

V is for vulnerable

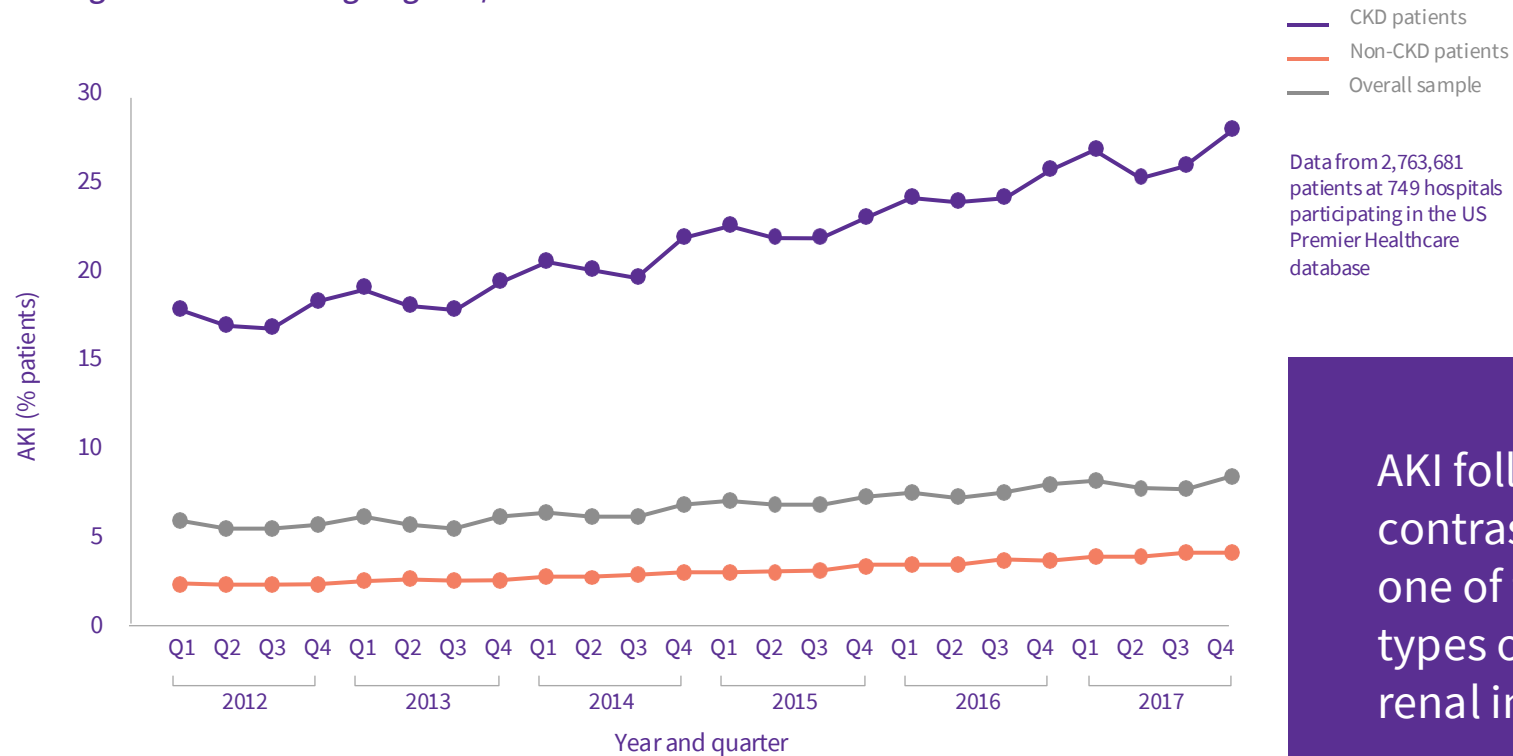
Mitigating the risk of CA-AKI
for high-risk PCI patients in the
cardiac catheterization lab

Please see Important Safety Information for Visipaque™ (Iodixanol) at the back

CA-AKI[#] is a growing concern¹

Vulnerable patient populations are growing, as is the complexity of procedures being performed²

In parallel, the incidence of AKI has increased among Americans undergoing CAG/PCI¹



Adapted from Prasad A et al. 2020.

AKI following iodinated contrast exposure* is now one of the most common types of hospital-acquired renal injuries in the US¹

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast³

*AKI following contrast exposure has historically been called CI-AKI; however, CA-AKI is becoming a more contemporary term

1. Prasad A, Rosenthal NA, Kartashov A, Knish K, Dreyfus J. *Catheter Cardiovasc Interv.* 2020;96(6):1184-1197.
2. Keuffel E, McCullough PA, Todoran TM, et al. *J Med Econ.* 2017;21(4):356-364.
3. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal.* 2022;73(3):499-514.

