Preventing contrast-induced acute kidney injury in diabetic patients

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ILLUSTRATION: Chris Whissen PHOTOS: shutterstock.com

- The first report of contrast-induced acute kidney injury (CIAKI) dates back to over half a century ago and prompted research that has led to more than 3,000 publication

Berlyne, N. & Berlyne, G. M. Acute renal failure following intravenous pyelography with hypaque. Acta Med. Scand. 171, 39–41 (1962).

- CIAKI is generally considered to rank third among the causes of hospital-acquired AKI based on data from a US urban tertiary care hospital

- If contrast media had been included in the medication category, the medication category would have been ranked second, accounting for 13% of all causes of AKI

  - Am. J. Kidney Dis. 39, 930–936 (2002).

CIAKI is a major health-care problem

- With more than 2 million cardiac catheterizations performed and over 30 million doses of iodinated contrast medium administered annually.
- Among at-risk patients (especially those with diabetes and CKD), the reported risk following coronary angiography with or without intervention is 10 to 30 percent

Diagnosis

- A plethora of measures have been used to detect CIAKI in preclinical as well as in some clinical studies, reflecting the emergence of various novel molecular markers such as neutrophil gelatinase-associated lipocalin (NGAL) and phosphatidylserine receptor kidney injury molecule-1 (KIM-1)),

- In routine clinical practice and in the vast majority of clinical studies, CIAKI is diagnosed by increased serum creatinine concentration within <72 h of administration of contrast media
- 20% of AKI diagnosed by other biomarkers is undetected by serum creatinine measurements (so-called subclinical AKI)

- The delayed rise in serum creatinine also means that CIAKI will often go undetected in outpatients.
- Moreover, different thresholds of serum creatinine levels are used seems appropriate to enable optimum patient care, even though low detection thresholds pose a problem for statistical assessment of CIAKI.

Biomarkers

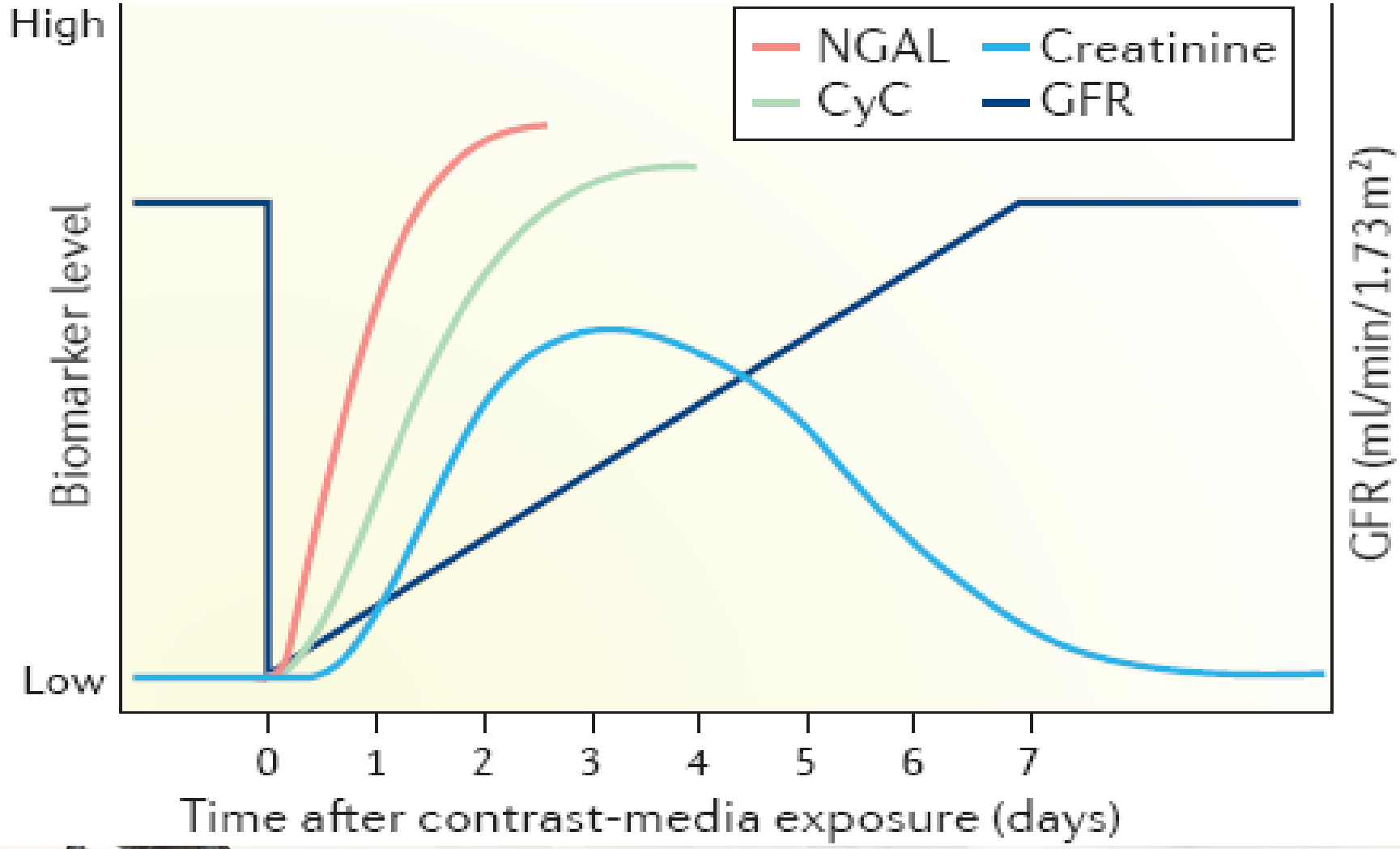
- Markers such as NGAL, cystatin C and KIM-1 expedite detection and treatment of CIAKI, as their concentrations increase during the first hours after the insult.
- Cystatin C remains in the extracellular space, which comprises only a third of total body water. As well as being a reliable marker for early detection of CIAKI, 24 h cystatin C levels predict CIAKI severity.

