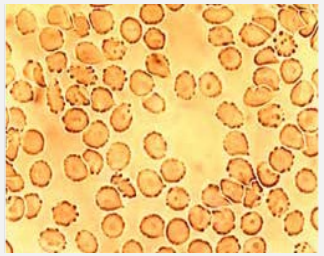
Prescribing information is available at the end of this presentation

1. Swanson DP *et al*. In: Pharmaceuticals in Medical Imaging. Collier MacMillan Publishers, London 1990.
2. Jakobsen JA. Eur J Radiol 2007; 62(Suppl.): s14-25.
3. Fountaine H *et al*. Acad Radiol 1996; 3(Suppl.3): S475-84.
4. Stacul F. Eur Radiol 2001; 11(4): 690-7.
5. McCullough PA, Capasso P. BMC Med Imaging 2011; 11: 12.
6. Palena LM *et al*. Catheter Cardiovasc Interv 2014; 84(6): 1019-25.

How large an effect does osmolality have on red blood cells?

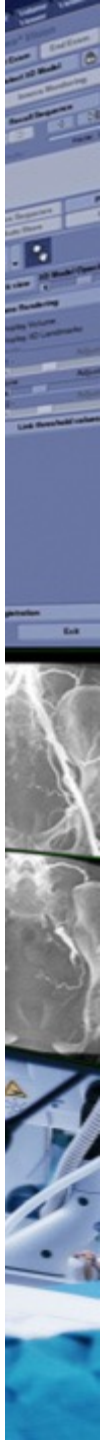
Percentage of normal erythrocytes affected following incubation *in vitro* in 40% CM solutions[1]

Iodixanol 320	Iomeprol 350	Iohexol 350	Iopromide 370
			
73%	**22%**	**21%**	**12%**

Adapted from Jung 2008[1]
Images courtesy of Professor Jung, Centre for Biomaterial Development, GKSS Research Centre, Teltow, Germany

Isosmolar CM may help to minimize impact on red blood cells[1,2]

CM: contrast media



Rx

Prescribing information is available at the end of this presentation

1. Jung F *et al*. Clin Hemorheol Microcirc 2008; 38(1): 1-11.
2. Kerl JM *et al*. Acta Radiol 2008; 49(3): 337-43.

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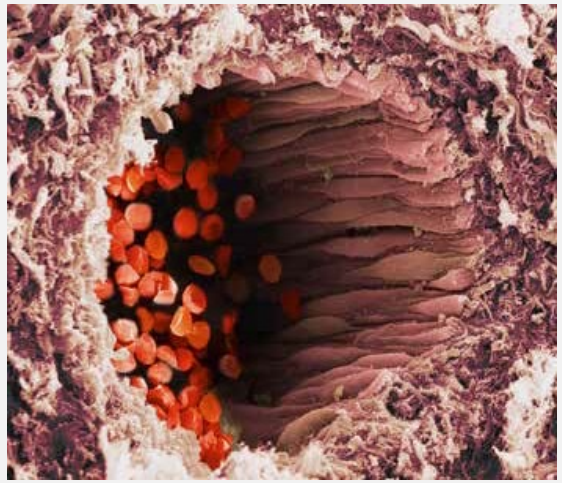
How does osmolality affect endothelial cells?

Another factor that may affect the microcirculation downstream of contrast injection is the impact of CM on capillary endothelial cells[1,2]

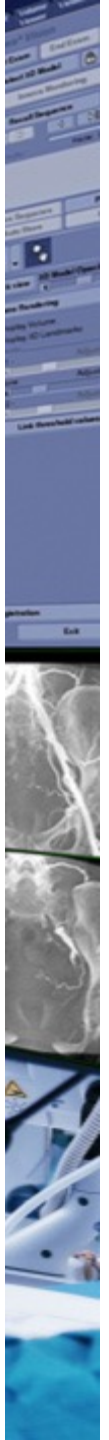


- Buckling of endothelial cells
- Narrowing of the free vascular lumen
- Potential to impede capillary blood flow
- **In addition, damage to endothelial cells may result in their loss of function[2]**

Isosmolar CM may help to minimize impact on endothelial cells[1-3]

Endothelial damage	*In vitro* results
Buckling of cells	Greater distortion with iomeprol, iopromide and ioxaglate than with isosmolar iodixanol[1,3]
Cell detachment	Greater cell loss with iomeprol than with isosmolar iodixanol[2]
Exposure of subendothelial matrix	More denuded areas with iomeprol and ioxaglate than with isosmolar iodixanol[2,3]

CM: contrast media



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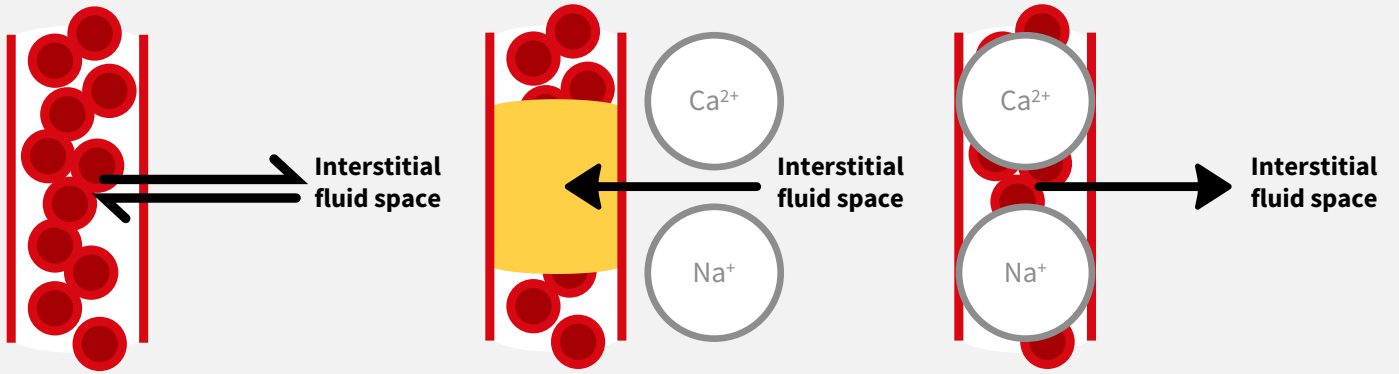
Prescribing information is available at the end of this presentation

1. Franke RP *et al.* Microvasc Res 2008; 76(2): 110-13.
2. Franke RP *et al*. Clin Hemorheol Microcirc 2011; 48(1): 41-56.
3. Barstad RM *et al*. Acta Radiol 1996; 37(6): 954-61.

Why does the electrolyte composition of CM matter?

Concentrations of key electrolytes in CM are generally lower than those present in blood[1,2]



In the normal state, ionic equilibrium exists between blood in the coronary artery and the surrounding interstitial fluid

When CM circulates, ionic flux occurs across interstitial space to re-equilibrate with CM in the artery

As blood washes through, ionic shift reverses to re-establish the original steady state equilibrium

Adapted from Pedersen 1996[1] and Jynge 1996[2]

Many of a CM's effects on the myocardium may be due to washout of normal extracellular electrolytes[1]

Low Ca^{2+} levels can diminish the force of ventricular contraction during systole, while low Na^{+} levels can interfere with normal depolarisation[3]

Aqueous solutions of iodixanol actually have a lower osmolality than blood[4]

- The osmolality gap is filled by the addition of the key electrolytes sodium and calcium
- The ratio between sodium and calcium in isosmolar iodixanol is the same as the physiological ratio

CM: contrast media

Rx

Prescribing information is available at the end of this presentation

1. Pedersen HK. Acta Radiol Suppl 1996; 37(Suppl.405): 1-31.
2. Jynge P. Eur Radiol 1996; 6(Suppl.2): S8-S12.
3. Chai C-M *et al.* Acad Radiol 2004; 11(5): 583-93.
4. Eivindvik K, Sjøgren CE. Acta Radiol 1995; 36(Suppl.399): 32-8.

What has been the driving force behind the evolution of iodixanol?

Safety profile and tolerability[1-4]

Towards lower chemotoxicity[1,2]

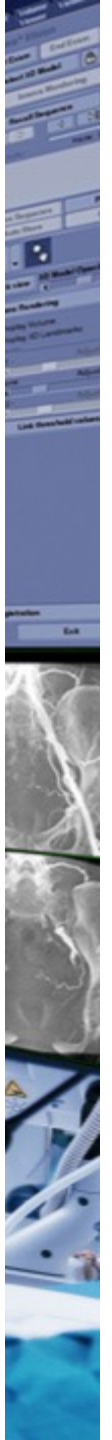
with an absence of ionising carboxyl groups and 9 hydrophilic hydroxyl groups

… and lower osmolality[1,3]

to counteract major fluid shifts across membranes and limit discomfort

… and balanced electrolytes[1,3]

to help minimize effects on cardiac contractile force/fibrillatory propensity



Rx

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1. Almén T. Acta Radiol 1995; 36(Suppl.399): 2-18.
2. Christiansen C. Toxicology 2005; 209(2): 185-7.
3. Fountaine H *et al*. Acad Radiol 1996; 3(Suppl.3): S475-84.
4. Widmark JM. Proc (Bayl Univ Med Cent) 2007; 20(4): 408-17.

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The IOCM iodixanol

Optimizing iodine and radiation doses in pediatric imaging

Visipaque™ (iodixanol) injection, HCP Important Safety Information

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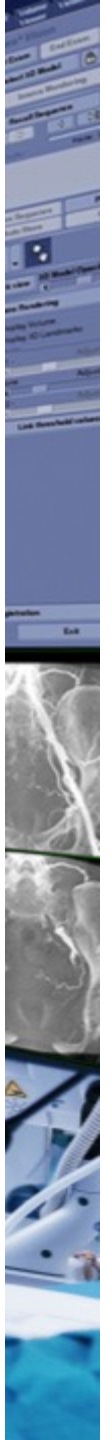

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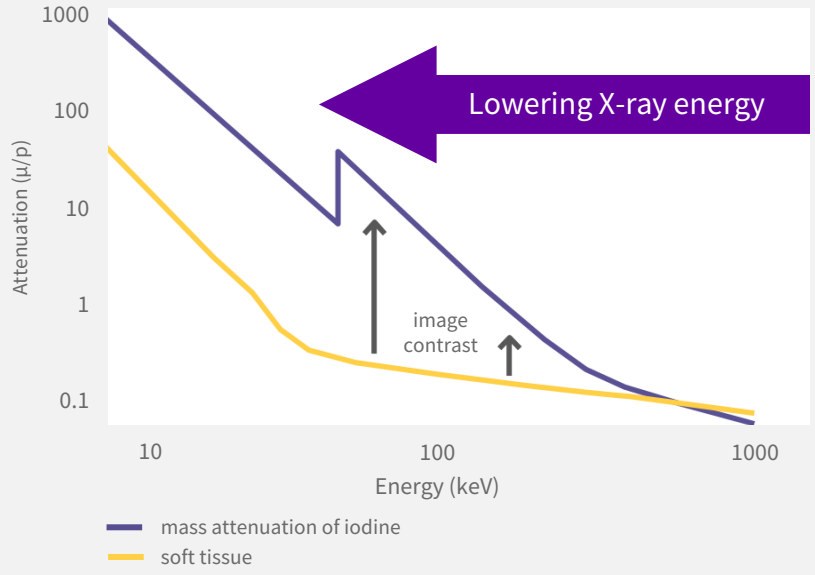
How do the properties of iodine enable lowering of both radiation and iodine dose?

Use of low iodine-concentration CM might be expected to result in lower enhancement characteristics[1]

However, contrast resolution depends not only on iodine concentration, but also on tube voltage and image noise[2]

Absorption of iodine is actually higher at lower tube voltages[2,3]



While lowering tube voltage leads to increased image noise, iterative reconstruction techniques can dramatically reduce image nose[1]

Adapted from Seibert 2005[3]

CM: contrast media

Rx

Prescribing information is available at the end of this presentation

1. Zheng M *et al*. Acad Radiol 2015; 22(2): 195-202.
2. Royal College of Radiologists. Standards of practice of CTCA in adult patients, 2014.
3. Seibert JA *et al*. J Nucl Med Technol 2005; 33(1): 3-18.

Can diagnostic images be obtained with low iodine and radiation loads in pediatric patients?

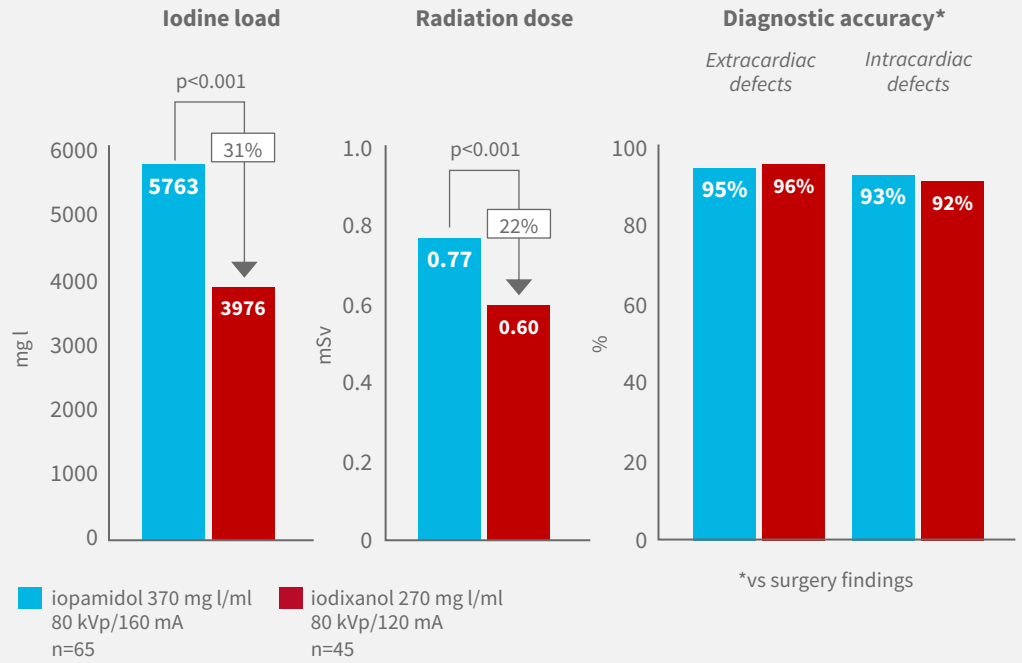
With children more sensitive to radiation than adults, and with the potential risks of CM, optimizing both CM and radiation dose is important in pediatric imaging[1]

Despite a lower iodine load, iodixanol 270 has demonstrated similar diagnostic images as higher concentrated iopamidol[2]

Iodixanol 270 vs iopamidol 370 in low-dose imaging of children with complex CHD (n=110)[2]

Prospective, randomized study of 110 consecutive pediatric patients with CHD undergoing cardiac CT

Mean age was 8.42 months



Adapted from Hou 2017[2]

CHD: congenital heart disease
CM: contrast media
CT: computed tomography

Rx

Prescribing information is available at the end of this presentation

1. Liu Z *et al*. Int J Clin Pract 2016; 70(Suppl. 9B): B22-8.
2. Hou QR *et al.* Br J Radiol 2017; 90(1070): 20160669.

The IOCM iodixanol

The renal impact of iodinated CM

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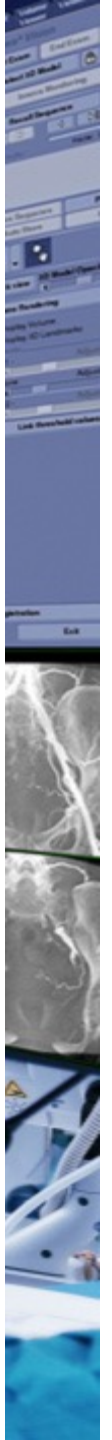

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What is CI-AKI? PC-AKI? CA-AKI?