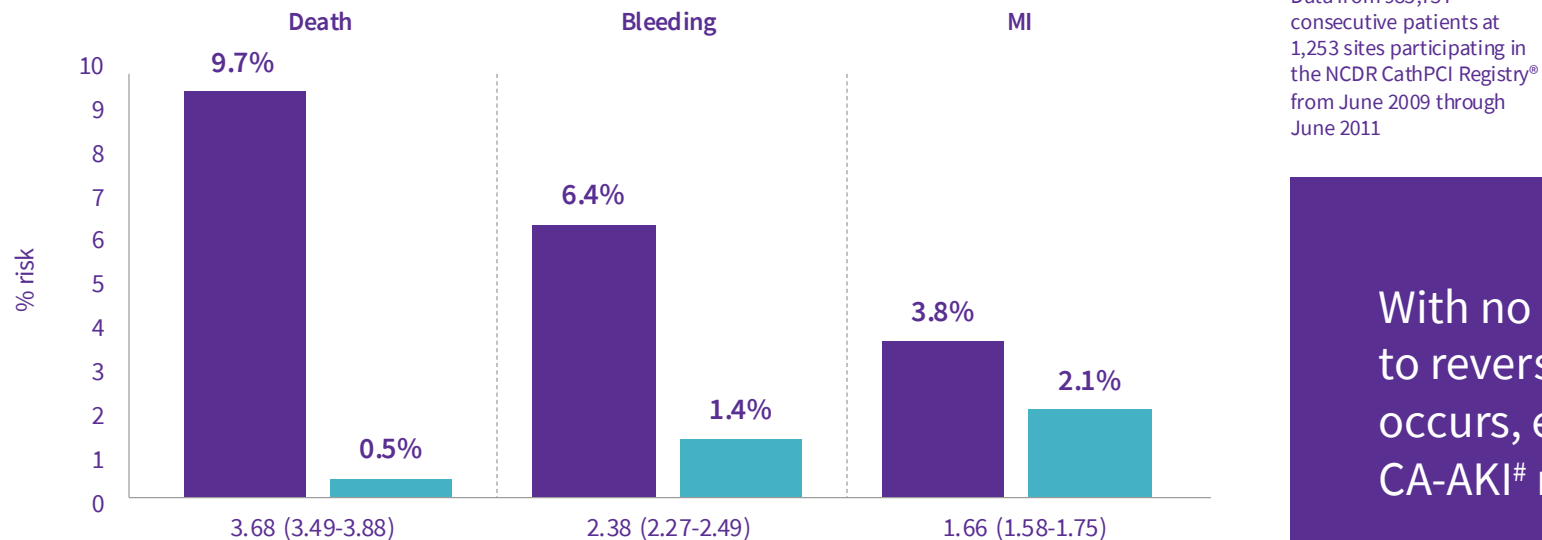
AKI, acute kidney injury
CA-AKI, contrast-associated AKI
CAG, coronary angiography
CKD, chronic kidney disease
PCI, percutaneous coronary intervention

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CA-AKI[#] carries a significant clinical burden¹⁻⁴

Development of CA-AKI[#] is associated with serious adverse outcomes, including an increased risk of CV events, irreversible kidney injury, need for dialysis, and death¹⁻³

Risk of death, bleeding, and MI in PCI patients with/without post-procedural AKI^{*4}



■ AKI ■ No AKI

Data from 985,737 consecutive patients at 1,253 sites participating in the NCDR CathPCI Registry[®] from June 2009 through June 2011

With no specific treatment to reverse the injury once it occurs, efforts to reduce CA-AKI[#] risk are warranted^{2,5}

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast⁶

^{*}AKI was defined as an absolute increase of ≥ 0.3 mg/dL or ≥ 1.5 -fold relative increase in SCr

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1. Azzalini L, Spagnoli V, Ly HQ. *Can J Cardiol*. 2016;32(2):247-255.
2. Prasad A, Rosenthal NA, Kartashov A, Knish K, Dreyfus J. *Catheter Cardiovasc Interv*. 2020;96(6):1184-1197.
3. Brown JR, Rezaee ME, Nichols EL, Marshall EJ, Siew ED, Matheny ME. *J Am Heart Assoc*. 2016;5(3):e002739.
4. Tsai TT, Patel UD, Chang TI, et al. *JACC Cardiovasc Interv*. 2014;7(1):1-9.

5. Almendarez M, Gurm HS, Mariani Jr J, et al. *JACC Cardiovasc Interv*. 2019;12(19):1877-1888.
6. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal*. 2022;73(3):499-514.

AKI, acute kidney injury
CI, confidence interval

CA-AKI, contrast-induced AKI
CV, cardiovascular events
MI, myocardial infarction
NCDR, National Cardiovascular Data Registry
OR, odds ratio
PCI, percutaneous coronary intervention
SCr, serum creatinine

Prevention is the cornerstone of managing high-risk PCI patients¹

ACC/AHA/SCAI guidelines recommend a three-pronged approach to the prevention of CA-AKI^{#,1,2}

1. Screen for risk

2. Ensure adequate hydration

3. Minimize CM volume

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast³

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1. Solomon R. *Am J Nephrol*. 2021;52(4):261-263.
2. Lawton JS, Tamis-Holland JE, Bangalore S, et al. *J AM Coll Cardiol*. 2022;79(2):e21-e129.
3. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal*. 2022;73(3):499-514.