- However, none of the new biochemical markers currently provide reliable point-of-care diagnosis for AKI.
- One reason for this failure might be that these molecules are indicative of injury rather than of early signalling events in the pathophysiological chain that ultimately leads to AKI.

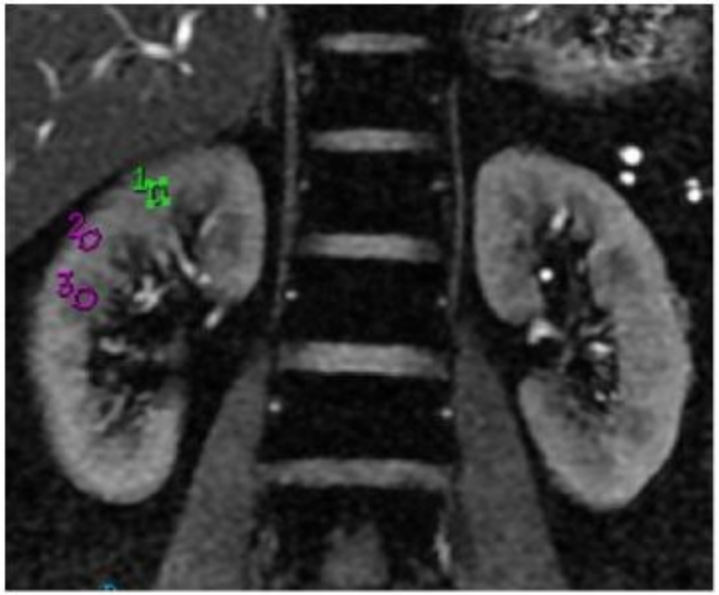
- These markers reflect the activation of diverse damaging pathways:
- Cystatin C and creatinine levels rise in response to decreased GFR, whereas an increase in KIM-1 levels indicates proximal tubular damage as the proximal epithelium detects and subsequently phagocytoses dead cells through KIM-1

- NGAL is indicative of distal nephron damage, as it is massively upregulated in the thick ascending limb of the loop of Henle, distal tubule and collecting duct.

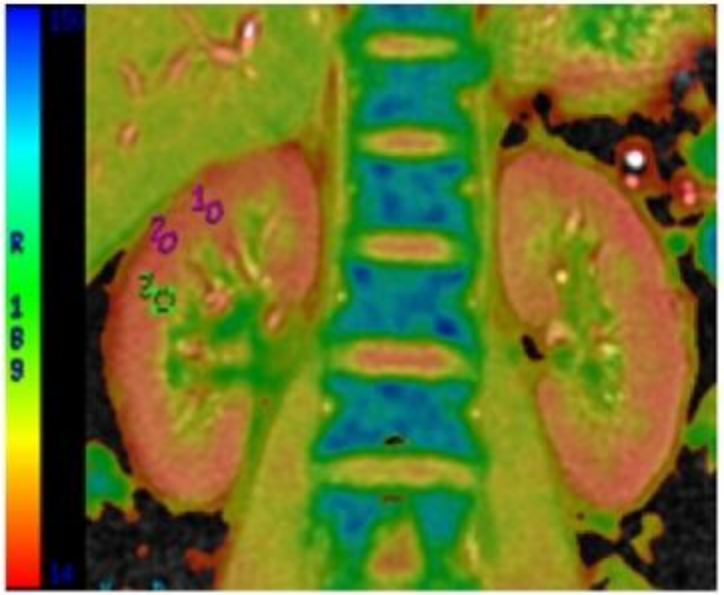
- The future gold standard in CIAKI diagnostics might not be found in one single biochemical marker but in a synergistic approach that includes biomarkers and functional imaging techniques.


High
Low
Biomarker level
NGAL
Creatinine
CyC
GFR
GFR (ml/min/1.73m²)
0
1
2
3
4
5
6
7
Time after contrast-media exposure (days)

- Novel imaging techniques such as blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) are, therefore, increasingly used to assess impaired kidney oxygenation following administration of contrast media.



(a)



(b)

Box 1 | **Definition of contrast-induced acute kidney injury***

- An increase in serum creatinine by more than 25% or 44 μmol/l (0.5 mg/dl)
- Within 3 days of the intravascular administration of contrast medium
- No alternative aetiology

*According to the European Society of Urogenital Radiology

Epidemiology

The incidence of CIAKI is reportedly high worldwide.

In sub-Saharan Africa, between 4.6% and 16.4% of patients undergoing computed tomography (CT) scans or angiography developed CIAKI, depending

on the definition used.

Similar incidences of CIAKI induced by intravenous administration of contrast media have been reported among patients in India (10%), and among pediatric patients undergoing CT scans in Germany (10.3%)

- Nonetheless, many studies published in the past 5 years showed that the incidence of CIAKI is lower than previously reported, as several other causes of AKI were not fully accounted for.
- Notably, a registry study that included 57,925 patients receiving contrast medium reported clinically relevant renal failure in only 0.8%−1.7% of patients