The possibility that iodinated CM might cause AKI was first raised in a 1954 case report of a multiple myeloma patient who developed anuria following IV pyelography with the high-osmolar agent, Diodone[1,2]

In 2012, the KDIGO Working Group adopted the term contrast-induced AKI (CI-AKI) to describe kidney injury precipitated by iodinated contrast media, defining AKI as:[3]

1	2	3
Absolute SCr increase ≥0.3 mg/dl (>26.4 µmol/l) ↑	A percentage increase in SCr ≥50% (≥1.5-fold above baseline) ↑	Urine output reduced to ≤0.5 ml/kg/hour for at least 6 hours ↓

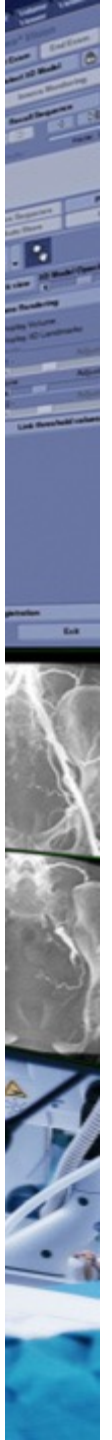
In clinical practice, however, it is often not possible to exclude other causes of AKI[4]

- As a result, post-contrast AKI (PC-AKI) and, more recently, contrast-associated AKI (CA-AKI) are used to distinguish a correlative rather than causative diagnosis[4-6]

CA-AKI describes any AKI event occurring within 48 hours of CM administration[5]

- It is a correlative diagnosis as it does not suggest a causal relationship between the AKI and the iodinated CM[5]

AKI: acute kidney injury
CA-AKI: contrast-associated AKI
CI-AKI: contrast-induced AKI
CM: contrast media
IV: intravenous
PC-AKI: post-contrast AKI
SCr: serum creatinine



Rx

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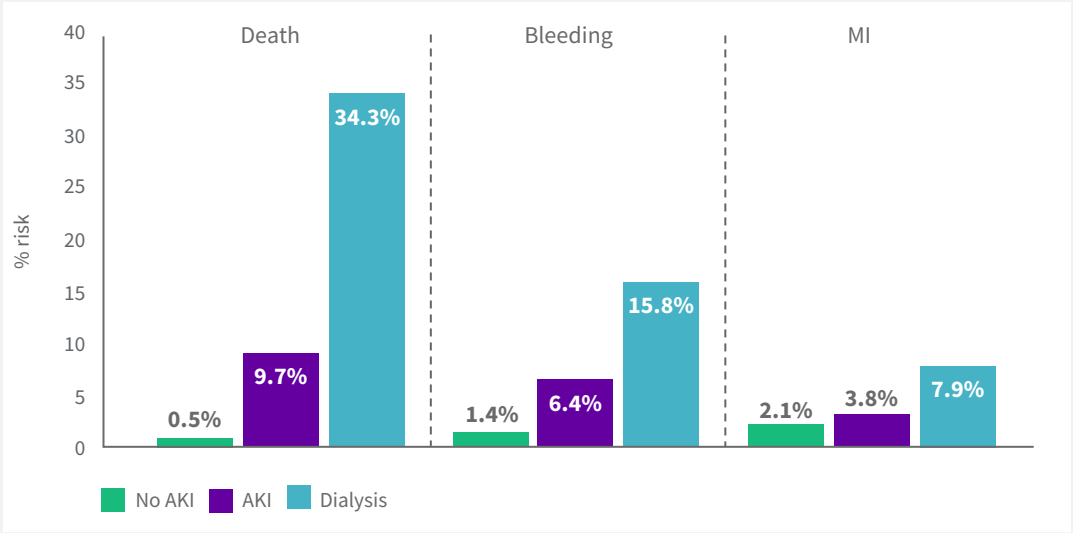
1. Bartels ED *et al.* Acta Med Scand 1954; 150(4): 297-302.
2. Pollack HM. History of iodinated contrast media. In: Thomsen H, Webb JAW (eds). Contrast Media: Safety Issues and ESUR Guidelines. Springer-Verlag, Berlin 2006.
3. Khwaja A. Nephron Clin Pract 2012; 120(4): c179-84.
4. van der Molen AJ *et al.* Eur Radiol 2018; 28(7): 2845-55.
5. Mehdi A *et al.* Cleve Clin J Med 2020; 87(11): 683-94.
6. ACR Committee on Drugs and Contrast Media. ACR Manual on Contrast Media. April 2022.

What are the consequences of AKI post-PCI?

Approximately 7% of patients undergoing a PCI experience AKI (0.3% requiring new dialysis), which is strongly associated with in-hospital mortality[1]

Risk of death, bleeding, and myocardial infarction in PCI patients with/without AKI (n=985,737)[1]

Data from 985,737 consecutive patients at 1,253 sites participating in the NCDR Cath-PCI registry from June 2009 through June 2011[1]



Adapted from Tsai 2014[1]

The economic burden of AKI is also high, with a single event consuming considerable healthcare resources[2,3]

- Overall, the average cost of AKI is double that of matched patients without AKI[4]

AKI: acute kidney injury
MI: myocardial infarction
NCDR: National Cardiovascular Data Registry
PCI: percutaneous coronary intervention

Rx

Prescribing information is available at the end of this presentation

1. Tsai TT *et al.* JACC Cardiovasc Interv 2014; 7(1): 1-9.
2. Subramanian S *et al.* J Med Econ 2007; 10(2): 119-34.
3. Amin AP *et al.* Am J Cardiol 2020; 125(1): 29-33.
4. Dasta JF, Kane-Gill S. J Pharm Pract 2019; 32(3): 292-302.

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What are potential sources of confusion when it comes to comparing CI-AKI trial findings?

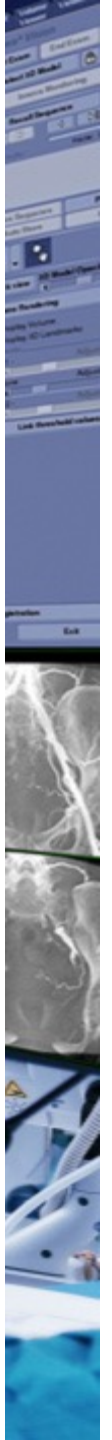
Considerable variation in study quality[1,2]	The risk profile of the study population[1-3]	Study protocol factors[1,2]
Blinding	Baseline SCr	Route of administration: IA or IV
Whether analysis is intent-to-treat	Threshold defining CKD	Volume expansion
Sample size	Diabetes mellitus prevalence	CM volume
Power of study	Type of procedure	Definition of CI-AKI
Quality of reporting		Number and timing of post-procedural SCr measurement

Lack of concordance in studies selected for meta-analyses – for example, not differentiating between IA and IV studies – may in part explain the divergent nature of results[2]

Both patient-related (e.g., CKD) and procedure-related factors (e.g. bleeding) are independently associated with the development of AKI[3]

- to separate CI-AKI from post-interventional AKI, a study must have a suitable control group to show a causal relationship between CM administration and a deterioration in renal function[4]

AKI: acute kidney injury
CI-AKI: contrast-induced AKI
CKD: chronic kidney disease
CM: contrast media
IA: intra-arterial
IV: intravenous
SCr: serum creatinine



Rx

Prescribing information is available at the end of this presentation

1. Reddan D *et al.* J Nephrol 2009; 22(3): 333-51.
2. McCullough P. Cardiorenal Med 2011; 1(4): 220-34.
3. Azzalini L, Kalra S. Interv Cardiol Clin 2020; 9(3): 299-309.
4. van der Molen AJ *et al.* Eur Radiol 2018; 28(7): 2845-55.

What do meta-analyses conclude about the risk of CI-AKI following IA procedures?

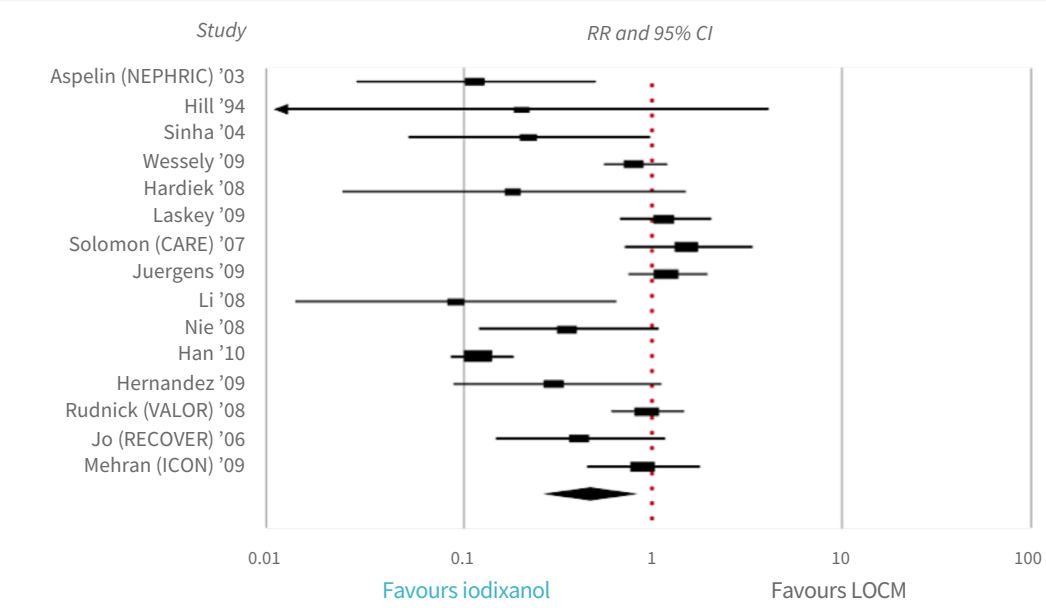
Intra-arterial use of iodixanol reduced the risk of CI-AKI* compared with multiple pooled LOCM† in the interventional cardiology setting by 54%[1]

CI-AKI* risk was lower with iodixanol than with multiple pooled LOCM† (n=4,769)[1]

Meta-analysis of head to-head, randomised studies published before 2011

**CI-AKI defined as SCr increase of ≥0.5 mg/dl from baseline measured up to 3 days after CM exposure*

†*Pool of LOCM (iohexol, iomeprol, iopamidol, iopromide, ioversol and ioxaglate)*



RR=0.46; CI: 0.27-0.79; p=0.004

Patients had, on average, moderately impaired renal function at baseline[1]

SCr: ≥1.6 mg/dl

GFR: ≤50 ml/min/1.73m²

Adapted from McCullough 2011[1]

CI: confidence interval
CI-AKI: contrast-induced acute kidney injury
CM: contrast media
GFR: glomerular filtration rate
IA: intra-arterial
LOCM: 'low' osmolar CM
RR: relative risk
SCr: serum creatinine

Rx

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What do meta-analyses conclude about the risk of CI-AKI following IA procedures?

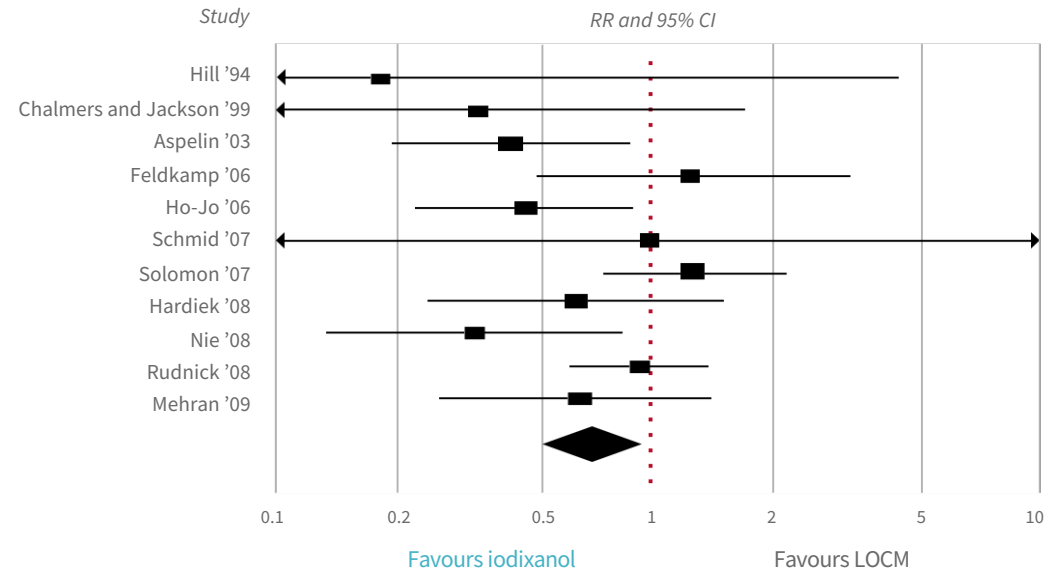
Intra-arterial use of iodixanol reduced the risk of CI-AKI* compared with multiple pooled LOCM† in the interventional cardiology setting by 32%[1]

CI-AKI* risk was lower with iodixanol than with multiple pooled LOCM† (n=2,210)[1]

Meta-analysis of head to-head, randomised studies, 1980 to 2010

**CI-AKI defined as SCr increase of ≥0.5 mg/dl or ≥25% from baseline measured up to 3 days after CM exposure*

†Pool of LOCM (iohexol, iomeprol, iopamidol, iopromide, ioversol and ioxaglate)



RR=0.68; CI: 0.50-0.92; p=0.01

The authors concluded that iodixanol may be a better choice than LOCM for patients in the interventional cardiology setting[1]

Adapted from Dong 2012[1]

CI: confidence interval
CI-AKI: contrast-induced acute kidney injury
CM: contrast media
LOCM: 'low' osmolar CM
RR: relative risk
SCr: serum creatinine

Rx

Prescribing information is available at the end of this presentation

1. Dong M *et al.* J Nephrol 2012; 25(3): 290-301.

The IOCM iodixanol

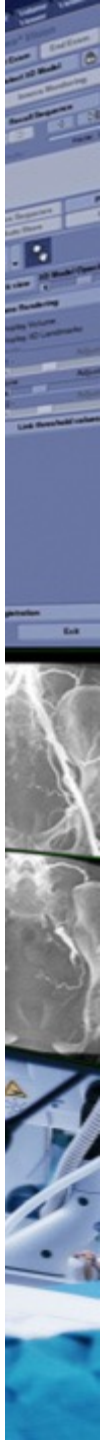
Renal outcomes in contrast enhanced CT

Visipaque™ (iodixanol) injection, HCP Important Safety Information

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

Please see Boxed Warning, Important Safety Information, and full Prescribing Information starting on slide 59.