ACC, American College of Cardiology
AHA, American Heart Association
CA-AKI, contrast-associated acute kidney injury
CM, contrast medium/media
PCI, percutaneous coronary intervention
SCAI, The Society for Cardiovascular Angiography and Interventions

A number of factors can contribute to a patient's risk of CA-AKI^{#,1}

Risk factors can be either patient-related, such as CKD, or procedure-related, such as CM volume²

The presence of multiple risk factors increases the likelihood of CA-AKI^{#,1,3}

Mehran risk score for CA-AKI^{#,1}

Risk factors

Integer score

Hypotension	5
IABP	5
CHF	5
Age >75 years	4
Anemia	3
Diabetes	3
Contrast media volume	1 for each 100 mL
SCr >1.5 mg/dL	4
or	2 for 40-60
eGFR <60 mL/min/1.73 m ²	4 for 20-40
	6 for <20

Risk score	Risk of CA-AKI [#]	Risk of dialysis
≤5	7.5%	0.04%
6 to 10	14%	0.12%
11 to 16	26.1%	1.09%
≥16	57.3%	12.6%

Adapted from Mehran R et al. 2004

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast⁴

1. Mehran R, Aymong ED, Nikolsky E, et al. *J Am Coll Cardiol.* 2004;44(7):1393-1399.
2. Cho E, Ko GJ. *Diagnostics (Basel).* 2022;12(1):180.
3. Mehran R, Owen R, Chiarito M, et al. *Lancet.* 2021;398(10315):1974-1983.
4. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal.* 2022;73(3):499-514

CHF, congestive heart failure
CA-AKI, contrast-associated acute kidney injury
CKD, chronic kidney disease
CM, contrast medium/media
eGFR, estimated glomerular filtration rate
IABP, intra-aortic balloon pump
SCr, serum creatinine

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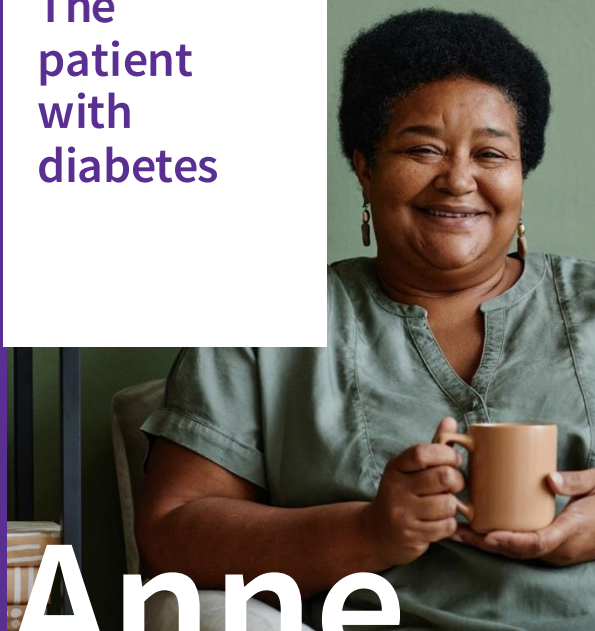
Which patients are at risk of CA-AKI in the cardiac catheterization lab?

The
patient
with CKD



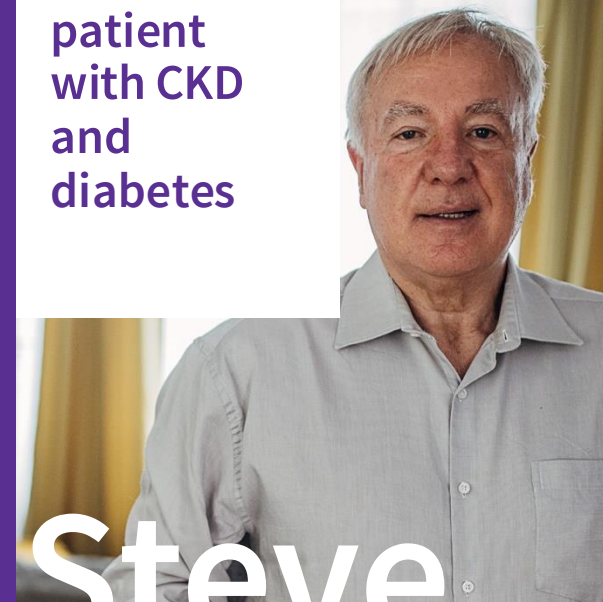
Earl

The
patient
with
diabetes



Anne

The
patient
with CKD
and
diabetes



Steve

Please see Important Safety Information for Visipaque™ (Iodixanol) at the back

CA-AKI, contrast-associated acute kidney injury
CKD, chronic kidney disease

Earl

is 60 and 241 lb

He has CKD

He is at high risk for CA-AKI



CA-AKI, contrast-associated acute kidney injury
CKD, chronic kidney disease

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With a reduced eGFR, contrast may remain in his circulation longer¹

Fewer working nephrons also means each has a larger load of contrast to filter, and the exposure burden per nephron is increased¹

As a result, a lower volume of contrast may result in adverse effects compared with someone with normal kidney function^{2,3}



X10

His risk of CA-AKI[#] may be over ten-fold greater than someone with normal kidney function²

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast⁴

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1. Solomon R. *Am J Nephrol*. 2021;52(4):261-263.