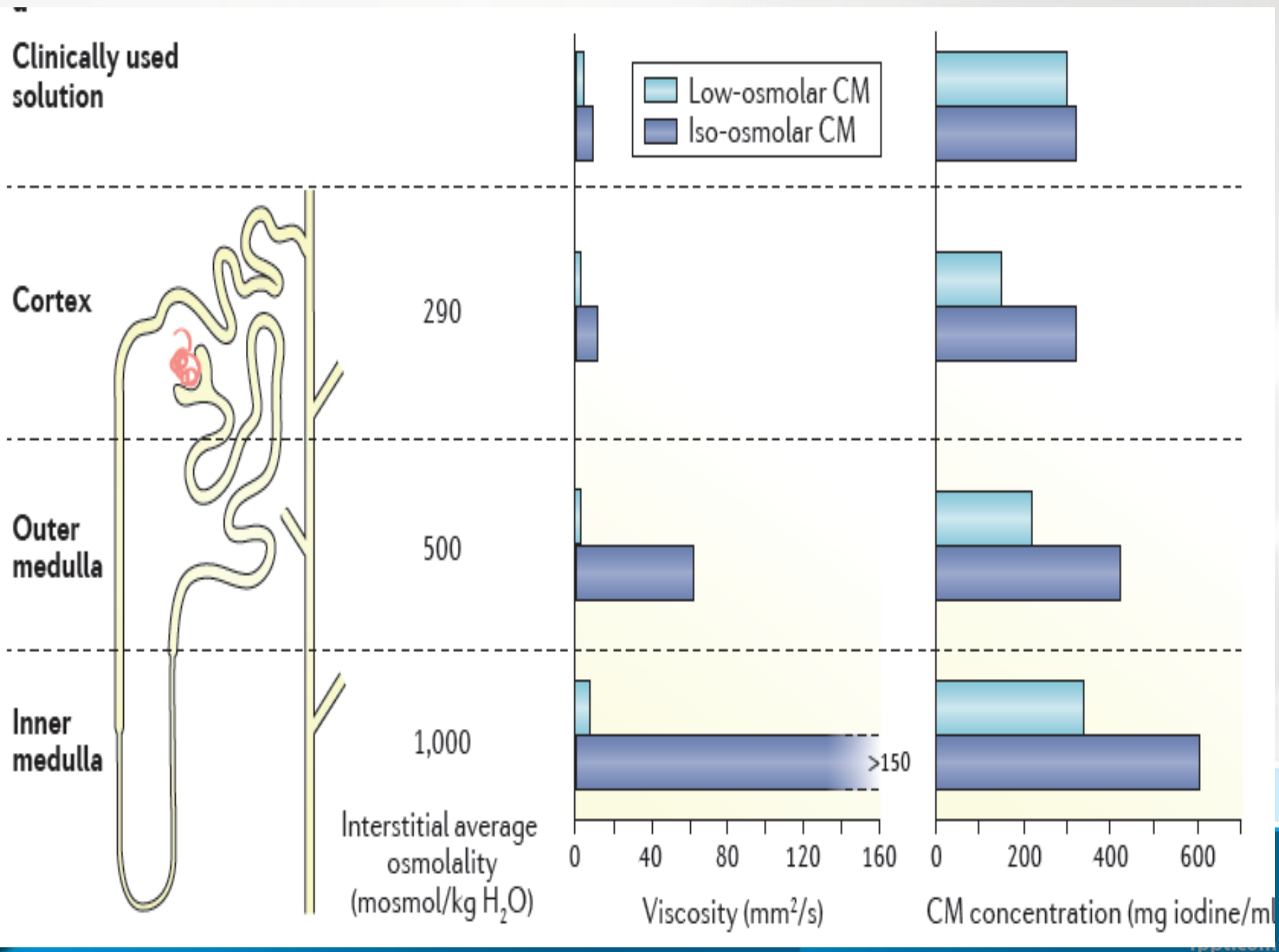
Intra-arterial vs intravenous

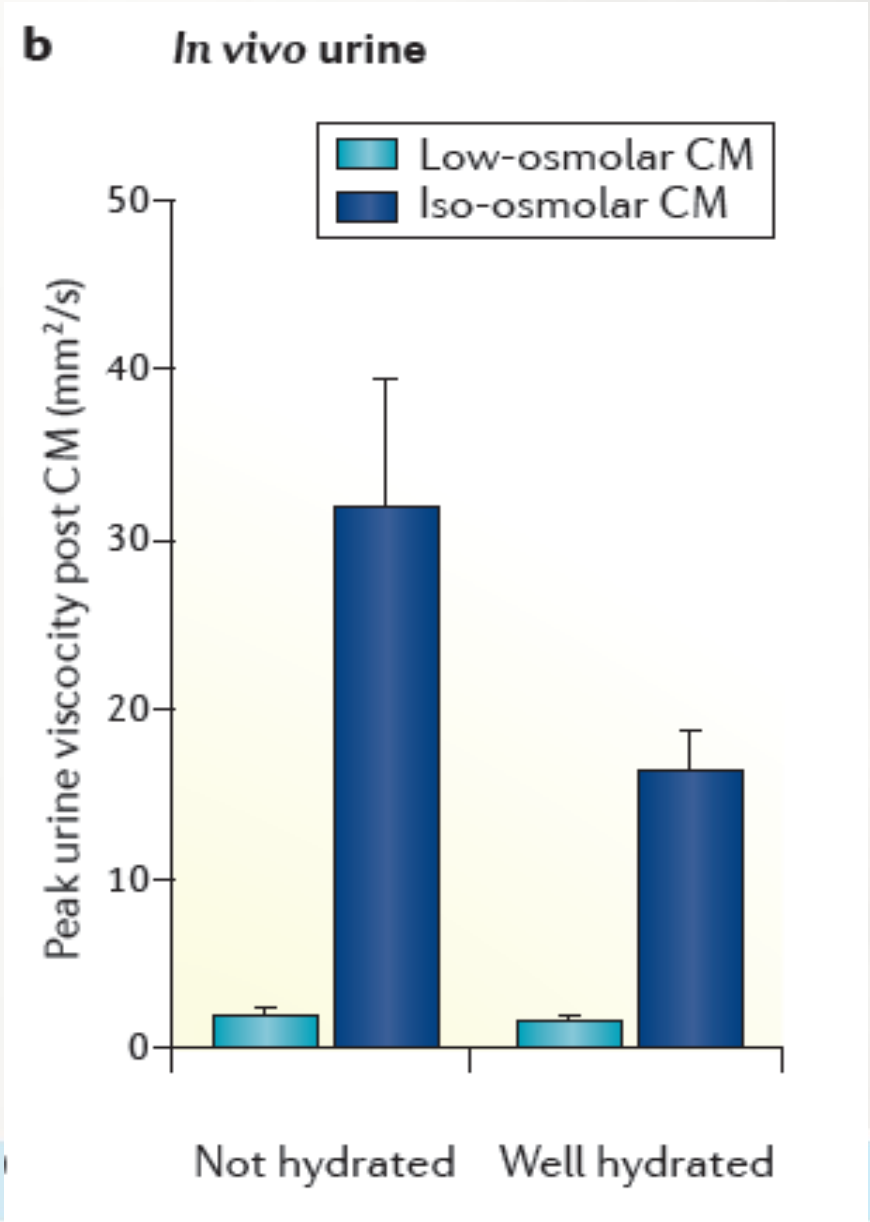
A 2016 study suggested that contrary to previous belief that use of intra-arterial and intravenous administration of contrast medium could reduce the risk of CIAKI, both delivery modes might be associated with similar incidences of CIAKI.