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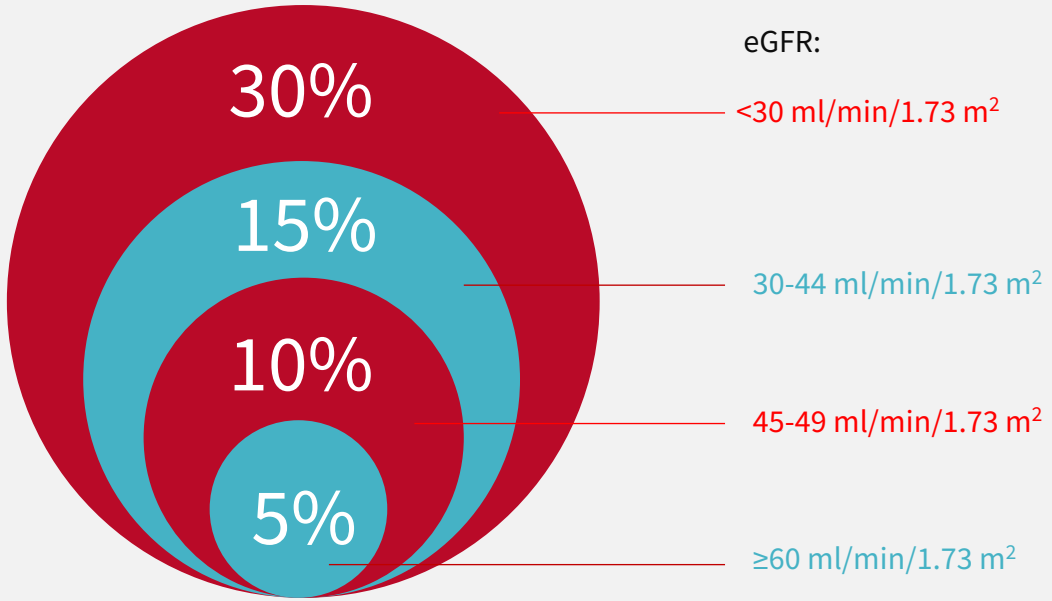
Are intravenous CM injections also nephrotoxic?

In daily clinical practice, contrast-enhanced CT has to be performed despite unstable renal function, heart failure, haemodynamic instability, uncontrolled diabetes, recent CM examinations etc.[1]

In patients with renal impairment (SCr level of ≥1.6 mg/dl), IV administered CM has been shown to be an independent risk factor for post-CT AKI[2]

Approximate risk of developing CA-AKI* in patients undergoing CECT[3]

*Using the KDIGO stage I SCr criteria, CA-AKI was defined by an increase in SCr of ≥0.3 mg/dl (≥26.5 µmol/l) or to 1.5-1.9 times baseline



Adapted from Davenport 2020[3]

AKI: acute kidney injury
CA-AKI: contrast-associated AKI
CECT: contrast-enhanced CT
CM: contrast media
CT: computed tomography
eGFR: estimate glomerular filtration rate
IV: intravenous
SCr: serum creatinine

Rx

Prescribing information is available at the end of this presentation

1. Nyman U *et al.* Eur Radiol 2012; 22(6): 1366-71.
2. Davenport MS *et al.* Radiology 2013; 267(1): 94-105.
3. Davenport MS *et al.* Kidney Med 2020; 2(1): 85-93.

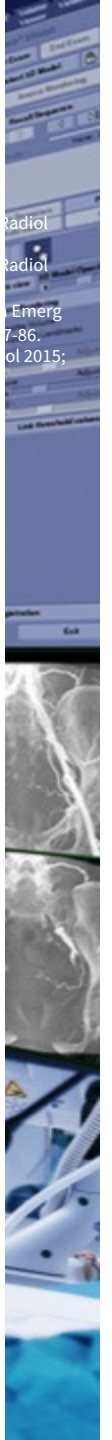
Is CI-AKI a true clinical entity in CT?

Recent observational studies have questioned whether CI-AKI is a true clinical entity in CT[1-3]

The hospitals in which these studies took place both use iodixanol[2,3] and one institution states that it is used for their high-risk patients[2]

The results of these trials are consistent with isosmolar contrast having limited nephrotoxic potential following IV administration[1-4]

CI-AKI: contrast-induced acute kidney injury
CT: computed tomography
eGFR: estimated glomerular filtration rate
IOCM: isosmolar contrast media
IV: intravenous
PC-AKI: post-contrast acute kidney injury
SCr: serum creatinine



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What impact can CM administration have post-CT?

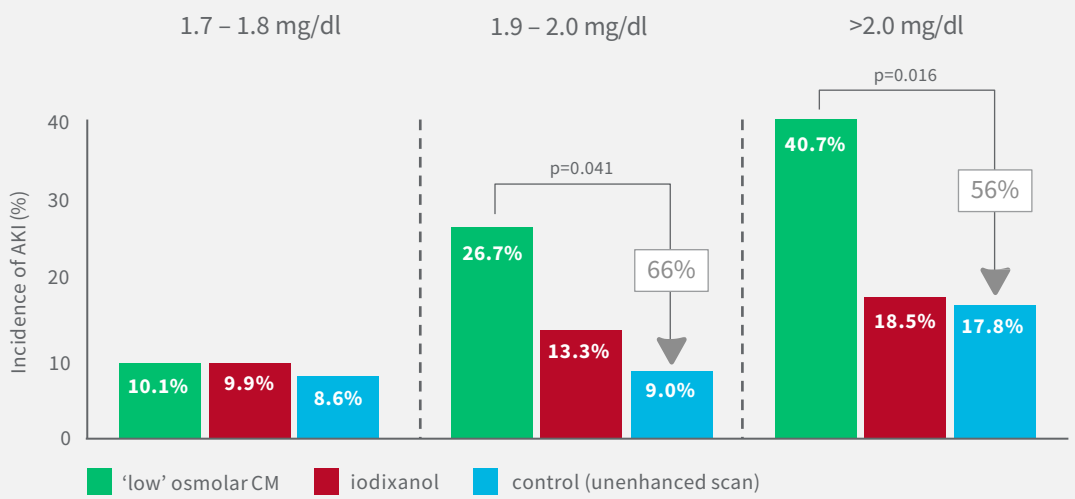
While a number of studies have found no association between IV contrast and increased frequency of kidney injury, others have reported increases in post-CT AKI with advancing CKD in LOCM-enhanced patients[1-5]

In a retrospective analysis, patients receiving iodixanol had a comparable risk of developing AKI* to patients who had unenhanced scans, even among those with a baseline creatine value >1.8 mg/dl[3]

AKI* stratified by baseline serum creatinine (n=11,588)[3]

Analysis of 11,588 patients undergoing CT (both contrast-enhanced and unenhanced) between January 2000 and December 2006[3]

**AKI defined as an SCr increase of ≥0.5 mg/dl or an eGFR decrease of ≥25% within 3 days*



Adapted from Bruce 2009[3]

Consistent with contrast administration protocols, iodixanol patients were older and more likely to have poor kidney function, to be hospitalized, to have diabetes, or to have proteinuria than those administered LOCM[3]

AKI: acute kidney injury
CKD: chronic kidney disease
CM: contrast media
CT: computed tomography
eGFR: estimated glomerular filtration rate
IV: intravenous
LOCM: 'low' osmolar CM
SCr: serum creatinine

Rx

Prescribing information is available at the end of this presentation

1. Hinson JS *et al*. Ann Emerg Med 2017; 69(5): 577-86.
2. McDonald JS *et al.* Radiology 2013; 267(1): 119-28.
3. Bruce RJ *et al*. AJR Am J Roentgenol 2009; 192(3): 711-8.
4. Alsafi A *et al*. Radiol Res Pract 2014; 2014: 459583.
5. Park S *et al.* Medicine (Baltimore) 2016; 95(18): e3560.

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How do CM compare when it comes to renal risk in CT patients with renal impairment?

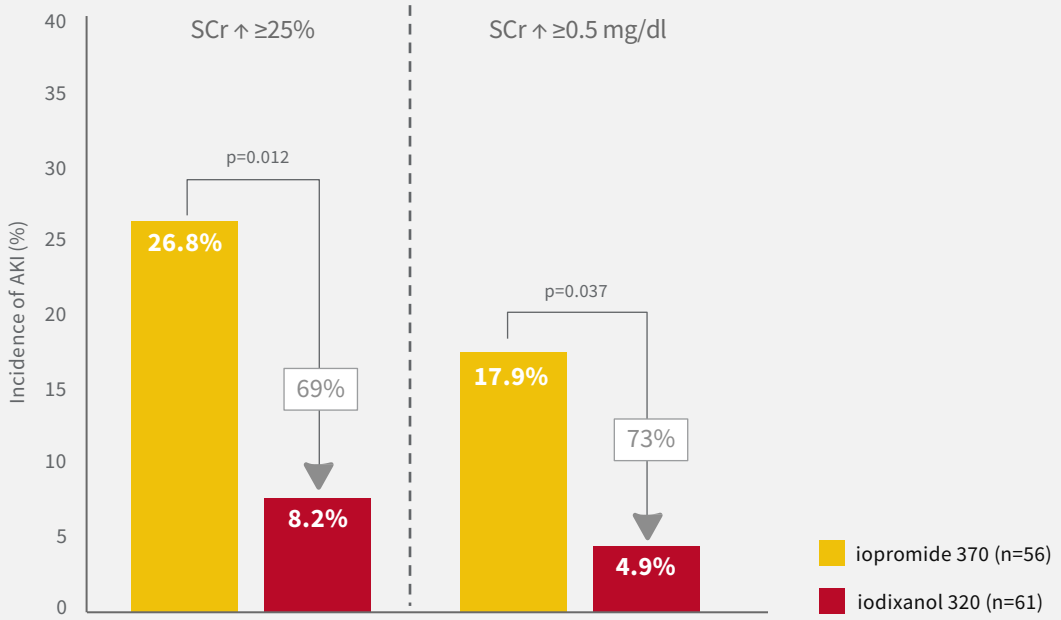
The rate of CI-AKI* in high-risk† patients undergoing CT with iopromide was over 3 times that of iodixanol[1]

Lower incidence of CI-AKI* with iodixanol versus iopromide in high-risk† CT patients (n=117)[1]

Double-blind, randomised study of 117 high-risk† patients

**CI-AKI defined as an SCr increase of ≥25% or ≥0.5 mg/dl*

†High-risk defined as impaired renal function (baseline SCr ≥1.5 mg/dl or GFR <60 ml/min)



Adapted from Nguyen 2008[1]

CI-AKI: contrast-induced acute kidney injury
CM: contrast media
CT: computed tomography
GFR: glomerular filtration rate
SCr: serum creatinine

Rx

Prescribing information is available at the end of this presentation

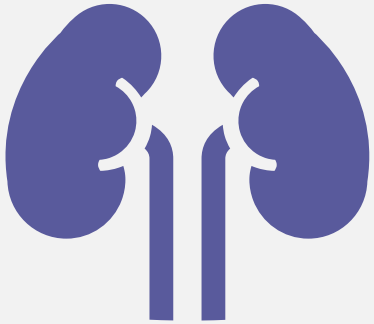
1. Nguyen SA *et al*. Radiology 2008; 248(1): 97-105.

Which patients receiving non-ionic CM are at risk of renal insult?

Underlying renal dysfunction is a major risk factor for contrast-induced nephropathy in patients receiving non-ionic CM; diabetes and the volume of CM administered further contribute to a patient's risk[1]

- Patients with paraproteinemias (myelomatosis and Waldenström's macroglobulinemia) may also be at risk[1]

Additional concerns to consider include:[1]



Dehydration

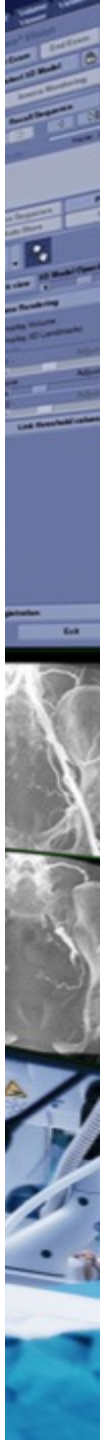
Advanced arteriosclerosis

Poor renal perfusion

Other nephrotoxic factors
e.g. certain medications or major surgery

Special care should be exercized when administering iodinated CM in patients who are at risk of acute renal failure[1]

CM: contrast media



Rx

Prescribing information is available at the end of this presentation

1. Visipaque. Summary of Product Characteristics, April 2021.

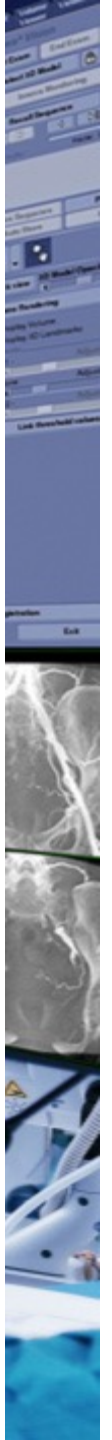
What should be done to reduce the risk of acute renal failure in at-risk patients?

As there is no effective therapeutic to reverse AKI once it occurs, prevention is the cornerstone of managing patients[1]

Preventative measures include:[2]

- **Identifying** high-risk patients
- **Ensuring** adequate hydration
- **Avoiding** additional strain on the kidneys until the CM has been cleared
- **Minimizing** the dose of CM
- **Postponing** repeat exams requiring CM until renal function returns to pre-exam levels

AKI: acute kidney injury
CM: contrast media



Rx

Prescribing information is available at the end of this presentation

1. Solomon R. Am J Nephrol 2021; 52(4): 261-3.
2. Visipaque. Summary of Product Characteristics, April 2021.

The IOCM iodixanol

Utility for CCTA diagnostic and pre-planning for PCI procedures

Visipaque™ (iodixanol) injection, HCP Important Safety Information

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

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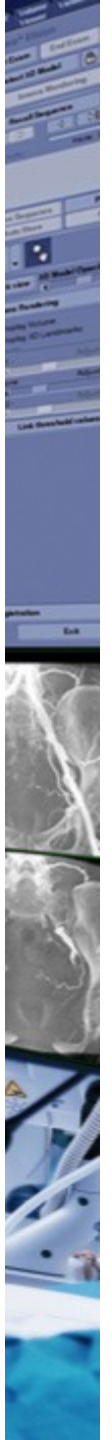

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Can quality diagnostic CCTA images also be obtained with low iodine loads in adults?