2. Sudarsky D, Nikolsky E. *Int J Nephrol Renovasc Dis*. 2011;4:85-99.

3. Almendarez M, Gurm HS, Mariani J Jr, et al. *JACC Cardiovasc Interv*. 2019;12(19):1877-1888.

4. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal*. 2022;73(3):499-514.

CA-AKI, contrast-associated acute kidney injury

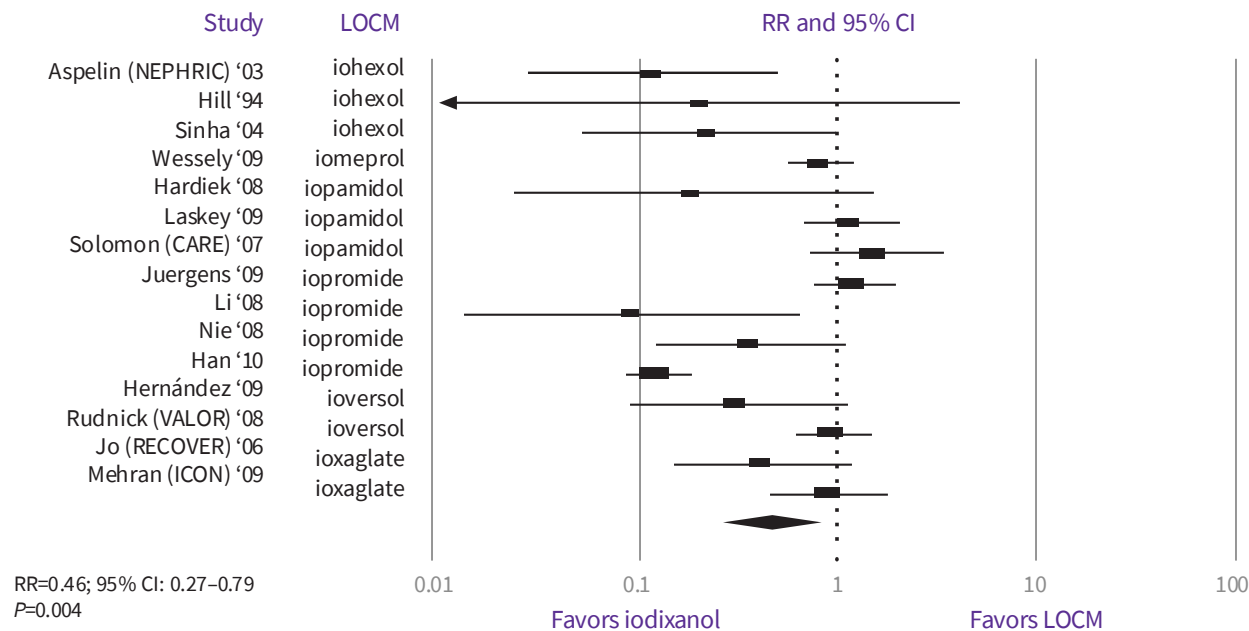
eGFR, eliminated glomerular filtration rate

Iodixanol may reduce the risk of CA-AKI[#] in patients with renal impairment vs pooled LOCM¹

Intra-arterial use of iodixanol reduced the risk of CA-AKI^{#,*} by 54% in patients with moderately impaired renal function vs pooled LOCMs¹



Reduction in risk of CA-AKI^{#,*} with iodixanol vs pooled LOCMs (n=4,769)¹



Study type

- Meta-analysis of head-to-head randomized studies published prior to 2011

At-risk population

- SCr of ≥ 1.6 mg/dL
- GFR of ≤ 50 mL/min/1.73 m²

Quality of studies

- Jadad score ≥ 2

[#]CA-AKI definition

- SCr increase of ≥ 0.5 mg/dL

Limitations

- RCT heterogeneity
- Significant difference in CA-AKI[#] risk was based on the metric studied (absolute vs relative difference in SCr from baseline)

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast²

1. McCullough PA, Brown JR. *Cardiorenal Med.* 2011;1(4):220-334.

2. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal.* 2022;73(3):499-514.