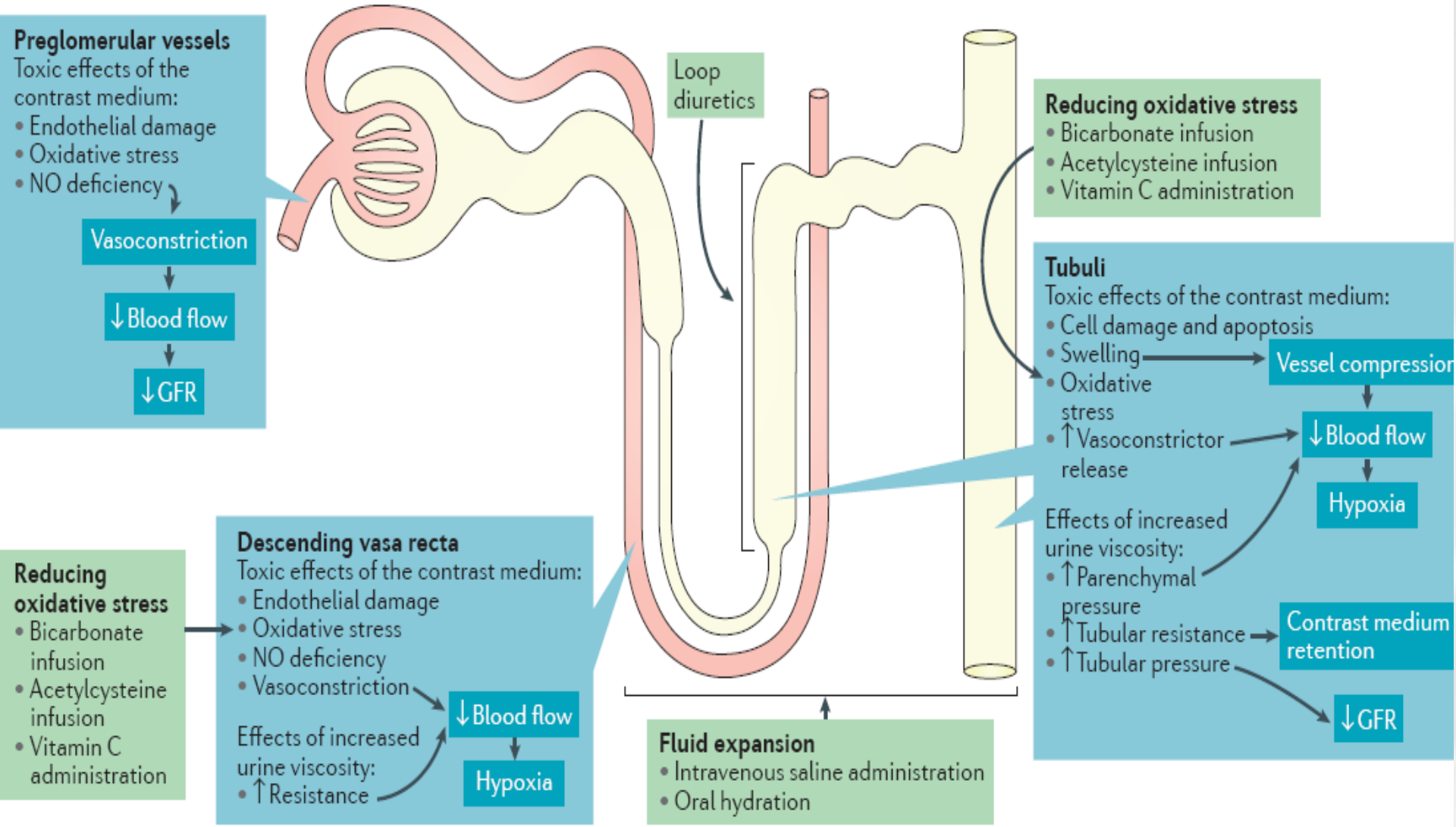
Invest. Radiol. 51, 804–809 (2016).