In multiple studies, iodixanol 320 has demonstrated similar or better diagnostic images than high concentration CM at similar or lower iodine delivery rates[1-7]

Özbülbül[3] 2010

Contrast media	Concentration (mgI/ml)	Volume injected (ml)	Flow rate (m/s)	Iodine delivery rate (gI/s)	Iodine load (gI)
iodixanol	320	130	4	1.28	41.6
iopamidol	370	130	4	1.48	48.1

Mean vascular attenuation

Ascending aorta:	317 ± 58 HU	324 ± 63 HU
LMC:	309 ± 58 HU	319 ± 59 HU
RCA:	299 ± 51 HU	314 ± 54 HU

There was no difference in image quality between the two groups on all evaluated segments[3]

Andreini[6] 2014

Contrast media	Concentration (mgI/ml)	Volume injected (ml)	Flow rate (m/s)		Iodine delivery rate (gI/s)		Iodine load (gI)	
iodixanol	320	80	6.2	5	2.0	1.6	25.6	25.6
iomeprol	400	80	5		2.0		32.0	

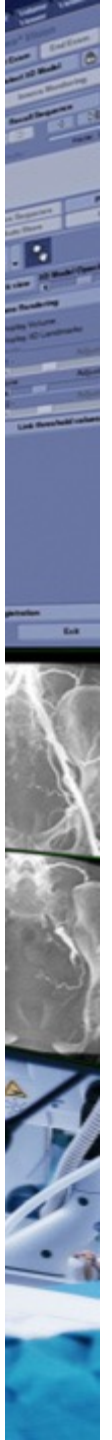
Evaluability of stented segments (flow rate: 5.0 m/s)

98% | 92%

Artifacts (flow rate: 5.0 m/s)

4% | 17%

CCTA: coronary computed tomography angiography
CM: contrast media
HU: Hounsfield unit
LMC: left main coronary arteries
RCA: right main coronary arteries



Rx

Prescribing information is available at the end of this presentation

1. Svensson A *et al.* Acta Radiologica 2010; 51(7): 722-6.
2. Becker CR *et al.* Invest Radiol 2011; 46(7): 457-64.
3. Özbülbül N *et al.* Coronary Artery Dis 2010; 21(7): 414-9.
4. Maffei C *et al.* World J Radiol 2012; 4(6): 265-72.
5. Faggioni L *et al.* Am J Roentgenol 2012; 199(6): 1220-5.
6. Andreini D *et al.* Cardiovasc Comput Tomogr 2014; 8(1): 44-51.
7. Standards and Guidelines Volume 4, Issue 6103664 June 2025. Coronary Computed Tomography Angiography to Guide Percutaneous Coronary Intervention: Expert Opinion from a SCAI/SCCT Roundtable: Yader Sandoval, MD (Chair); Jonathon A. Leipsic, MD (Co-Chair); Carlos Collet, MD, PhD; Arnold H. Seto, MD; Evan Shlofmitz, DO; Emmanouil S. Brilakis, MD, PhD

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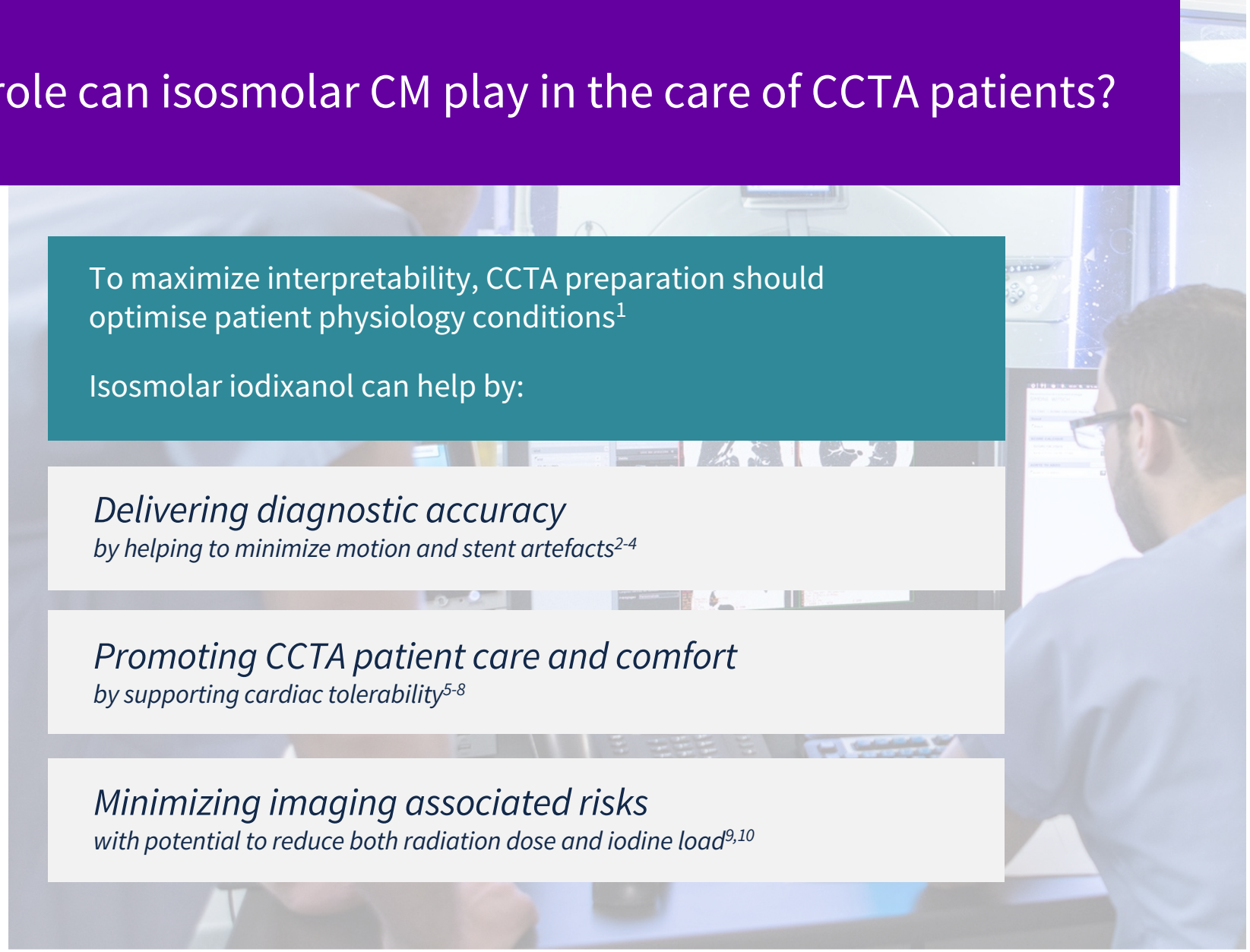
What role can isosmolar CM play in the care of CCTA patients?



To maximize interpretability, CCTA preparation should optimise patient physiology conditions[1]

Isosmolar iodixanol can help by:

Delivering diagnostic accuracy
by helping to minimize motion and stent artefacts[2-4]

Promoting CCTA patient care and comfort
by supporting cardiac tolerability[5-8]

Minimizing imaging associated risks
with potential to reduce both radiation dose and iodine load[9,10]

CCTA: coronary computed tomography angiography
CM: contrast media

Rx

Prescribing information is available at the end of this presentation

1. Andreini D *et al*. J Cardiovasc Med 2016; 17(2): 73-84.
2. Roche T *et al*. Arch Cardiovasc Imaging 2014; 2(3): e20708.
3. Andreini D *et al*. Cardiovasc Comput Tomogr 2014; 8(1): 44-51.
4. Svensson A *et al*. Acta Radiologica 2010; 51(7): 722-6.
5. Almén T. Acta Radiol 1995; 36(Suppl.399): 2-18.
6. Fountaine H *et al*. Acad Radiol 1996; 3(Suppl.3): S475-84.
7. Jynge P. Eur Radiol 1996; 6(Suppl.2): S8-12.
8. Pedersen HK. Acta Radiol Suppl 1996; 37(Suppl.405): 1-31.
9. Zheng M *et al*. Acad Radiol 2015; 22(2): 195-202.
10. Bae KT. Radiology 2010; 256(1): 32-61.

The IOCM iodixanol

Real-world data: CM use in patients undergoing IA procedures

Visipaque™ (iodixanol) injection, HCP Important Safety Information

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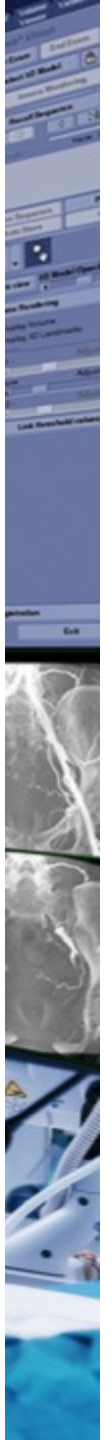

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How does the risk of major adverse events differ between CM in angioplasty patients?

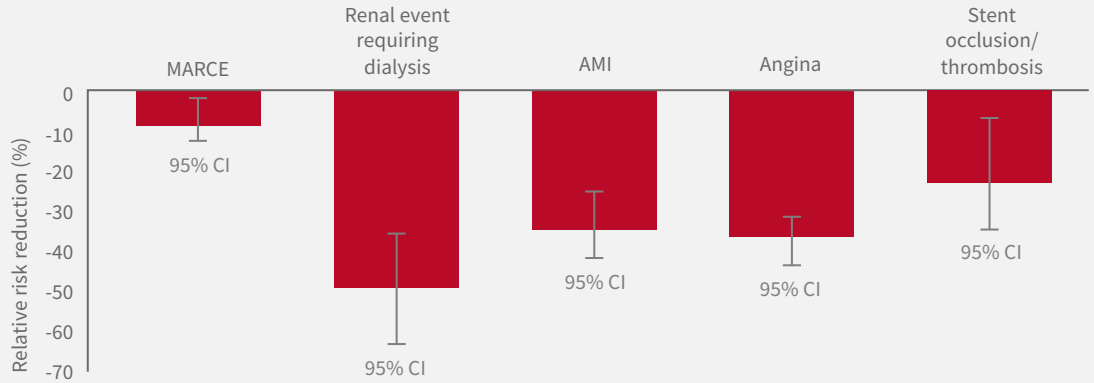
The Premier Hospital Database has provided data for several large real-world studies that compared iodixanol with multiple pooled LOCM in a range of contrast-enhanced procedures[1-5]

Among all-comer patients undergoing angioplasty, iodixanol was associated with 0.7% fewer MARCE events (equivalent to a RRR of 9.3%) after controlling for variables* vs multiple pooled LOCM†[1]

Reduction in risk of adverse events with iodixanol vs multiple pooled LOCM† (n=333,533)[1]

**Patient demographics, comorbid conditions, hospital characteristics, year of visit*

†Pool of LOCM (iohexol, ioversol, iopamidol, ioxaglate, ioxilan, iopromide)

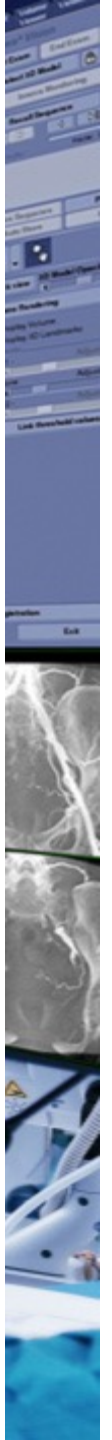


	MARCE	Renal event requiring dialysis	AMI	Angina	Stent occlusion/ thrombosis
Prevalence	7.41%	0.4%	1.1%	2.1%	0.5%
ARR	0.69%	0.2%	0.4%	0.8%	0.1%
RRR	9.32%	50%	34%	38%	21%

Adapted from McCullough 2017[1]

MARCE defined as a composite outcome of renal failure with dialysis, AKI with or without dialysis, CI-AKI, AMI, angina, stroke, TIA, or death.
The definition of MARCE may differ between studies

AKI: acute kidney injury
AMI: acute myocardial infarction
ARR: absolute risk reduction
CI: confidence interval
CI-AKI: contrast-induced AKI
CM: contrast media
LOCM: 'low' osmolar CM
MARCE: major adverse renal and cardiac events
RRR: relative risk reduction
TIA: transient ischaemic attack



Rx

Prescribing information is available at the end of this presentation

1. McCullough PA *et al.* J Comp Eff Res 2017; 7(4): 331-41.
2. McCullough P *et al.* Cardiorenal Med 2021; 11(4): 193–9.
3. Amin AP *et al.* J Invasive Cardiol 2021; 33(8): E640-6.
4. Prasad A *et al.* Catheter Cardiovasc Interv 2022; 99(4): 1335-42.
5. Moser FG *et al.* Am J Neuroradiol 2022; 43(3): 381-7.

GE HealthCare

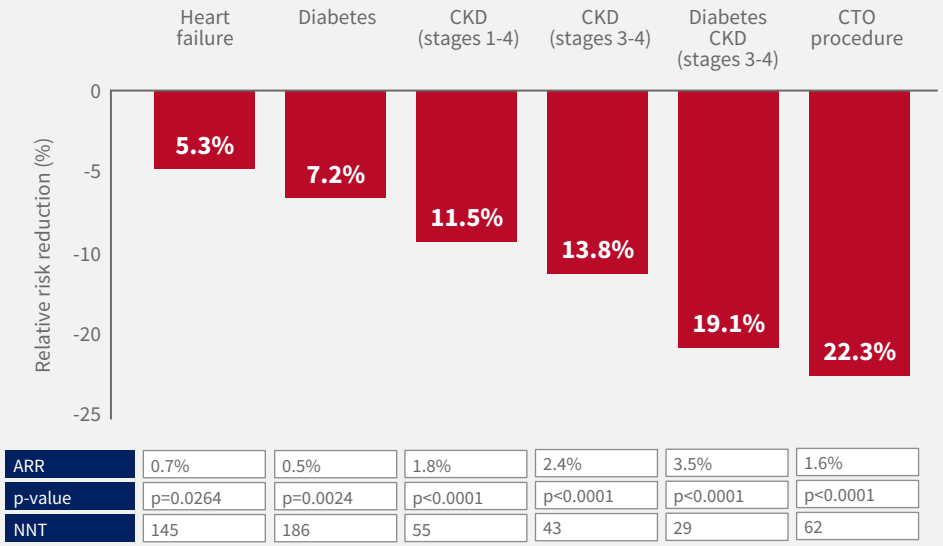
How does the risk of major adverse events differ between CM in comorbid patients?