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CI, confidence interval

CA-AKI, contrast-associated acute kidney injury

GFR, glomerular filtration rate

LOCM, low-osmolar CM

RCT, randomized controlled trial

RR, relative risk

SCr, serum creatinine

Anne

is 56 and 155 lb

She has T2D

She is at high risk for CA-AKI



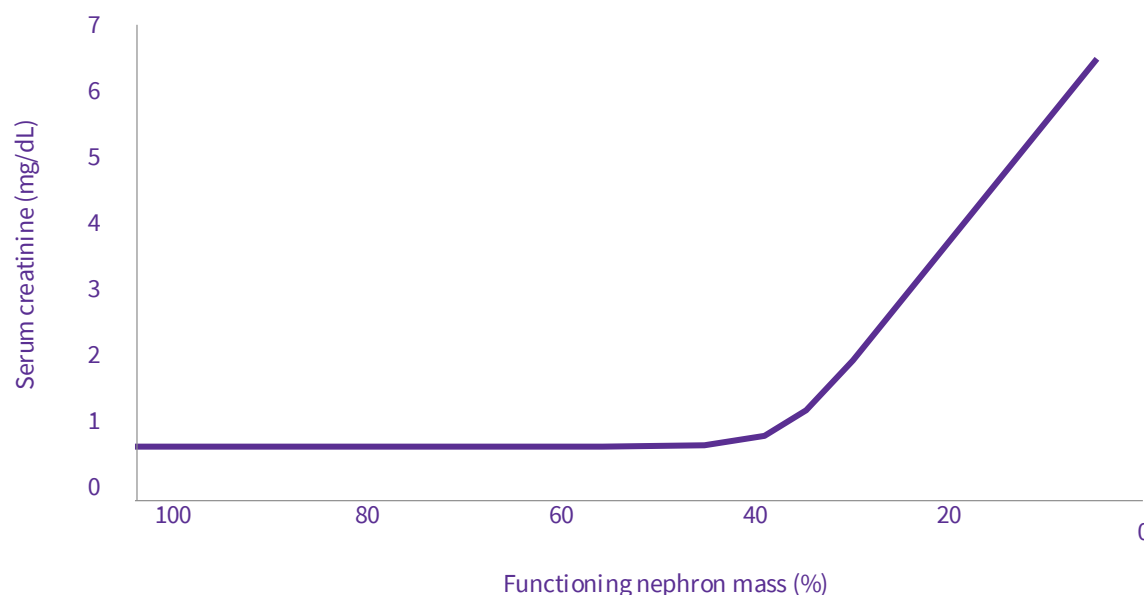
CA-AKI, contrast-associated acute kidney injury
T2D, type 2 diabetes

Please see Important Safety Information for Visipaque™ (Iodixanol) at the back

High blood sugar associated with her diabetes can cause kidney damage¹

Many patients with diabetes, however, exhibit normal SCr levels despite having some degree of renal dysfunction²

Up to 50% of nephrons may be lost before there is an increase in SCr³



Adapted from Chawla LS. 2016.



With screening tools for early renal function decline in patients with diabetes lacking, CA-AKI[#] prophylaxis may be considered regardless of renal function⁴

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast⁵

1. Alicic RZ, Rooney MT, Tuttle KR. *Clin J Am Soc Nephrol*. 2017;12(12):2032-2045.
2. Hernández F, Mora L, García-Tejada J, et al. *Rev Esp Cardiol*. 2009;62:1373-1380.
3. Chawla LS, Ronco C. *Kidney Int Rep*. 2016;1(1):57-63.
4. Calvin AD, Misra S, Pflueger A. *Nat Rev Nephrol*. 2010;6(11):679-688.
5. Macdonald DB, Hurrell C, Costa AF, et al.

Canadian Association of Radiologists
Guidance on Contrast Associated Acute
Kidney Injury. *Canadian Association of
Radiologists Journal*. 2022;73(3):499-514.

CA-AKI, contrast-associated acute kidney injury
SCr, serum creatinine

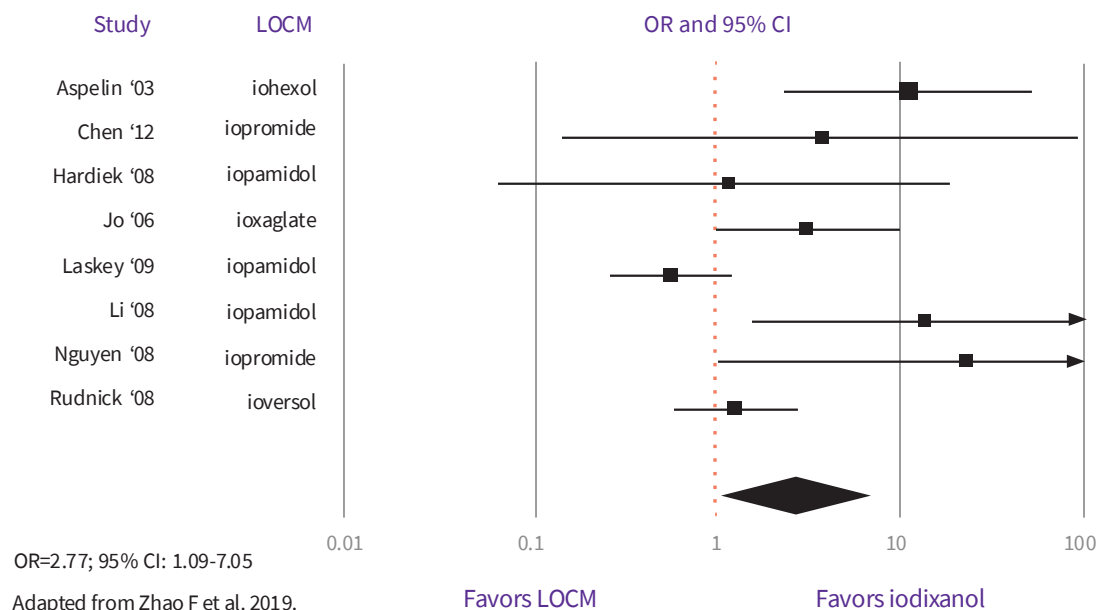
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Iodixanol may reduce the risk of CA-AKI[#] in patients with diabetes vs pooled LOCM¹