Box 2 | **Common risk factors for contrast-induced acute kidney injury**

- Associated with the patient
  - Concomitant acute kidney injury of other origins
  - Reduced glomerular filtration rate (<45 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2 for intravenous or intra-arterial administration, respectively)
  - Previous acute kidney injury or chronic kidney disease
  - Diabetic nephropathy
  - Dehydration
  - Anaemia
  - Poor haemodynamic status
  - Age >70 years
  - Concurrent nephrotoxic drug treatment
- Associated with the procedure
  - Large doses of contrast medium
  - Multiple administrations of contrast medium
  - Use of contrast medium with excessive osmolality or viscosity
  - Intra-arterial administration (debated)


Clinically used solution
Low-osmolar CM
Iso-osmolar CM
Cortex
290
Outer medulla
500
Inner medulla
1,000
>150
Interstitial average osmolality (mosmol/kg H_2O)
0
40
80
120
160
Viscosity (mm^2/s)
0
200
400
600
CM concentration (mg iodine/ml


b
In vivo urine
Low-osmolar CM
Iso-osmolar CM
Peak urine viscocity post CM (mm²/s)
50
40
30
20
10
0
Not hydrated
Well hydrated


Preglomerular vessels
Toxic effects of the contrast medium:
• Endothelial damage
• Oxidative stress
• NO deficiency
Vasoconstriction
↓Blood flow
↓GFR
Loop diuretics
Reducing oxidative stress
• Bicarbonate infusion
• Acetylcysteine infusion
• Vitamin C administration
Tubuli
Toxic effects of the contrast medium:
• Cell damage and apoptosis
• Swelling
• Oxidative stress
• ↑Vasoconstrictor release
Vessel compression
↓Blood flow
Hypoxia
Effects of increased urine viscosity:
• ↑Parenchymal pressure
• ↑Tubular resistance
• ↑Tubular pressure
Contrast medium retention
↓GFR
Reducing oxidative stress
• Bicarbonate infusion
• Acetylcysteine infusion
• Vitamin C administration
Descending vasa recta
Toxic effects of the contrast medium:
• Endothelial damage
• Oxidative stress
• NO deficiency
• Vasoconstriction
↓Blood flow
Hypoxia
Effects of increased urine viscosity:
• ↑Resistance
Fluid expansion
• Intravenous saline administration
• Oral hydration

Box 3 | **Renal damage induced by contrast agents**

- Cellular effects
  - Direct cell membrane damage
  - Perturbation of mitochondrial function
  - Generation of reactive oxygen species
  - Apoptosis
- Hypoxia and vasoconstriction
  - Constriction of afferent arterioles and/or vasa recta
  - Enhanced renal vascular responsiveness to angiotensin II and endothelin-1
  - Endothelial damage with subsequent vasoconstriction
  - Increased vascular resistance by congestion
  - Acute hypotension (anaphylaxia)
- Tubular effects
  - Perturbed tubuloglomerular feedback
  - Cytotoxic effects
  - Tubulovascular crosstalk with subsequent vasoconstriction
  - Tubular obstruction by increased fluid viscosity

- In a randomized trial that included 341 patients with serum creatinine ≤1.5 mg/dL (133 mmol/L), there was no difference in the incidence of contrast nephropathy between diabetic and nondiabetic patients

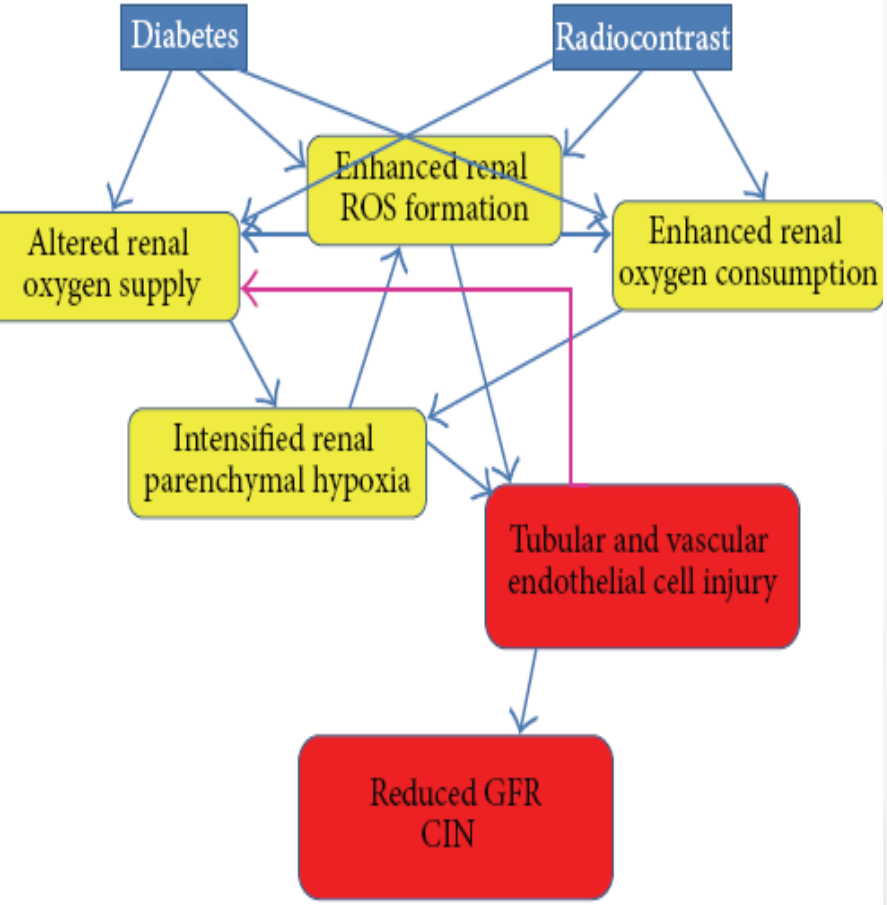
In a review of 1826 consecutive patients, dialysis-requiring AKI developed following interventional coronary angiography in 19.5 percent of diabetic patients versus 12.8 percent of nondiabetic CKD patients; however, no patient who had a baseline creatinine clearance >47 mL/min developed dialysis-requiring AKI.