IA use of iodixanol was associated with a significantly lower risk of MARCE in patients with single, and combined risk factors for AKI vs multiple pooled LOCM*[1]

Reduction in risk of MARCE with iodixanol vs multiple pooled LOCM* (n=536,013)[1]

All patients underwent IA procedures and had comorbid conditions that increased their risk of AKI (including diabetes, heart failure, CKD [stages 1-4], or a diagnosis of CTO)

**Pool of LOCM (iohexol, ioversol, iopamidol, and other)*



	Heart failure	Diabetes	CKD (stages 1-4)	CKD (stages 3-4)	Diabetes CKD (stages 3-4)	CTO procedure
ARR	0.7%	0.5%	1.8%	2.4%	3.5%	1.6%
p-value	p=0.0264	p=0.0024	p<0.0001	p<0.0001	p<0.0001	p<0.0001
NNT	145	186	55	43	29	62

RRR was not calculated for Diabetes + CKD (stages 3-4) + CTO; ARR (2.8%) bordered on significance (p=0.0592), likely due to a small sample size (n=5,824) and model complexity

Adapted from McCullough 2021[1]

MARCE defined as a composite outcome of renal failure with dialysis, AKI with or without dialysis, AMI, stroke, TIA, stent occlusion/thrombosis, or death

AKI: acute kidney injury
AMI: acute myocardial infarction
ARR: absolute risk reduction
CKD: chronic kidney disease
CM: contrast media
CTO: chronic total occlusion
IA: intra-arterial
LOCM: 'low' osmolar CM
MARCE: major adverse renal and cardiovascular events
NNT: number needed to treat
RRR: relative risk reduction
TIA: transient ischemic attack

Rx

Prescribing information is available at the end of this presentation

1. McCullough P *et al.* Cardiorenal Med 2021; 11(4): 193–9.

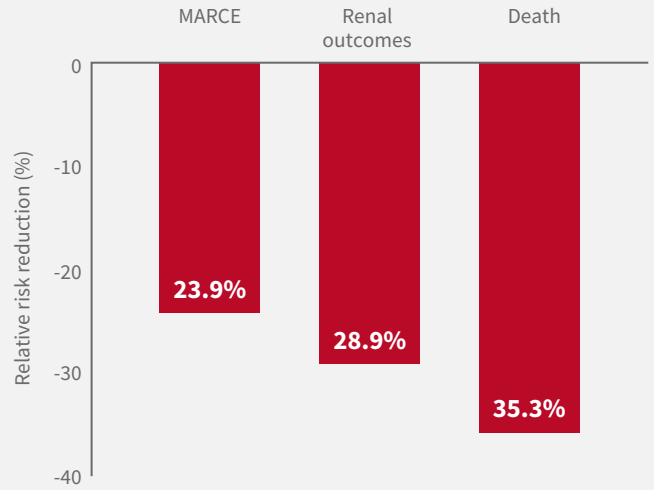
How does the risk of major adverse events differ between CM in EVAR patients?

IA use of iodixanol was associated with a lower risk of MARCE, adverse renal outcomes, and death in high-risk* EVAR patients vs multiple pooled LOCM†[1]

Reduction in risk of adverse events with iodixanol vs multiple pooled LOCM† (n=15,777)[1]

*Patients were age ≥75 years, or had one or more of the following comorbidities: diabetes, anaemia, CKD (stages 1-4 or unspecified) or CHF

†Pool of LOCM (iopamidol [42%], iohexol [38%], ioversol [18%], and other [2%])



	MARCE	Renal outcomes	Death
ARR	1.8%	1.3%	0.9%
CI	0.4% - 3.3%	0.1% - 2.6%	0.1% - 1.7%
p-value	p=0.0130	p=0.0319	p=0.0371

Adapted from Amin 2021[1]

The authors concluded that iodixanol may help "reduce morbidity and mortality in these challenging patients" vs LOCM[1]

MARCE defined as a composite outcome of renal failure with dialysis, AKI with or without dialysis, AMI, stroke, TIA, or death

AKI: acute kidney injury
AMI: acute myocardial infarction
ARR: absolute risk reduction
CHF: congestive heart failure
CKD: chronic kidney disease
CI: confidence interval
CM: contrast media
EVAR: endovascular aneurysm repair
IA: intra-arterial
LOCM: 'low' osmolar CM
MARCE: major adverse renal and cardiac events
TIA: transient ischemic attack

Rx

Prescribing information is available at the end of this presentation

1. Amin AP *et al*. J Invasive Cardiol 2021; 33(8): E640-6.

GE HealthCare

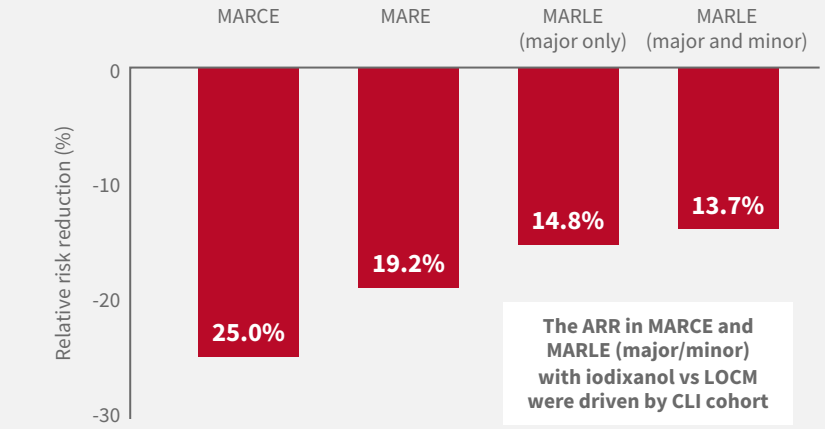
How does the risk of major adverse events differ between CM in patients with PAD?

In high-risk* patients with PAD (claudication or CLI) undergoing peripheral revascularization procedures, use of iodixanol was associated with a lower risk of major adverse cardiorenal or limb events vs multiple pooled LOCM†[1]

Reduction in risk of MARCE, MARE, and MARLE with iodixanol vs multiple pooled LOCM† (n=20,689)[1]

**High-risk as defined by ≥1 of the following: ≥75 years, CKD (stage 1-4 or unspecified), diabetes, anaemia, CHF*

†Pool of LOCM (iopamidol, iohexol, ioversol, and other)



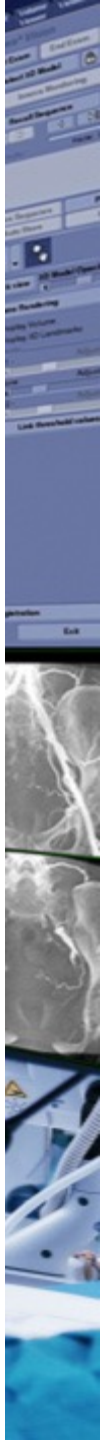
	MARCE	MARE	MARLE (major only)	MARLE (major and minor)
ARR	2.2%	1.4%	1.5%	2.0%
p-value	p<0.0001	p=0.0072	p=0.0113	p=0.0043
NNT	46	72	66	52

This was the first study to observe an association between contrast type and a reduction in major amputation risk[1]

Adapted from Prasad 2022[1]

MARCE defined as a composite outcome of renal failure with dialysis, AKI with or without dialysis, CI-AKI, AMI, stroke, TIA, or death. MARE defined as a composite of renal outcomes. MARLE defined as a composite of renal outcomes with major amputations ± minor amputations

AKI: acute kidney injury
AMI: acute myocardial infarction
ARR: absolute risk reduction
CHF: congestive heart failure
CI-AKI: contrast-induced AKI
CKD: chronic kidney disease
CLI: critical limb ischemia
CM: contrast media
LOCM: 'low' osmolar CM
MARCE: major adverse renal and cardiovascular events
MARE: major adverse renal events
MARLE: major adverse renal and limb events
NNT: number needed to treat
PAD: peripheral artery disease
TIA: transient ischemic attack



Rx

Prescribing information is available at the end of this presentation

1. Prasad A *et al.* Catheter Cardiovasc Interv 2022; 99(4): 1335-42.

GE HealthCare

The IOCM iodixanol

CM and adverse cardiac events

Visipaque™ (iodixanol) injection, HCP Important Safety Information

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

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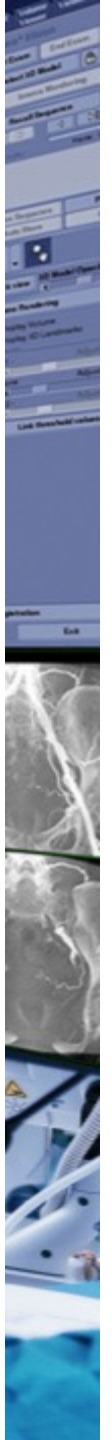

Rx

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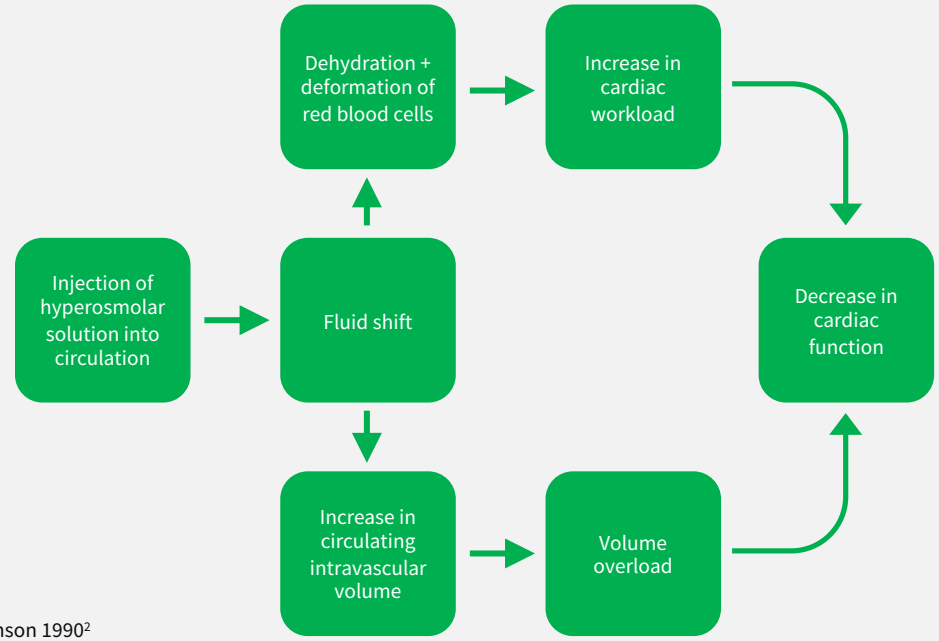
How might the administration of CM influence cardiac function?

The osmolality of a CM is an important predictor of its cardiac effects; the greater the osmolality, the more likely and pronounced the changes[1]



Adapted from Swanson 1990[2]

The washout of normal extracellular electrolytes as a CM circulates may also influence both ventricular contraction and normal depolarisation[3,4]

Several large prospective clinical trials have shown that isosmolar iodixanol is associated with significantly fewer major adverse cardiac events than specific LOCMs[5-7]

CM: contrast media
LOCM: 'low' osmolar CM

Rx

Prescribing information is available at the end of this presentation

1. Spencer CM, Goa KL. Drugs 1996; 52(6): 899–927.
2. Swanson DP *et al.* In: Pharmaceuticals in Medical Imaging. Collier MacMillan Publishers, London 1990.
3. Pedersen HK. Acta Radiol Suppl 1996; 37(Suppl.405): 1–31.
4. Chai C-M *et al.* Acad Radiol 2004; 11(5): 583-93.
5. Harrison JK *et al.* Am Heart J 2004; 147(4): 613-4.
6. Davidson CJ *et al.* Circulation 2000; 101(18): 2172-7.
7. Nie B *et al.* Cathet Cardiovasc Intervent 2008; 72(7): 958-65.

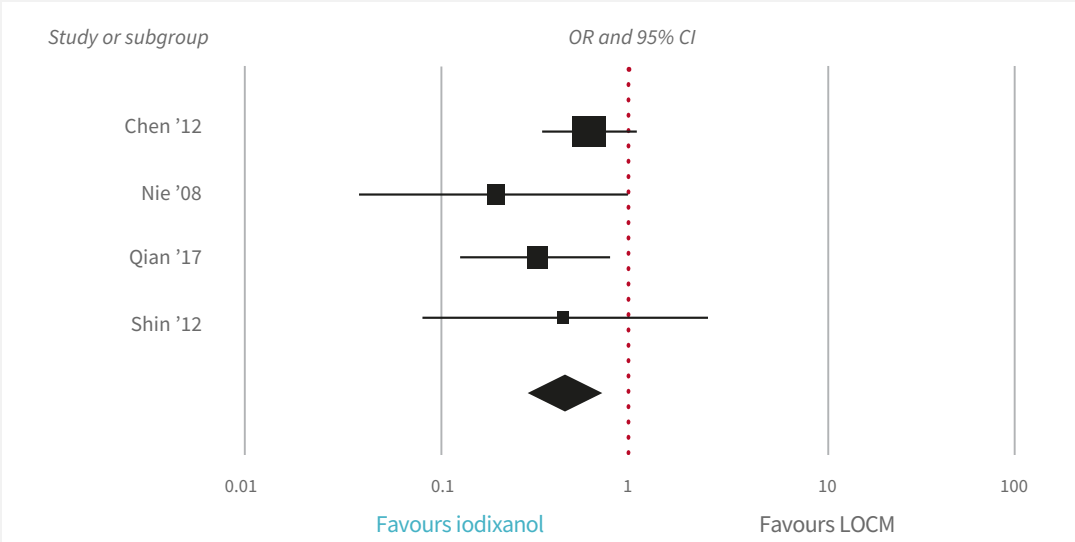
What does a meta-analysis conclude about the risk of adverse cardiac events following IA procedures?

IA use of iodixanol reduced the risk of adverse cardiovascular events* in patients undergoing coronary angiography with/without PCI vs iopromide[1]

Lower risk of adverse cardiac events* with iodixanol vs iopromide (n=1,280)[1]

Meta-analysis of head-to-head, randomised studies, 1995 to March 2017

**Adverse cardiac events included all cause death, stroke, MI, angina pectoris, new arrhythmias, AHF, and repeat revascularisation*



OR=0.47; 95% CI: 0.30-0.73; p=0.0009

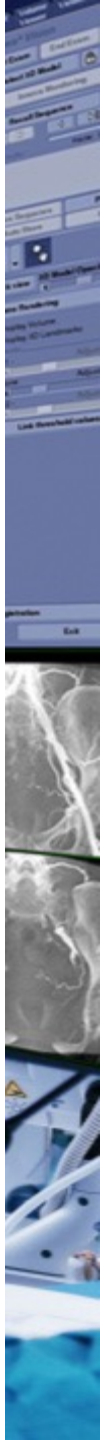
Patients had impaired renal function[1]

CrCl: ≤60 ml/min

eGFR: ≤60 ml/min/1.73 m^2

Adapted from Zhang 2018[1]

AHF: acute heart failure
CI: confidence interval
CrCl: creatinine clearance
eGFR: estimated glomerular filtration rate
IA: intra-arterial
MI: myocardial infarction
OR: odds ratio
PCI: percutaneous coronary intervention



Rx

Prescribing information is available at the end of this presentation

1. Zhang J *et al.* Medicine (Baltimore) 2018; 97(18): e0617.

GE HealthCare

The IOCM iodixanol

Considerations in acute ischemic stroke

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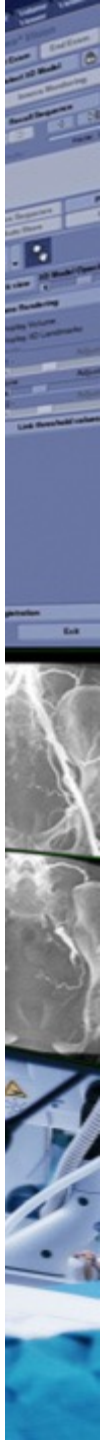

Rx

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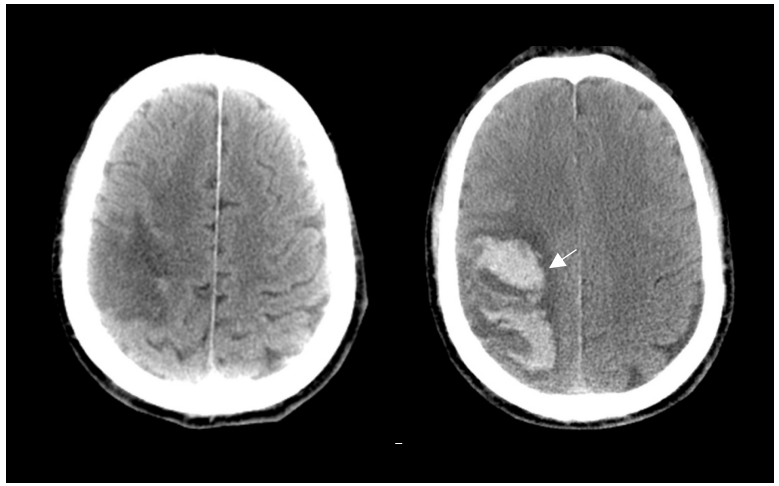
What is hemorrhagic transformation?