In a meta-analysis of 8 head-to-head RCTs, iodixanol was associated with a significantly lower risk of CA-AKI^{#,*} in patients with diabetes vs pooled LOCMs¹



Reduction in risk of CA-AKI^{#,*} with iodixanol vs pooled LOCMs (n=1,190)¹



Study type

- Meta-analysis of head-to-head randomized studies published prior to June 2017; 7 IA studies, 1 IV study

At-risk population

- All patients had diabetes +/- CKD (eGFR of <60 mL/min/1.73 m²)

[#]CA-AKI definition

- SCr increase of ≥0.5 mg/dL baseline up to 72h after CM exposure

Limitations

- RCT heterogeneity and risk of publication bias
- Significant difference in CA-AKI[#] risk was based on the metric studied (absolute vs relative difference in SCr from baseline)

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast²

1. Zhao F, Lei R, Yang SK, et al. *Cancer Imaging*. 2019;19(1):1-8.

2. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal*. 2022;73(3):499-514.

CI, confidence interval

CA-AKI, contrast-associated acute kidney injury

CKD, chronic kidney disease

eGFR, estimated glomerular filtration rate

IA, intra-arterial

IV, intravenous

LOCM, low-osmolar CM

OR, odds ratio

RCT, randomized controlled trial

SCr, serum creatinine

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Steve

is 61 and 235 lb

He has CKD and diabetes

He is at high risk for CA-AKI



CA-AKI, contrast-associated acute kidney injury
CKD, chronic kidney disease

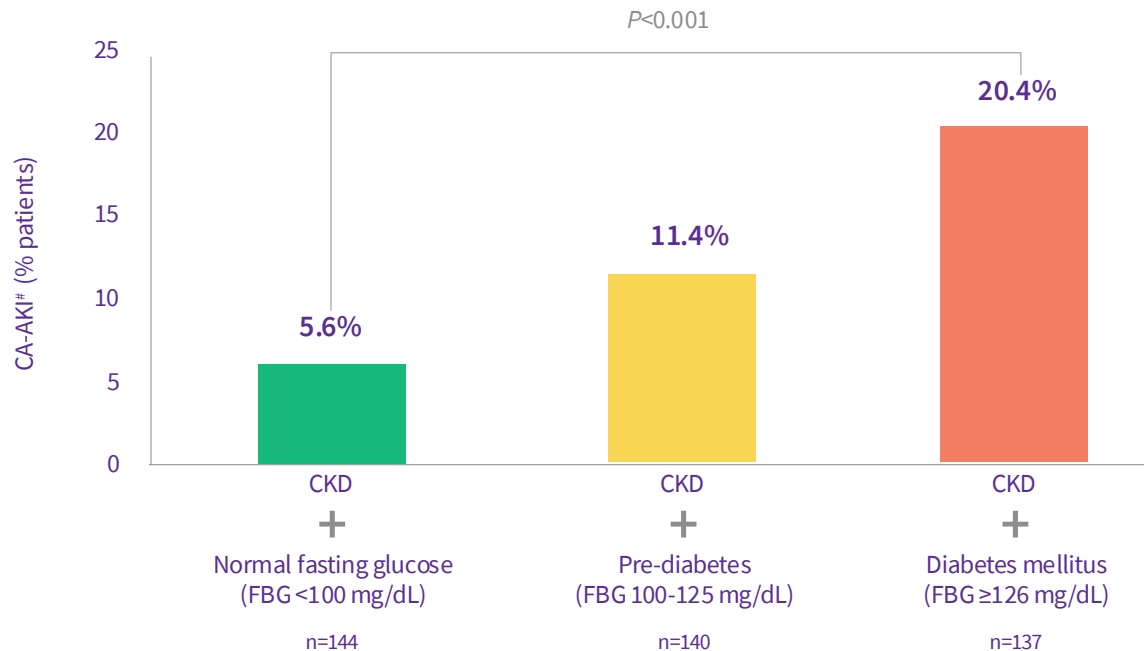
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With both CKD and diabetes, his risk of CA-AKI[#] is magnified¹

Diabetes is a risk multiplier for CA-AKI[#] in patients with concomitant CKD¹



Increasing CA-AKI^{#,*} risk with progression of diabetes in patients with CKD (n=421)¹



Single center, prospective cohort study of 421 patients with CKD (91% stage 3) referred for nonemergency diagnostic coronary angiography

Even patients with CKD in a prediabetic state may be at increased risk of CA-AKI[#] compared with those with CKD and normal fasting glucose¹

Adapted from Toprak O et al. 2007.

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast²

^{*}CA-AKI was defined as an increase of ≥25% in SCr within 48 hours

1. Toprak O, Cirit M, Yesil M, et al. *Nephrol Dial Transplant*. 2007;22(3):819-826.

2. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal*. 2022;73(3):499-514.