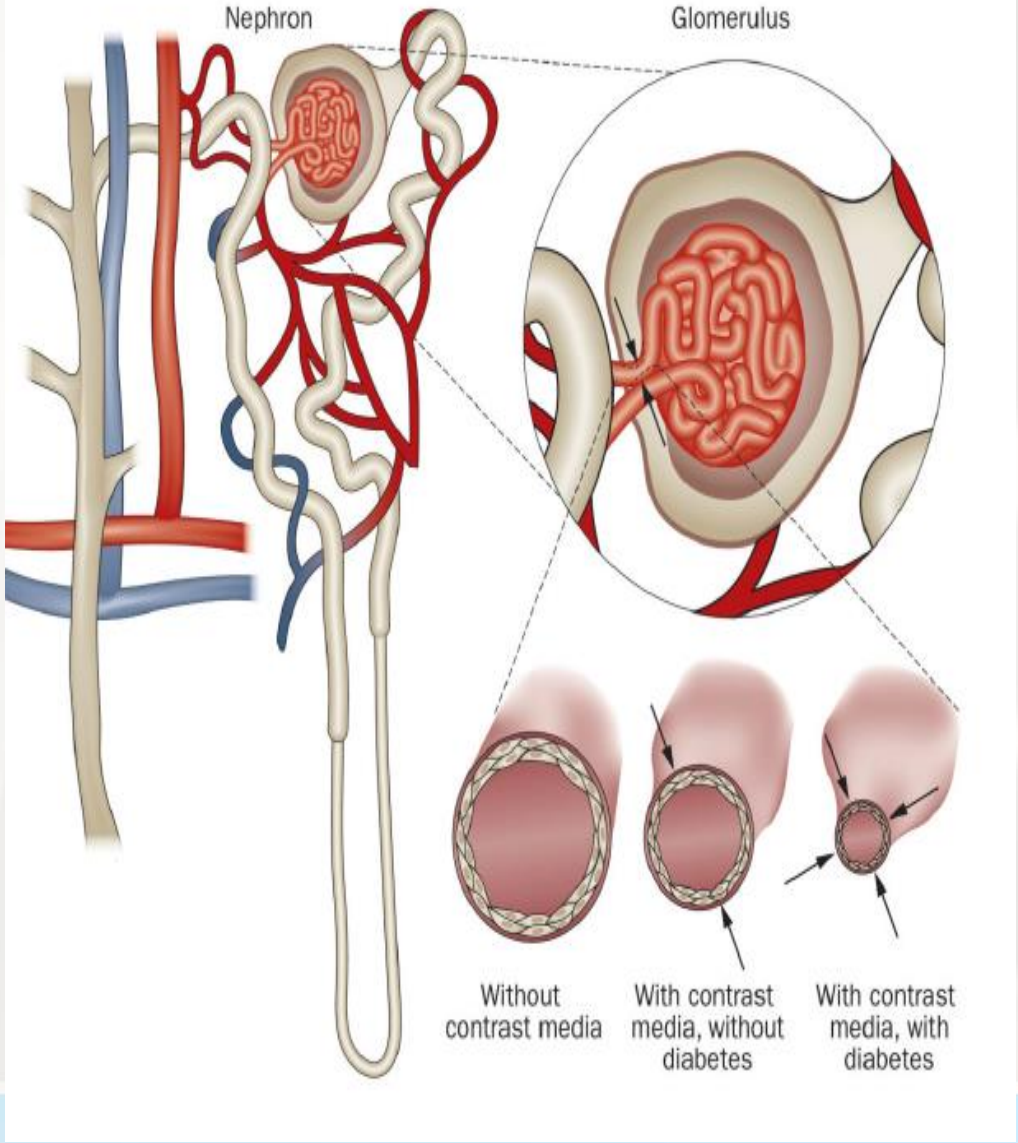
Why Is Diabetes Mellitus a Risk Factor for Contrast-Induced Nephropathy?