HT is a frequent and potentially catastrophic complication of acute ischemic stroke that is associated with an increase in stroke morbidity and mortality[1,2]



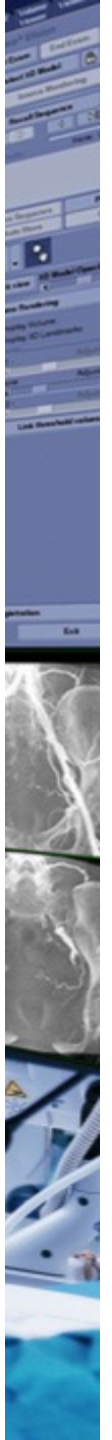
HT occurs when the blood-brain barrier (BBB) is sufficiently disrupted to permit extravasation of peripheral blood into the brain[2]

The presence of HT after a contrast-enhanced procedure has been suggested to potentially represent a direct or indirect effect of the CM itself[3]

- Studies have shown that around half of ischemic stroke patients who undergo endovascular treatment and who have CM deposition in the brain on CT develop HT[1]

Image:
Author: Ya-Yun Cao *et al*.
Article title: Hemorrhagic transformation after acute ischemic stroke caused by polycythemia vera: Report of two case
Journal: World Journal of Clinical Cases
DOI: 10.12998/wjcc.v9.i25.7551
Date of publication: 2021
Original publisher: Baishideng

CM: contrast media
CT: computed tomography
HT: hemorrhagic transformation



Rx

Prescribing information is available at the end of this presentation

1. Morales H *et al.* J Neurointerv Surg 2017; 9(12): 1248-52.
2. Spronk E. Front Neurol 2021; 12: 661955.
3. Moser FG *et al.* Am J Neuroradiol 2022; 43(3): 381-7.

What does a real-world study conclude about the rate of HT with different CM?

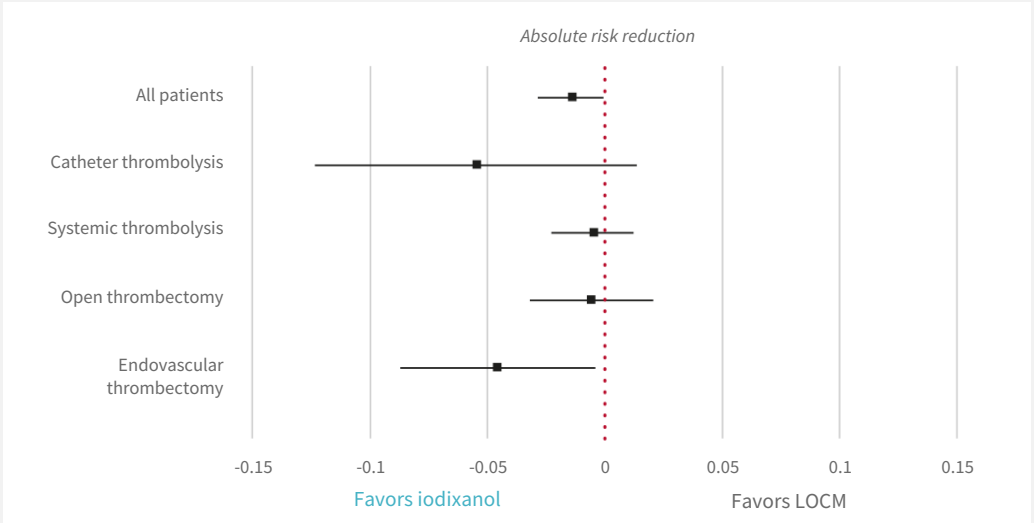
It has been suggested that differences in physicochemical properties between LOCM and iodixanol may affect the risk of HT[1,2]

In patients with ischemic stroke, use of isosmolar iodixanol reduced the relative risk of HT by 12.5% compared with LOCM*[1]

HT risk was lower with iodixanol than with LOCM* (n=42,172)*[1]

Analysis of 42,172 patients in the US Premier database hospitalized with ischemic stroke

**Pool of LOCM (iohexol, ioversol, iopamidol, and other)*



ARR: 1.4%
95% CI: 2.7%-0.1%
p=0.032; NNT:70

The authors concluded that iodixanol may be the CM of choice for the diagnosis and treatment of ischemic stroke[1]

Adapted from Moser 2022[1]

ARR: absolute risk reduction
CI: confidence interval
CM: contrast media
HT: hemorrhagic transformation
LOCM: 'low' osmolar CM
NNT: number needed to treat

Rx

Prescribing information is available at the end of this presentation

1. Moser FG *et al.* Am J Neuroradiol 2022; 43(3): 381-7.
2. Tomsick TA *et al.* AJNR Am J Neuroradiol 2015; 36(11): 2074-81.

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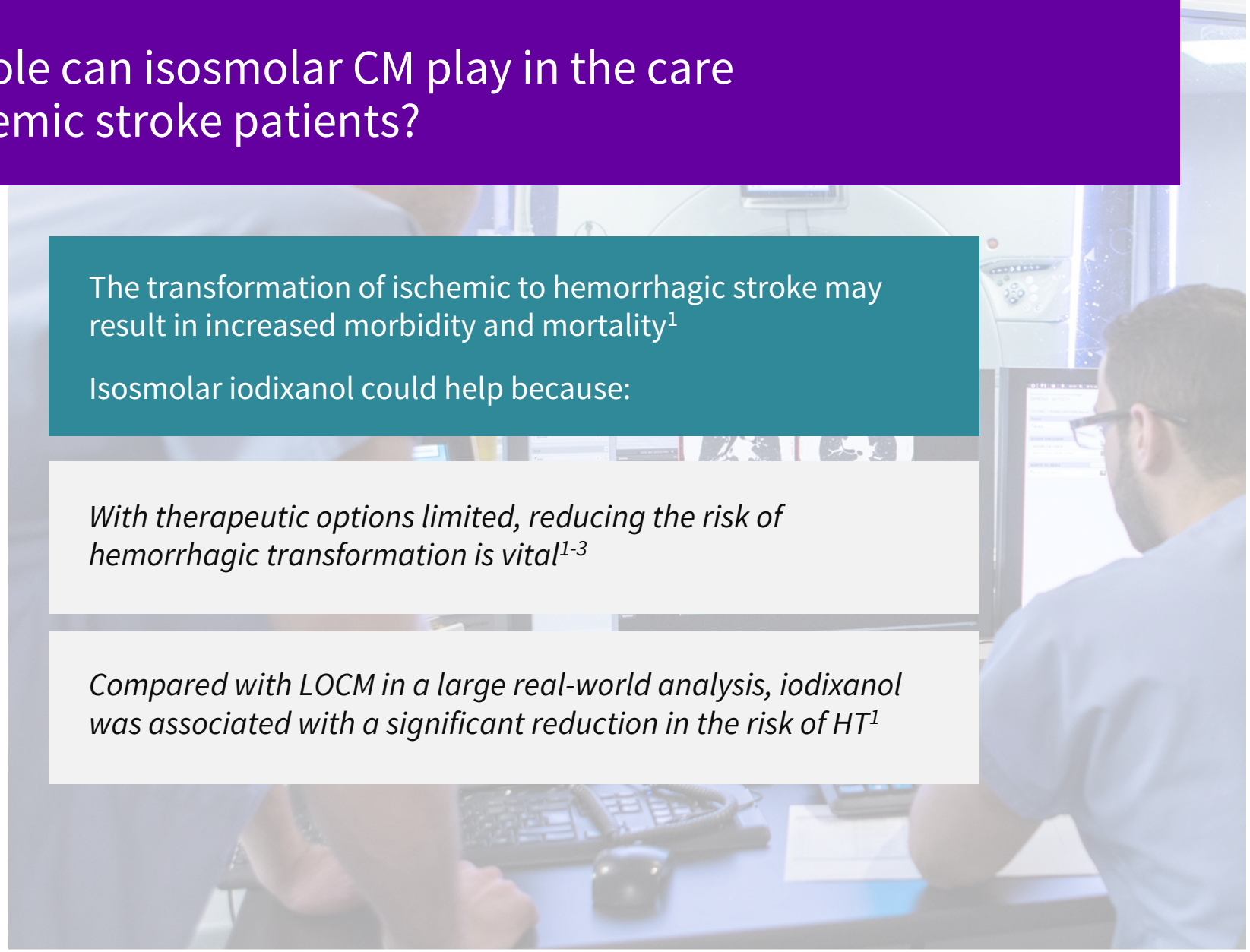
What role can isosmolar CM play in the care of ischemic stroke patients?



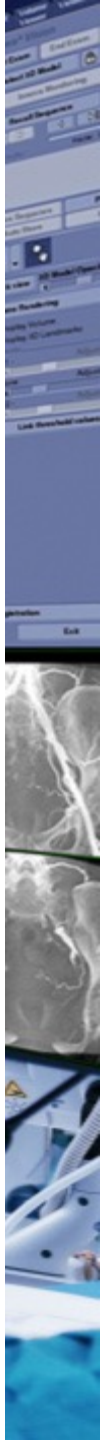
The transformation of ischemic to hemorrhagic stroke may result in increased morbidity and mortality[1]

Isosmolar iodixanol could help because:

With therapeutic options limited, reducing the risk of hemorrhagic transformation is vital[1-3]

Compared with LOCM in a large real-world analysis, iodixanol was associated with a significant reduction in the risk of HT[1]

CM: contrast media
HT: haemorrhagic transformation
LOCM: 'low' osmolar CM



Rx

Prescribing information is available at the end of this presentation

1. Moser FG *et al.* Am J Neuroradiol 2022; 43(3): 381-7.
2. Waziry R *et al*. Stroke 2020; 51(3): 824-9.
3. Zhang J *et al*. Ann Transl Med 2014; 2(8): 81.

The IOCM iodixanol

Imaging-related risks in oncology cancer patients

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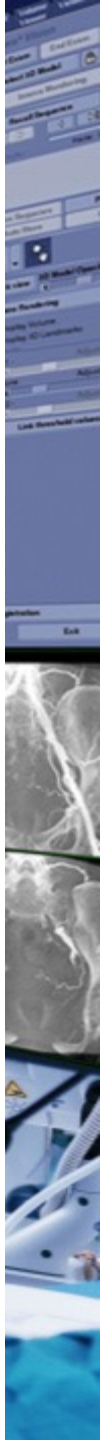

Rx

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GE HealthCare

Does having cancer increase the likelihood of developing AKI?

In a retrospective, multi-centre study, a diagnosis of cancer in patients undergoing contrast-enhanced CT increased the absolute risk of an acute renal AE by 0.9%[1]

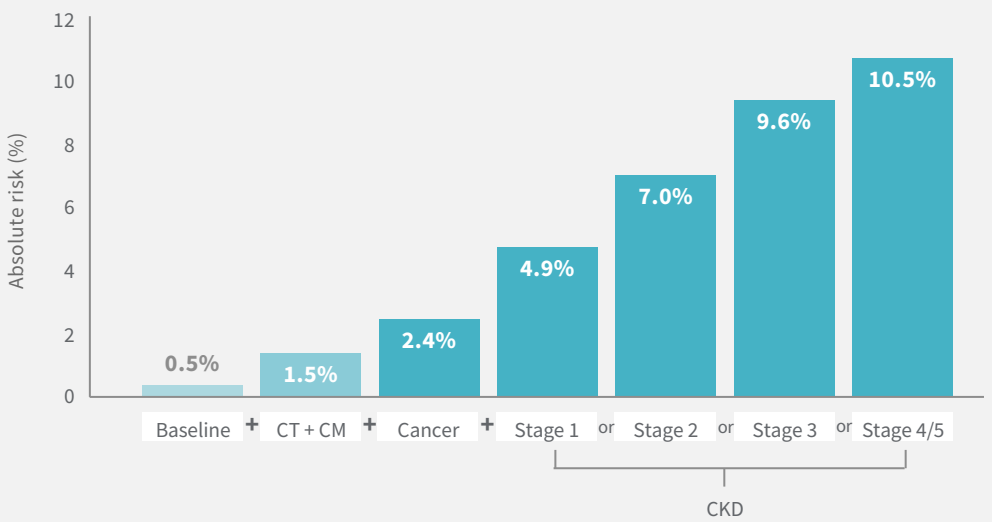
Certain types of cancer, such as colorectal cancer (+1.7%), leukemia (+2.2%) and urinary cancer (+2.3%), posed a particular threat[1]

Risk of developing an acute renal AE (n=29,850,475)[1]

Retrospective database analysis

29,850,475 patient visits:

- *7.4% received a CT scan*
- *3.4% had the primary diagnosis of cancer*
- *5.9% had CKD*



Adapted from Ng 2018[1]

The presence of concomitant CKD further exacerbated a patient's risk[1]

- the absolute risk of an acute renal AE increased with CKD stage, reaching 10.5% in patients with both cancer and stage 4 or 5 CKD[1]

AE: adverse event
AKI: acute kidney injury
CKD: chronic kidney disease
CM: contrast media
CT: computed tomography

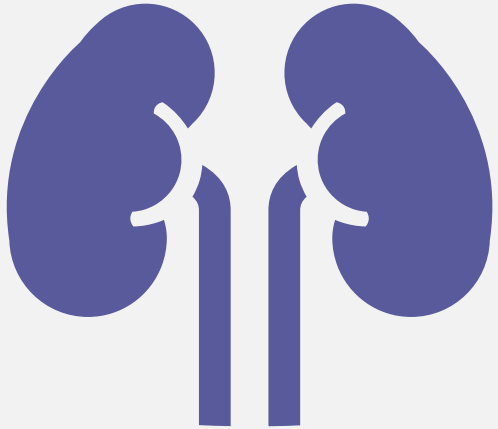
Rx

Prescribing information is available at the end of this presentation

1. Ng SC *et al*. Cancer Imaging 2018; 18(1): 38.

How high is the risk for CI-AKI among oncology patients?