Please see Important Safety Information for Visipaque™ (Iodixanol) at the back

CA-AKI, contrast-associated acute kidney injury
CKD, chronic kidney disease
FBG, fasting blood glucose
SCr, serum creatine

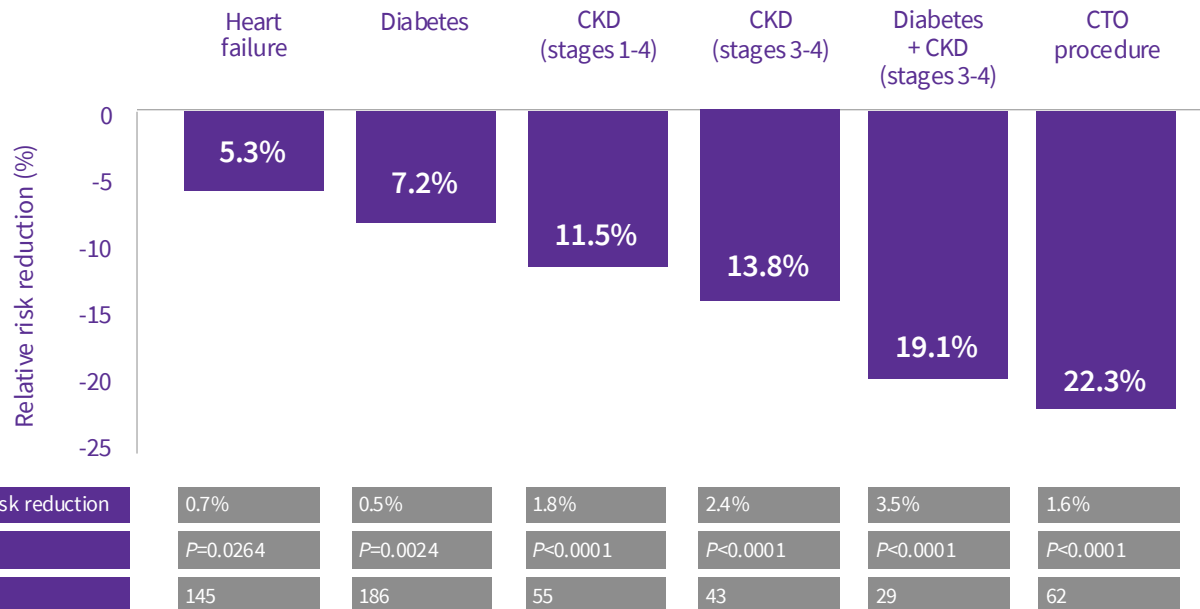
Iodixanol may reduce the risk of MARCE in high-risk patients vs pooled LOCM¹

MARCE (major adverse renal and cardiovascular events) reflects the multifaceted nature of CA-AKI[#] related adverse outcomes¹

Intra-arterial use of iodixanol significantly reduced the risk of MARCE* in patients with single and combined risk factors for AKI vs pooled LOCMs¹



Reduction in risk of MARCE* with iodixanol vs pooled LOCMs (n=536,013)¹



Study type

- Multivariable regression analysis of the US Premier Hospital database

At-risk population

- Patients had comorbid conditions that made them at risk for AKI

Pooled LOCMs

- iohexol, ioversol, iopamidol, and other

*MARCE definition

- Composite outcome of renal failure with dialysis, AKI with or without dialysis, AMI, stroke, TIA, stent occlusion/thrombosis, or death

Limitations

- Patients were not tracked longitudinally
- Study did not evaluate iodixanol vs individual LOCM

Adapted from McCullough P et al. 2021.

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast²

1. McCullough P, Ng CS, Ryan M, Baker ER, Mehta R. *Cardiorenal Med.* 2021;11(4):193-199.
2. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal.* 2022;73(3):499-514.

AKI, acute kidney injury
AMI, acute myocardial infarction
CA-AKI, contrast-associated AKI
CKD, chronic kidney disease
CTO, chronic total occlusion

LOCM, low-osmolar contrast media
MARCE, major adverse renal and cardiovascular events
NNT, number needed to treat
TIA, transient ischemic attack

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V is for vulnerable

With increasingly complex disease and increasingly compromised patients, the risk for CA-AKI[#] is also increased¹⁻³

V is for Visipaque

With evidence showing favorable post-procedural rates of MARCE when using Visipaque vs LOCMs in higher risk patients⁴

[#] 'Associated' makes the distinction that AKI cannot be directly attributed to contrast⁵

1. Potts J, Kwok CS, Ensor J, et al. *Am J Cardiol*. 2018;122(5):712-722.
2. Mehran R, Aymong ED, Nikolsky E, et al. *J Am Coll Cardiol*. 2004;44(7):1393-1399.
3. Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA. *Am J Kidney Dis*. 2015;65(6):860-886.
4. McCullough P, Ng CS, Ryan M, Baker ER, Mehta R. *Cardiorenal Med*. 2021;11(4):193-199.
5. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists Guidance on Contrast

Associated Acute Kidney Injury. *Canadian Association of Radiologists Journal*. 2022;73(3):499-514
CA-AKI, contrast-associated acute kidney injury
LOCM, low-osmolar contrast media
MARCE, major adverse renal and cardiovascular events