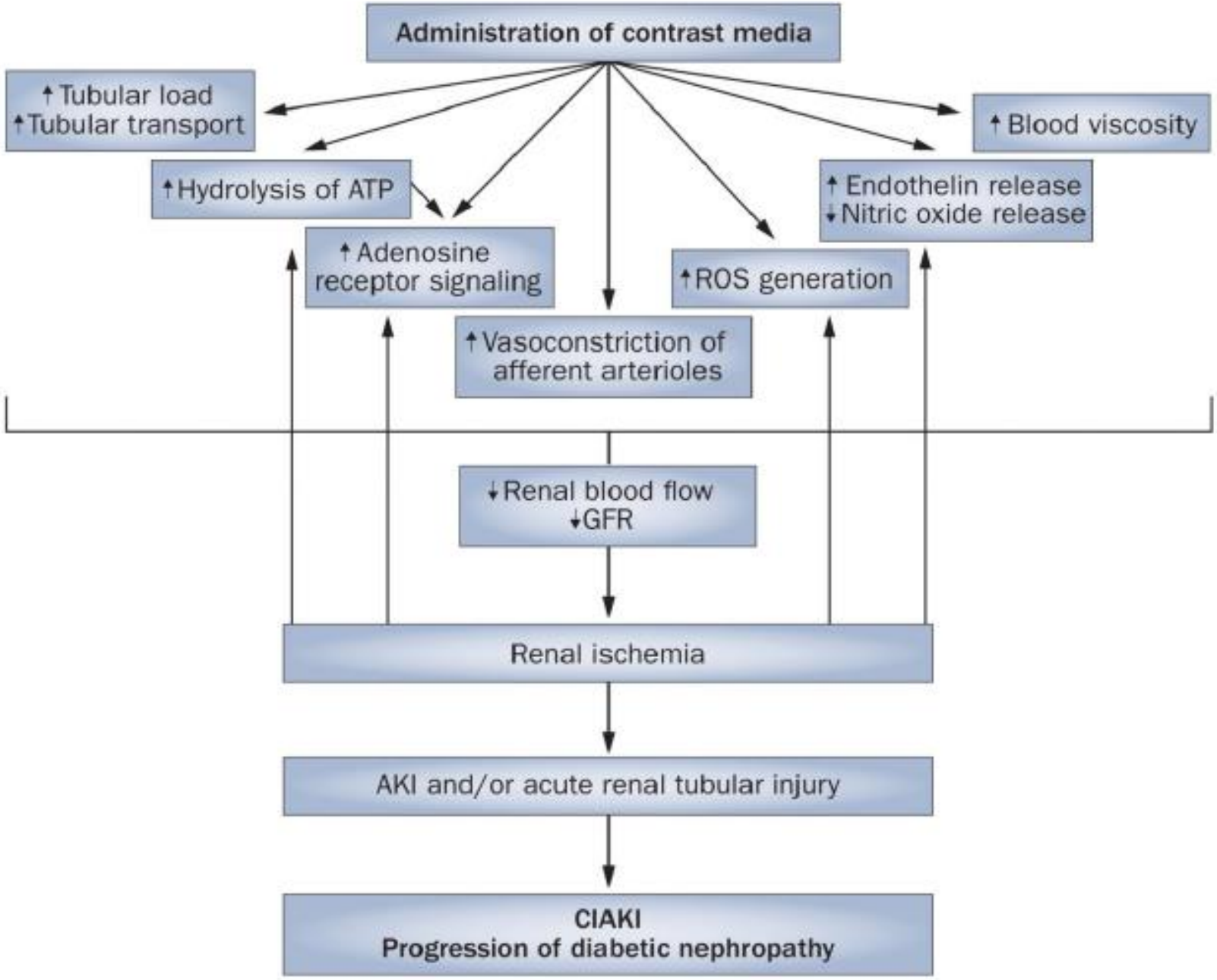
Pathogenesis of diabetic nephropathy

- Patients with diabetes have an up to 40% lifetime risk of developing diabetic nephropathy
- Diabetic nephropathy is characterized by renal vascular dysfunction, which manifests as an increased sensitivity to renal vasoconstrictors and renal ischemia, and a decrease in nitric oxide-dependent vasodilation.

- oxygen delivery is impaired in patients with early stages of diabetic nephropathy. This effect might be at least partly accounted for by vascular and/or endothelial dysfunction
- other factors might also contribute to this impairment in renal blood oxygenation, including defective nitric oxide production, high concentrations of advanced glycosylation end products, increased generation of cytokines, and increased generation of ROS.


Diabetes
Radiocontrast
Enhanced renal ROS formation
Altered renal oxygen supply
Enhanced renal oxygen consumption
Intensified renal parenchymal hypoxia
Tubular and vascular endothelial cell injury
Reduced GFR CIN


Nephron
Glomerulus
Without contrast media
With contrast media, without diabetes
With contrast media, with diabetes


Administration of contrast media
↑Tubular load
↑Tubular transport
↑Blood viscosity
↑Hydrolysis of ATP
↑Endothelin release
↓Nitric oxide release
↑Adenosine receptor signaling
↑ROS generation
↑Vasoconstriction of afferent arterioles
↓Renal blood flow
↓GFR
Renal ischemia
AKI and/or acute renal tubular injury
CIAKI
Progression of diabetic nephropathy

Preventative strategies

Box 2 | **Common risk factors for contrast-induced acute kidney injury**

- Associated with the patient
  - Concomitant acute kidney injury of other origins
  - Reduced glomerular filtration rate (<45 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2 for intravenous or intra-arterial administration, respectively)
  - Previous acute kidney injury or chronic kidney disease
  - Diabetic nephropathy
  - Dehydration
  - Anaemia
  - Poor haemodynamic status
  - Age >70 years
  - Concurrent nephrotoxic drug treatment
- Associated with the procedure
  - Large doses of contrast medium
  - Multiple administrations of contrast medium
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  - Intra-arterial administration (debated)

Major risk factors

- Chronic kidney disease
- Diabetic nephropathy with reduced estimated GFR
- Dose and type of contrast agent
- Speciecific radiologic procedure
- Other:
  - Hyperglycemia
  - ACE inhibitors and/or ARBs??

Hyperglycemia

- Hyperglycemia may increase the risk for contrast nephropathy independent of a pre-existing diagnosis of diabetes mellitus.
- In a study of 6358 patients, the adjusted risk of AKI following angiography incrementally increased with higher glucosel evels among patients without diabetes mellitus

J Am Coll Cardiol 2010; 55:1433.

ACE inhibitors and/or ARBs

In a randomized trial of 220 patients with eGFR of 15 to 60 mL/min/1.73 m2, there was no deference in the incidence of contrast nephropathy between patients who were on ACE inhibitors and/or ARBs prior to angiography and patients who had a similarly reduced eGFR but were not on ACE inhibitors and/or ARBs

Int Urol Nephrol 2008; 40:749

Identifying patients at risk

- All patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 who have significant proteinuria

  (defined as albuminuria >300 mg/day, which corresponds to proteinuria > 500 mg/day).

- All patients with eGFR <60 mL/min/1.73 m2 and comorbidities including diabetes, heart failure, liver failure, or multiple myeloma.

Identifying patients at risk

- All patients with eGFR <45 mL/min/1.73/m2 even in the absence of proteinuria or any other comorbidities.
- Patients who have eGFR <45 mL/min/1.73 m2 and have proteinuria and diabetes or other comorbidities and all patients with eGFR <30 mL/min/1.73 m2 should be considered at highest risk.