IV iodinated contrast is a common cause of AKI in patients with cancer[1-3]



Exposure to nephrotoxic agents
e.g. cytotoxic drugs, antibiotics, analgesics[2]

Complicated by other issues
e.g. anemia, hypercalcemia, hyperuricemia[2]

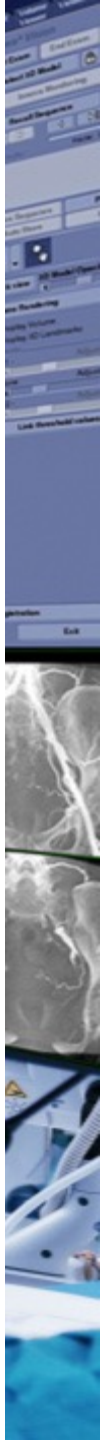
Compromized by advancing age
predisposed to dehydration,[3] *declining renal function*[4]

Even when baseline SCr is normal/near normal, a significant portion of cancer patients still seem to be at risk for CI-AKI[3]

- With creatinine a by-product of muscle metabolism, a low muscle mass may result in a low SCr that masks underlying renal insufficiency[3]
- -Rfunction tests may remain within normal ranges, despite up to 50% of nephrons being lost and the kidney being susceptible to further insults[5]

Iodixanol resulted in a low incidence of AKI, indicating it may help cancer patients with normal renal function avoid kidney deterioration[6]

AKI: acute kidney injury
CI-AKI: contrast-induced AKI
IV: intravenous
SCr: serum creatinine



Rx

Prescribing information is available at the end of this presentation

1. Cicin I *et al.* Eur Radiol 2014; 24(1): 184-90.
2. American Society of Nephrology. Onco-Nephrology Curriculum. Available at: www.asn-online.org/education/distancelearning/curricula/onco/ Accessed on: 15.08.16.
3. Hong SI *et al.* Support Care Cancer 2016; 24(3): 1011-7.
4. American Society of Nephrology. Geriatric Nephrology Curriculum. Available at: www.asn-online.org/education/distancelearning/curricula/geriatrics/ Accessed on: 15.08.16.
5. Sharma A *et al.* Nephron Clin Pract 2014; 127(1-4): 94-100.
6. Terrenato I *et al.* J Cell Physiol 2018; 233(3): 2572-80.

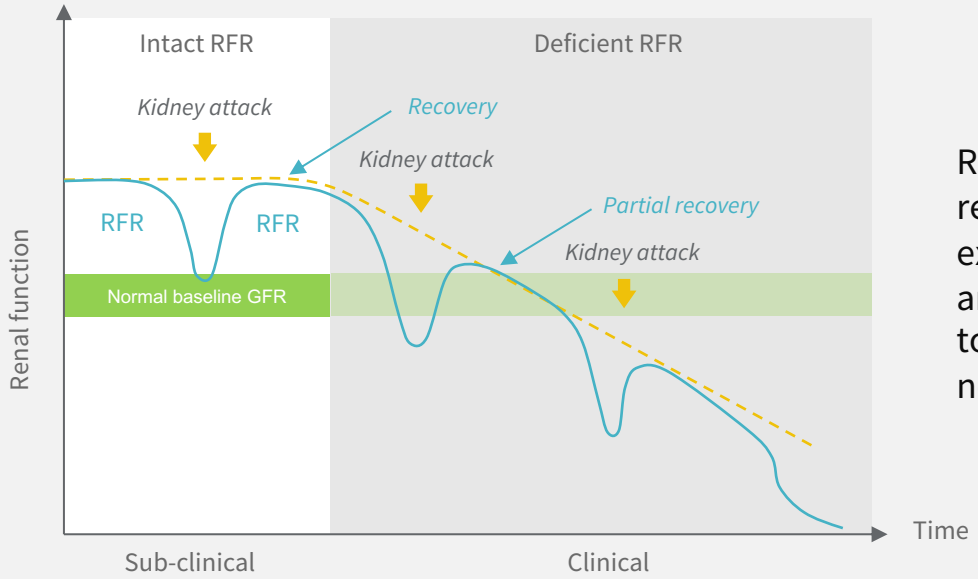
GE HealthCare

What impact do acute renal insults have on glomerular filtration rate/renal functional reserve (RFR)?

If RFR is intact, an insult may remain subclinical and never display a reduction in GFR[1]

With sufficient renal function, up to 50% of nephrons can be lost with no impact on GFR or SCr levels[1]

In case of a clinically evident AKI, even if GFR is affected, recovery of renal function may be sustained by RFR despite nephron loss[1,2]



Adapted from Sharma 2014[1]

RFR may be lost with repeated renal injury, exposing the patient to an increased susceptibility to AKI in case of future nephrotoxic exposure[1,2]

AKI: acute kidney injury
GFR: glomerular filtration rate
RFR: renal functional reserve
SCr: serum creatinine

Rx

Prescribing information is available at the end of this presentation

1. Sharma A *et al*. Nephron Clin Pract 2014; 127(1-4): 94-100.
2. Khullar D. In: API Textbook of Medicine, Volume 2, p. 600-2. 11th Edition, 2017.

Why is CM-associated pain particularly important in cancer patients?

Cancer patients may require repeated venous punctures[1]

Their venous integrity may be compromised by chemotherapy agents that are toxic to the veins[2]

Pain following contrast administration seems to be related to the status of patients' veins[3]

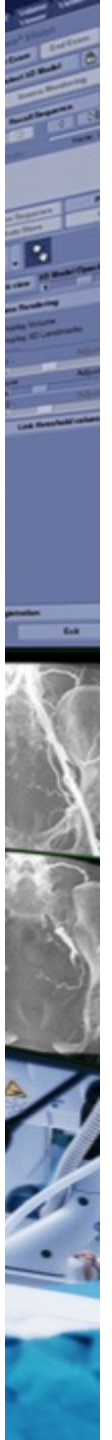
Pain and heat sensation may be severe in cancer patients[4]

The principal cause of pain/heat sensation following contrast medium administration appears to be the higher osmolality of CM as compared with blood[5]

Consensus statement:

Isosmolar CM should be used to minimize discomfort in cancer patients[6]

CM: contrast media



Rx

Prescribing information is available at the end of this presentation

1. Vescia S *et al*. Ann Oncol 2008; 19(1): 9-15.
2. Kreis H *et al*. Eur J Surg Oncol 2007; 33(1): 39-43.
3. Häussler MD. Acta Radiol 2010; 51(8): 924-33.
4. Weiland FL *et al.* Acta Radiol 2014; 55(6): 715-24.
5. Jakobsen JA. Eur J Radiol 2007; 62(Suppl.): S14–25.
6. Del Mastro L *et al.* Blood Purif 2018; 46: 59-69.

The IOCM iodixanol

Osmolality and patient comfort

Visipaque™ (iodixanol) injection, HCP Important Safety Information

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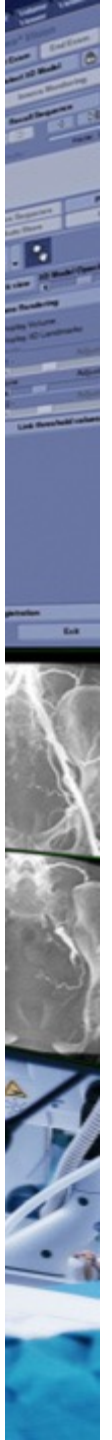

Rx

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GE HealthCare

What is the impact of isosmolar CM on patient comfort in IA procedures?

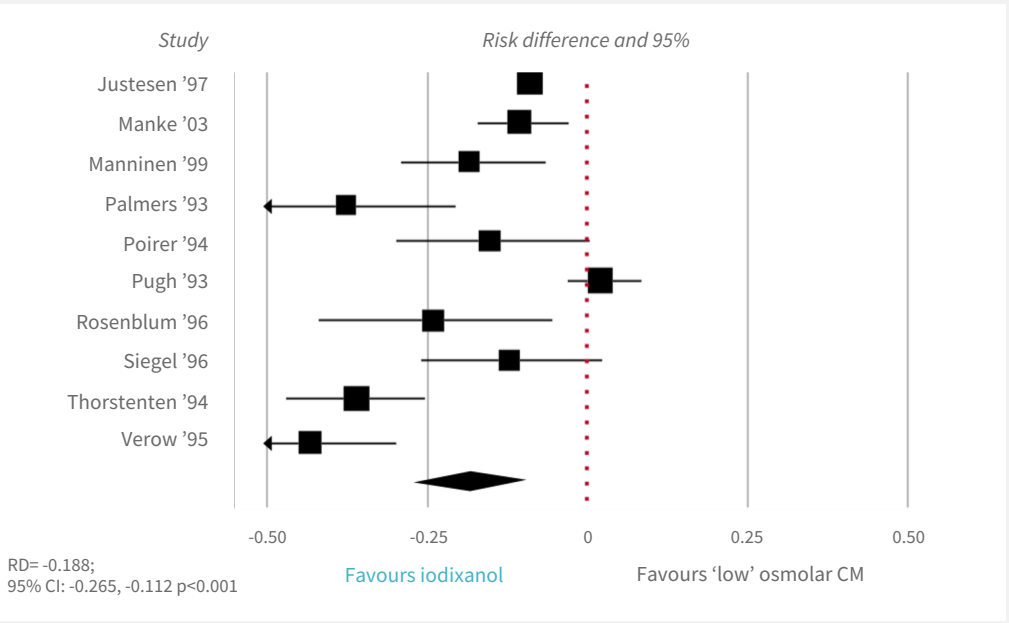
Enhancing procedural comfort is not only important for patients, it could help support efficiency by easing operator 'pain'[1]

Patient discomfort may lead to patient movement, increased motion artifacts, suboptimal images, and compromised treatment[2,3]

IA administered iodixanol is associated with less pain than multiple pooled LOCM† (n=8,087)[3]

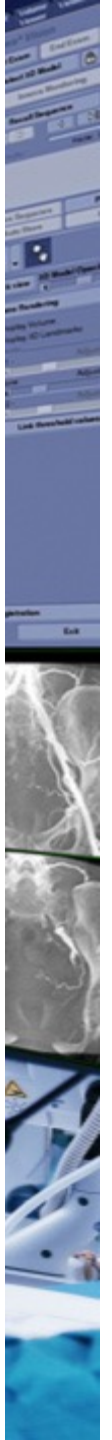
Meta-analysis of head-to-head, randomised studies, 1990 to 2009

†Pool of LOCM (iohexol, iomeprol, iopromide, ioxaglate, iopamidol)



Adapted from McCullough 2011[3]

CI: confidence interval
CM: contrast media
IA: intra-arterial
LOCM: 'low' osmolar CM
RD: risk difference



Rx

Prescribing information is available at the end of this presentation

1. Ortiz-Lopez C, Prasad A. Catheter Cardiovasc Interv 2014; 84(6): 1026-7.
2. Palena LM *et al*. Catheter Cardiovasc Interv 2014; 84(6): 1019-25.
3. McCullough PA, Capasso P. BMC Med Imaging 2011; 11: 12.

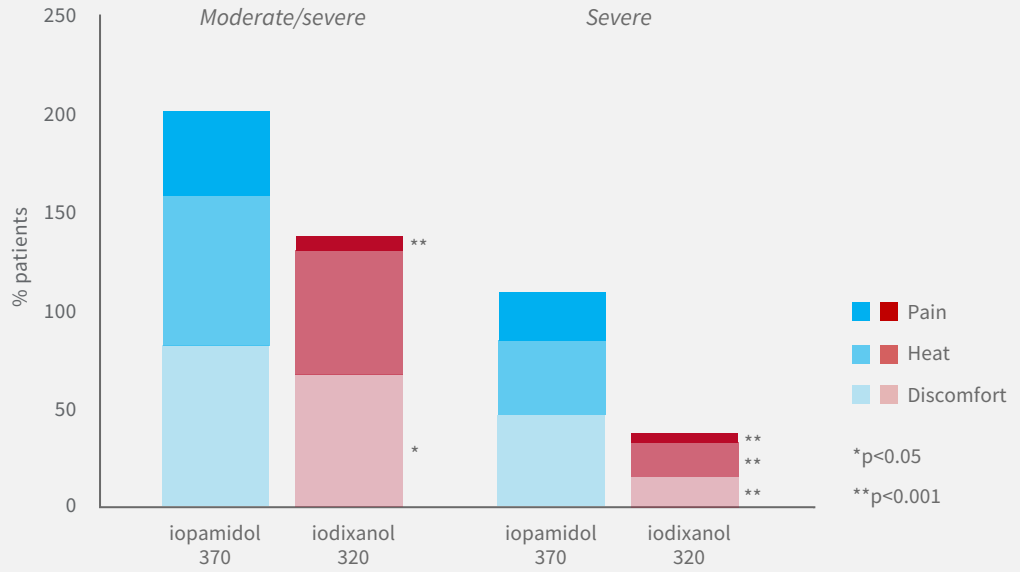
GE HealthCare

What is the impact of isosmolar CM on patient comfort in peripheral procedures?

Among patients undergoing peripheral arteriography, more than 1 in 5 iopamidol patients experienced severe pain during the diagnostic phase of the exam compared with fewer than 1 in 40 iodixanol patients[1]

Iodixanol was associated with less patient discomfort than iopamidol (n=253)[1]

Prospective, double-blind, randomized, multicentre study in 253 patients undergoing peripheral arteriography; 72% had atherosclerosis, 21% had diabetic angiopathy



Adapted from Rosenberg 2017[1]

Similar results have been reported among patients with diabetes undergoing diagnostic angiography + revascularization for CLI, with iodixanol associated with less frequent, and less severe discomfort than ioversol[2]

CLI: critical limb ischaemia
CM: contrast media

Rx

Prescribing information is available at the end of this presentation

1. Rosenberg C *et al.* J Invasive Cardiol 2017; 29(1): 9-15.
2. Palena LM *et al.* Catheter Cardiovasc Interv 2014; 84(6): 1019-25.

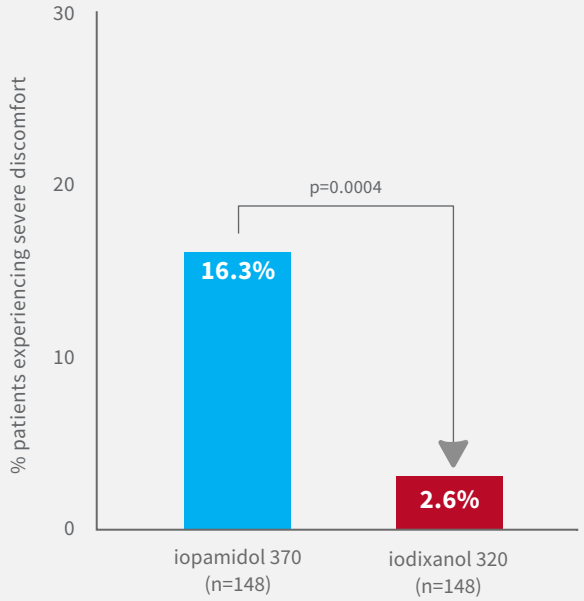
What is the impact of isosmolar CM on patient comfort in CT procedures?