Please see Important Safety Information for Visipaque™ (Iodixanol) at the back

VISIPAQUE™
(IODIXANOL) INJECTION

PRODUCT INDICATIONS AND USE

- VISIPAQUE (iodixanol) 320 mg I/mL is indicated for use in angiocardiology (left ventriculography, aortic root injections and selective coronary arteriography) and can be used in the diagnosis of coronary artery disease as well as evaluation of the function of the chambers of the heart and heart valves.
- VISIPAQUE 320 mg I/mL is indicated for visualization of the aorta and its branches and for selective peripheral and visceral arteriography and in diagnosing arterial occlusive diseases, aneurysms, arteriovenous malformations and tumors. It may be used for both conventional radiography and digital subtraction angiography (DSA).
- VISIPAQUE 270 mg I/mL is also indicated for visualization of the aorta and its branches and for selective visceral arteriography and in diagnosing arterial occlusive diseases and tumors.
- VISIPAQUE 320 mg I/mL or 270 mg I/mL administered intravenously is indicated in refining diagnostic precision in areas of the brain that may not otherwise be satisfactorily visualized.
- VISIPAQUE 320 mg I/mL or 270 mg I/mL administered intravenously is indicated for enhancement of computed tomographic images for detection and evaluation of lesions in the liver, pancreas, kidney, aorta, mediastinum, pelvis, abdominal cavity, thoracic space, and retroperitoneal space.
- VISIPAQUE 320 mg I/mL or 270 mg I/mL administered intravenously is indicated in excretory urography to provide diagnostic contrast of the urinary tract and in the diagnosis of prostate enlargement, renal calculi, obstructive uropathy, urinary tract anomalies, neurogenic bladder, and urinary tract malignancies.
- VISIPAQUE 270 mg I/mL administered intravenously is indicated for venography and is useful in the diagnosis of thrombosis, phlebitis, or obstructed venous system.

Important Safety Information About Visipaque

CONTRAINDICATIONS: Visipaque (iodixanol) should not be administered to patients with known or suspected hypersensitivity to iodixanol.

MOST SERIOUS WARNINGS AND PRECAUTIONS

Concentration Used: Use the recommended Visipaque concentration for the particular procedure to be undertaken.

Fatal Reactions: Serious or fatal reactions have been associated with the administration of water soluble contrast media. It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate facilities and appropriate personnel be readily available in case a severe reaction should occur.

Other serious warnings and precautions:

- Hypersensitivity including serious, life-threatening, fatal anaphylactic/anaphylactoid reactions. Patients should be observed for at least 30 minutes after administration.
- Contrast media-induced nephrotoxicity, presenting as transient impairment of renal function, may occur after intravascular Visipaque administration.
- Patients with pre-existing renal impairment, diabetes mellitus, sepsis, hypotension, dehydration, cardiovascular disease, elderly patients, and patients with multiple myeloma, hypertension, patients on medications which alter renal function and patients with hyperuricemia, are at increased risk of this condition. Patients with both renal impairment and diabetes are at the highest risk for contrast media-induced nephrotoxicity.

- Pheochromocytoma
- Sickle cell
- Multiple myeloma
- Coagulation with serious, rarely fatal thromboembolic events
- Use with vasopressors, general anesthesia, metformin, cholecystographic agents, adrenergic beta-blockers, or inotropic agents
- Ensure patients are well hydrated prior to administration
- Patients with a history of allergy, bronchial asthma or other allergic manifestations, combined renal and hepatic disease, the elderly, debilitated or severely ill patients, those with homocystinuria, endotoxemia, elevated body temperature, severe hypertension or congestive heart failure and other cardiovascular diseases, Buerger's disease, severe ischemia, suspected thrombosis, ischemic disease, local infection, significantly obstructed vascular system, chronic obstructive pulmonary disease, ventricular failure, pulmonary hypertension, stenotic pulmonary vascular beds, hyperthyroidism and recent renal transplant recipients, as well as patients sensitive to iodine, present an additional risk and call for careful benefit/risk ratio assessment.
- Increased intracranial pressure, cerebral thrombosis or embolism, primary or metastatic cerebral lesions, subarachnoid hemorrhage, arterial spasm, transient ischemic attacks, and in any condition when the blood brain barrier is breached or the transit time of the contrast material through the cerebral vasculature is prolonged.
 - Ensure proper catheter placement
 - Aortic administration
 - Monitor vital signs and ECG through the procedure
 - Myelography and CT scan of the head
 - Breastfeeding
 - Safety and efficacy not established in children
 - Radioactive iodine uptake studies and Multistix® measurements

Prior to administration, please read the Product Monograph for Visipaque and the Important Safety Information About Iodinated Contrast Media, which is available by calling 1 800 654 0118 (option 2, then option 3) or through an email request to canadainfo@ge.com.

To report SUSPECTED ADVERSE REACTIONS, contact GE HealthCare at 1 800 654 0118 (option 2, then option 1), or email canadainfo@ge.com to request an adverse events form, or fax a request for a form to 905 847 5849. Adverse reactions can also be reported to Health Canada as follows:

- Online at MedEffect.com
- By calling 1 866 234 2345 (toll-free)
- By completing a Canada Vigilance Reporting Form and sending it by:
 - Fax to 1 866 678 6789 (toll-free)
 - Mail to Canada Vigilance Program, Health Canada, Postal Locator 0701E Ottawa, ON K1A 0K9
- Postage-paid labels and the Canada Vigilance Reporting Form are available at MedEffect.com

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