Preventive measures

- Avoid volume depletion and NSAIDs

➢ Patients who are to receive intra-arterial contrast should avoid volume depletion and withhold nonsteroidal anti-inflammatory agents (NSAIDs) for 24 to 48 hours prior to the procedure

➢ Both volume depletion and NSAIDs can increase renal vasoconstriction, which increases the risk of contrast nephropathy.

Preventive measures

- Dose and type of contrast agent

➢ Use the lowest effective dose possible of contrast and avoid performing repeated studies that are closely spaced (within 48 to 72 hours)

➢ use the iso-osmolal agent, iodixanol, or nonionic low-osmolal agents, such as iopamidol or ioversol, rather than iohexol.

American College of Cardiology/American Heart Association (ACC/AHA) guidelines

- Do not use high-osmolal agents (1400 to 1800 mosmol/kg). Nonionic, iso- or low-osmolal agents are safer than ionic high-osmolal agents.
- use of either an iso-osmolal contrast agent or

a low-molecular-weight contrast agent other than iohexol or the ionic low-osmolal agent, ioxaglat

- Lower doses (<125 mL) of contrast tend to be safer, though are not free of risk .
- Very small amounts of contrast (<10 mL) have been safely used in patients with advanced kidney disease for examination of arteriovenous fistulas
- However, diabetic patients with a serum creatinine concentration >5 mg/dL (440 micromol/L) may be at risk from as little as 20 to 30 mL of contrast

Fluid administration

- Outpatients – give 3 mL/kg over one hour preprocedure and 1 to 1.5 mL/kg/hour during and for four to six hours postprocedure, with administration of at least 6 mL/kg post procedure.
- Inpatients – give 1 mL/kg/hour for 6 to 12 hours preprocedure, intraprocedure, and for 6 to 12 hours
- postprocedure.

- Intravenous volume administration prior to intravascular contrast administration for patients at risk for contrast induced nephropathy is the standard of care despite an **absence of adequately designed randomized trials demonstrating benefit**

- non-placebo-controlled randomized trial (POSEIDON)
- single-center, randomized trial (AMACING) found no benefit of intravenous saline compared with no saline in preventing AKI among 603 patients with eGFR between 30 and 59 mL/min/1.73 m2

Isotonic saline

- Isotonic saline appears to be better than more hypotonic fluids (ie, one-half isotonic saline) .

In a randomized trial of 1620 patients, compared with half-isotonic saline, isotonic saline reduced the risk of contrast nephropathy (2 versus0.7 percent)

- The benefit of isotonic saline was greater in diabetic patients (5.5 percent versus 0) and those given

  >250 mL of contrast (3 versus 0 percent)

Arch Intern Med 2002; 162:329.

Saline versus bicarbonate

- Both are effective, but bicarbonate provides no additional benefit to saline, needs to be compounded, and is more expensive.

The most defnitive data are from a subsequently published randomized trial that included

4993 high-risk patients undergoing scheduled angiography that found that both treatments were associated with similar outcomes

N Engl J Med 2018; 378:603

Acetylcysteine

In general, modest benefits were noted in meta-analyses that did not account for a large degree of heterogeneity between studies .

However, the largest randomized trial, which was published after the meta-analyses, did not find improved outcomes with oral acetylcysteine in 4993 high-risk patients undergoing scheduled angiography.

N Engl J Med 2018; 378:603.

Remote ischemic preconditioning

- RIPC is a method by which the deliberate induction of transient nonlethal ischemia of an organ protects against
- subsequent ischemic injury of another organ. Some, but not all, studies have suggested that RIPC prior to cardiac surgery protects against acute kidney injury (AKI).

Prophylactic hemodialysis

- A 2012 meta-analysis that included eight studies of hemodialysis and three studies of

hemofilltration/hemodiafiltration showed no benefit of renal replacement therapy (RRT).

- no studies that support immediate dialysis after intravascular contrast media administration in

order to preserve residual renal function or limit the risk of allergic reaction in hemodialysis patients

A systematic review. Am J Med 2012; 125:66.

Withholding ACE inhibitors and/or ARBs

There was no significant deference in the incidence of contrast nephropathy

between patients who had the ACE inhibitor and/or ARB withdrawn and those who did not.

Int Urol Nephrol 2008; 40:749.

Statins

- Most of the statin studies were performed in relatively low-risk patients
- A meta-analysis of eight studies (n = 5024) did not show a conclusive benefit of statins plus intravenous saline compared with saline alone.

- Ann Intern Med 2016; 164:406.

In addition, some studies suggest that acute administration of **rosuvastatin** is associated with an increase in normal eGFR, which confounds interpretation of AKI studies

Am J Cardiol 2005; 96:1290.

Diuretics or mannitol

- These agents do not appear to be benefcial for the prevention of contrast-induced acute kidney injury (AKI) .
- However, diuretics may be required to treat volume overload.

- N Engl J Med 1994; 331:1416.
- Kidney Int 1994; 45:259.

Other

- oral sodium citrate,
- atrial natriuretic peptide,
- ascorbic acid,
- trimetazidine,

inhibitors of vasoconstriction, (theophylline oraminophylline, nifedipine, captopril, prostaglandin E or I2, low-dose dopamine, and fenoldopam)

- diuretics.

PROGNOSIS

- In most cases, contrast-induced acute kidney injury (AKI) is reversible; the estimated glomerular filtration rate (eGFR) recovers in 5 to 10 days.
- However, in patients who have severely reduced eGFR at baseline, the creatinine may not return to baseline values.
-

PROGNOSIS

- Even if the creatinine returns to baseline, the development of contrast nephropathy has been associated with short- and long-term adverse outcomes

There are no randomized trials that have proven that specific interventions to prevent AKI decrease mortality or major cardiovascular events.


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