Iodixanol minimizes the impact of CM on patient comfort during IV injection[1,2]

Iodixanol was less likely to cause severe discomfort than iopamidol (n=299)[1]

Double-blind, randomised, multicentre study of 299 patients undergoing abdominal/pelvic CT

Discomfort (heat, pain, coldness) was compared following iodixanol and iopamidol administration



A history of malignancy was the reason for the scan in 47.5% of patients[1]

This result was primarily driven by a reduction in heat sensation with iodixanol vs iopamidol[1]

Adapted from Weiland 2014[1]

CM: contrast medium/media
CT: computed tomography
IV: intravenous

Rx

Prescribing information is available at the end of this presentation

1. Weiland FL *et al*. Acta Radiol 2014; 55: 715-24.
2. Del Mastro L *et al.* Blood Purif 2018; 46: 59-69.

The IOCM iodixanol

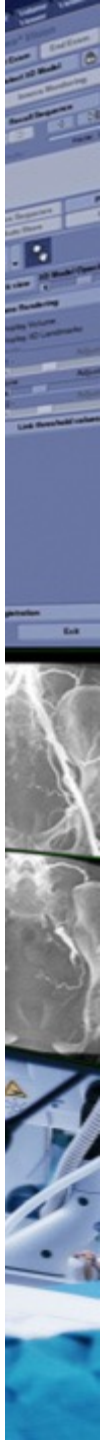
The economic impact of CM choice

Visipaque™ (iodixanol) injection, HCP Important Safety Information

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

Please see Boxed Warning, Important Safety Information, and full Prescribing Information starting on slide 59.



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What is the economic impact of reducing CI-AKI risk in at risk patients?

Substituting LOCM* with iodixanol in patients undergoing cardiac catheterization may lead to cost savings by reducing the risk of CI-AKI† and its associated hospital costs[1]

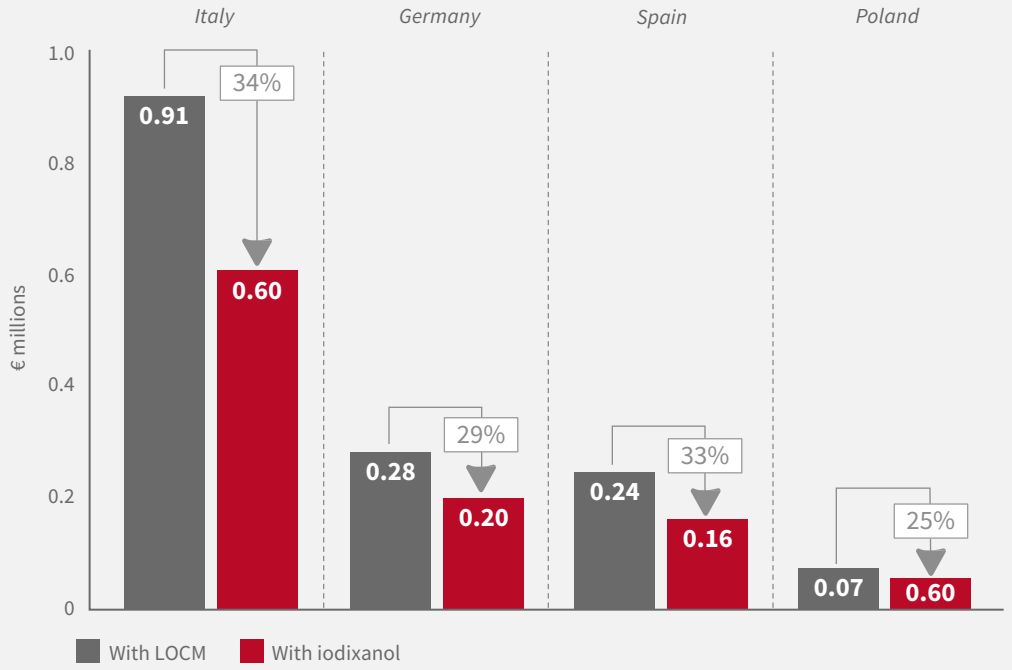
The study was a budget impact analysis comparing a scenario with iodixanol to a scenario without in patients at increased risk of CI-AKI†[1]

3-year cumulative impact on hospital budget with/without iodixanol[1]

Total costs were calculated by summing up CM and CI-AKI management cost accrued during inpatient hospital stay

**Pool of LOCM (iohexol, iopromide, iomeprol, iobitridol, iopamidol, ioversol and, ioxaglate)*

†CI-AKI defined as an increase in SCr of ≥0.5 mg/dl or ≥25% from baseline within 72 hours of CM administration



Adapted from De Francesco 2016[1]

CI-AKI: contrast-induced acute kidney injury
CM: contrast media
LOCM: 'low' osmolar CM
SCr: serum creatinine

Rx

Prescribing information is available at the end of this presentation

1. De Francesco M *et al.* J Med Econ 2016; 19(2): 158-68.

What is the economic impact of reducing MARCE risk in patients undergoing inpatient angioplasties?

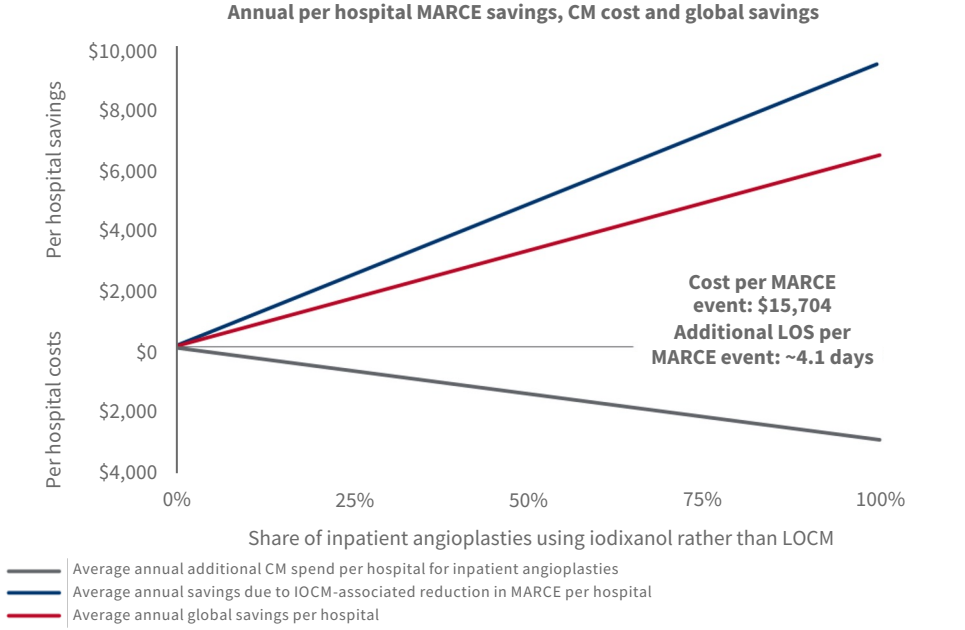
Based on a RWD analysis of Premier hospital data, substituting LOCM* with iodixanol may lead to annual cost savings when used for inpatient angioplasties by reducing the risk of MARCE[1]

Annual per hospital savings using iodixanol rather than LOCM*[1]

Budget impact analysis evaluating the economic impact of using iodixanol for inpatient angioplasty procedures

The model estimated 513,882 patients annually; ~12% of patients were not eligible for CM, and 6.8% developed MARCE

**Pool of LOCM (iohexol, ioversol, iopamidol, ioxaglate, ioxilan, and/or iopromide)*



Adapted from Keuffel 2018[1]

MARCE defined as a composite outcome of renal failure with dialysis, AKI with and without dialysis, AMI, angina, stent occlusion/thrombosis, stroke, TIA, or death occurring during the inpatient visit

AKI: acute kidney injury
AMI: acute myocardial infarction
CM: contrast media
IOCM: isosmolar CM
LOCM: 'low' osmolar CM
LOS: length of stay
MARCE: major adverse renal and cardiac events
RWD: real-world data
TIA: transient ischemic attack

Rx

Prescribing information is available at the end of this presentation

1. Keuffel E *et al.* J Med Econ 2018; 21(4): 356-64.

INDICATIONS AND USE – VISIPAQUE™ (IODIXANOL)

Intra-Arterial Procedures

Adult and pediatric patients 12 years of age and older: Intra-arterial digital subtraction angiography (270 and 320 mg iodine/mL); angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography (320 mg iodine/mL). **Pediatric patients less than 12 years of age:** Angiocardiography, cerebral arteriography, and visceral arteriography (320mg iodine/mL)

Intravenous Procedures

Adult and pediatric patients 12 years of age and older: Computed tomography (CT) imaging of the head andbody (270 and 320 mg iodine/mL); excretory urography (270 and 320 mg iodine/mL); peripheral venography (270 mg iodine/mL); coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease (320 mg iodine/mL). **Pediatric patients less than12 years of age:** CT imaging of the head and body (270 mg iodine/mL); excretory urography (270 mg iodine/mL)

IMPORTANT SAFETY INFORMATION FOR VISIPAQUE (iodixanol) INJECTION

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

CONTRAINDICATION:

Visipaque injection is contraindicated for intrathecal use.

WARNINGS AND PRECAUTIONS:

- **Hypersensitivity Reactions:** Life-threatening or fatal reactions can occur. Most severe reactions develop shortly after the start of the injection, but reactions can occur up to hours later. Always have emergency equipment and trained personnel available.
- **Contrast-Induced Acute Kidney Injury:** Acute injury including renal failure can occur. Minimize dose and maintain adequate hydration to minimize risk.
- **Cardiovascular Adverse Reactions:** Life-threatening or fatal cardiovascular reactions, including hypotension, shock, and cardiac arrest have occurred with the use of Visipaque. Most deaths occur during injection or five to ten minutes later, with cardiovascular disease as the main aggravating factor. Use the lowest necessary dose of Visipaque in patients with congestive heart failure.
- **Thromboembolic Events:** Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke can occur during angiocardiography procedures with both ionic and nonionic contrast agents.
- **Extravasation and Injection Site Reactions:** Extravasation of Visipaque injection may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease. Ensure intravascular placement of catheters prior to injection.
- **Thyroid Storm in Patients with Hyperthyroidism:** Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule.
- **Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age:** Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media (ICM) in patients 0 to 3 years of age.
- **Hypertensive Crisis in Patients with Pheochromocytoma:** Hypertensive crisis has occurred after the use of iodinated contrast agents in patients with pheochromocytoma. Inject the minimum amount of contrast necessary, assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.
- **Sickle Cell Crisis in Patients with Sickle Cell Disease:** Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease.
- **Severe Cutaneous Adverse Reactions (SCAR):** SCAR may develop from one hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS). Avoid administering Visipaque to patients with a history of a SCAR to Visipaque.

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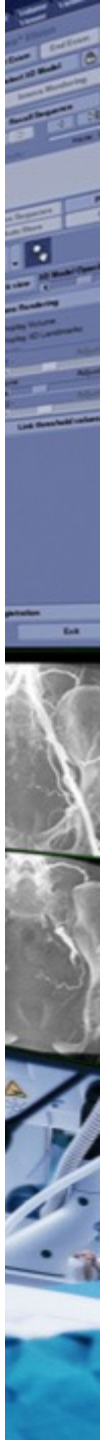

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INDICATIONS AND USE – VISIPAQUE™ (IODIXANOL) (continued)

USE IN SPECIFIC POPULATIONS:

- **Pediatric Use:** Pediatric patients at high risk of adverse reactions during and after administration of contrast agents include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, chronic heart failure, or a serum creatinine >1.5 mg/dL. Patients with immature renal function or dehydration may be at increased risk due to prolonged elimination of iodinated contrast agents.
- **Geriatric Use:** While no overall differences in safety or effectiveness were observed in patients >65 years, greater sensitivity regarding some older individuals cannot be ruled out.

ADVERSE REACTIONS:

- Serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated withthe administration of iodine-containing contrast agents, including Visipaque Injection.
- Most common adverse reactions (incidence greater than 0.5%) in adult patients after Visipaque injection:Discomfort, warmth, pain; Cardiovascular: angina. Gastrointestinal: diarrhea, nausea, vomiting. NervousSystem: agitation, anxiety, insomnia, nervousness, dizziness, headache, migraine, unusual skin sensations, sensory disturbance, fainting, sensation of spinning. Skin: itchy rash, severe itching, hives. Special Senses: Smell, taste, and vision alteration. Pediatric patients experienced similar adverse reactions.

DRUG-DRUG INTERACTIONS:

- **Metformin:** In patients with renal impairment, metformin can cause lactic acidosis. Iodinated contrast agents appear to increase the risk of metformin-induced lactic acidosis, possibly as a result of worsening renal function. Stop metformin at the time of, or prior to, Visipaque administration in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure and reinstitute metformin only after renal function is stable.
- **Radioactive Iodine:** Administration of iodinated contrast agents may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy in patients with carcinoma of the thyroid. The decrease in efficacy lasts 6 to 8 weeks.
- **Beta-adrenergic Blocking Agents:** The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and the responsiveness of treatment of hypersensitivity reactions with epinephrine. Because of the risk of hypersensitivity reactions, use caution when administering Visipaque to patients taking beta-blockers.
- **Oral Cholecystographic Contrast Agents:** Renal toxicity has been reported in patients with liver dysfunction who were given an oral cholecystographic agent followed by intravascular iodinated contrast agents. Postpone the administration of Visipaque in patients who have recently received an oral cholecystographic agent

Click here to see the full Prescribing Information, including boxed warning and additional Important Safety Information.

To report SUSPECTED ADVERSE REACTIONS, contact GE HealthCare at 800 654 0118 (option 2, then option 1), or the FDA at 800 FDA 1088 or www.fda.gov/medwatch.

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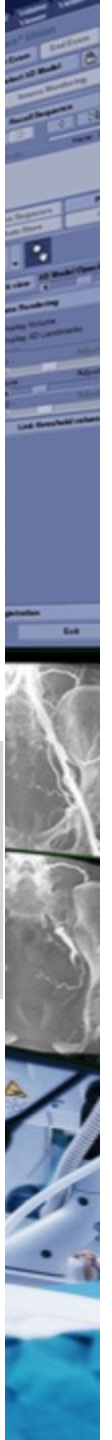

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INDICATIONS AND USE – VISIPAQUE™ (IODIXANOL)

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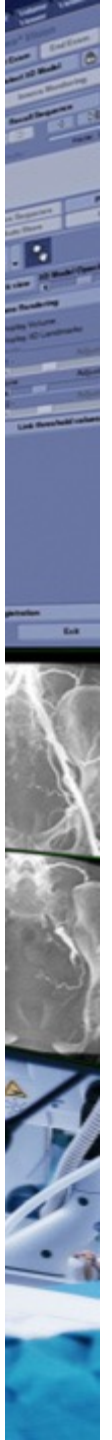

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