Contrastmittelnephropatie – Can we forget it?

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Objectives

- History
- Increasing risk with decreasing function
- Difference between non-ionic agents and nephrotoxic potential
- Recent developments
- S-Creatinine

The kidney is the main route for elimination of CM

- In patients with normal GFR (> 60 ml/min):
  - > 95% is out within 24 hours
- In patients with abnormal GFR (< 10 ml/ml)
  - It may take weeks

- The concentration increases along the tubules, and in the collecting tubules the concentration is higher than it was in the vial. The lower osmolality, the higher concentration and chemotoxic potential.

Combined data from a comparative study of a monomer and a dimer

eGFR (MDRD)	Relative risk of CIN
> 40 ml/min	0.6%
< 40 ml/min	4.6%
15 – 30 ml/min	7.8%

Thomsen & Morcos. Eur Radiol 2009; 19: 891-897

Incidence of CIN after CT (520 patients with eGFR < 60)

eGFR (ml/min/1.73 m^2)	CIN (%)
45 – 59	0
30 – 44	2.9
< 30	12.1

Kim SM et al. Am J Kidney Dis 2010; 55:1018-25

Unsolved issue

- Patients with GFR below 20 ml/min 1.73m^2:

- What is the risk?

Hot topic 2003-2009

- Difference between the non-ionic dimer and the monomers regarding nephrotoxic potential?

IOCM vs LOCM angiography, diabetic patients with moderate renal impairment (Nephric I)

Comparing Iodixanol vs Iohexol in coronary angiography

- Incidence of CIN (>44 µmol/L)
  - Iohexol 26%
  - Iodixanol 3%

Significant difference in the risk of CIN between iohexol and iodixanol in 129 patients

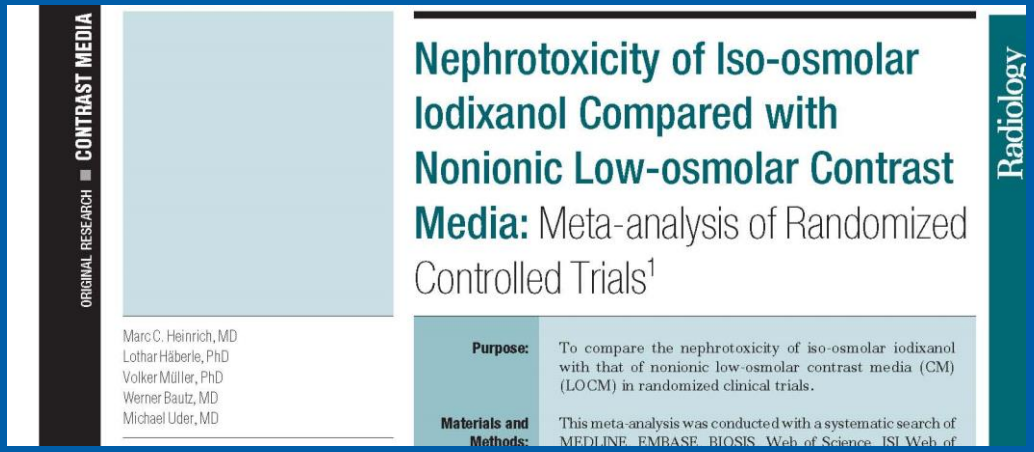
Aspelin et al. (Nephric 1), New Engl J Med 2003; 348: 91-98

CIN comparative studies of IV-Injection in high-risk patients (20-60 ml/min)

Study	LOCM (monomers)	Iodixanol	Criteria
Carraro et al.(1998)	0/32 (iopromide)	1/32	50% ↑ SCr
Nguyen et al. (2008)	10/65 (iopromide)	3/61	44 μmol/L ↑ SCr
Kolehmainen et al. (2003)	4/25 (iobiditrol)	4/25	44 μmol/L ↑ SCr
Barrett et al. (2006)	0/77 (iopamidol)	2/76	44 μmol/L ↑ SCr
Thomsen et al. (2008)	0/76 (iomeron)	5/72	44 μmol/L ↑ SCr
Kuhn et al. (2008)	7/125 (iopamidol)	6/123	25% ↑ SCr
F-R Chuang (2009) (intravenous urography)	1/25 (iohexol)	1/25	25% ↑ SCr
TOTAL	**22/425 (5.18%)**	**22/418 (5.26%)**	**NO DIFFERENCE**

Meta-analysis – 1950 to Aug 2007

- Based on 25 trials
- Iodixanol is not associated with a significantly reduced risk of CIN compared to the LOCM pooled together.
- However, in patients with intraarterial administration and renal insufficiency, iodixanol is associated with a reduced risk of CIN compared to iohexol, whereas no significant difference between iodixanol and other LOCM could be found.



ORIGINAL RESEARCH ■ CONTRAST MEDIA

Nephrotoxicity of Iso-osmolar Iodixanol Compared with Nonionic Low-osmolar Contrast Media: Meta-analysis of Randomized Controlled Trials[1]

Radiology

Marc C. Heinrich, MD
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Werner Bautz, MD
Michael Uder, MD

Purpose: To compare the nephrotoxicity of iso-osmolar iodixanol with that of nonionic low-osmolar contrast media (CM) (LOCM) in randomized clinical trials.

Materials and Methods: This meta-analysis was conducted with a systematic search of MEDLINE, EMBASE, BIOSIS, Web of Science, ISI Web of

IOCM vs LOCM angiography, diabetic patients with renal impairment (Nephric II)

Comparing Iodixanol vs Iopamidol in coronary angiography

- Incidence of CIN
  - Iopamidol 9.8%
  - Iodixanol 11.2%

No significant difference in the risk of CIN between iopamidol and iodixanol in 418 patients

Laskey et al. (Nephric 2), Am Heart J 2009; 158:822-823

Conclusion since 2009

- Difference between non-ionic dimer and monomers regarding nephrotoxic potential?

NO

Applicable for both IV- and IA-injection

Recent developments

- A control group
- What happens in patients who are scanned without contrast medium (unenhanced)?

From a biochemical database

- Database of all patients seen at a large hospital:
- Similar incidence of AKI not significantly different from the incidences reported for CIN after administration of CM.
- Thus, one can find similar changes in P-Creatinine levels (or eGFR) in patients who had CM and who had no CM.

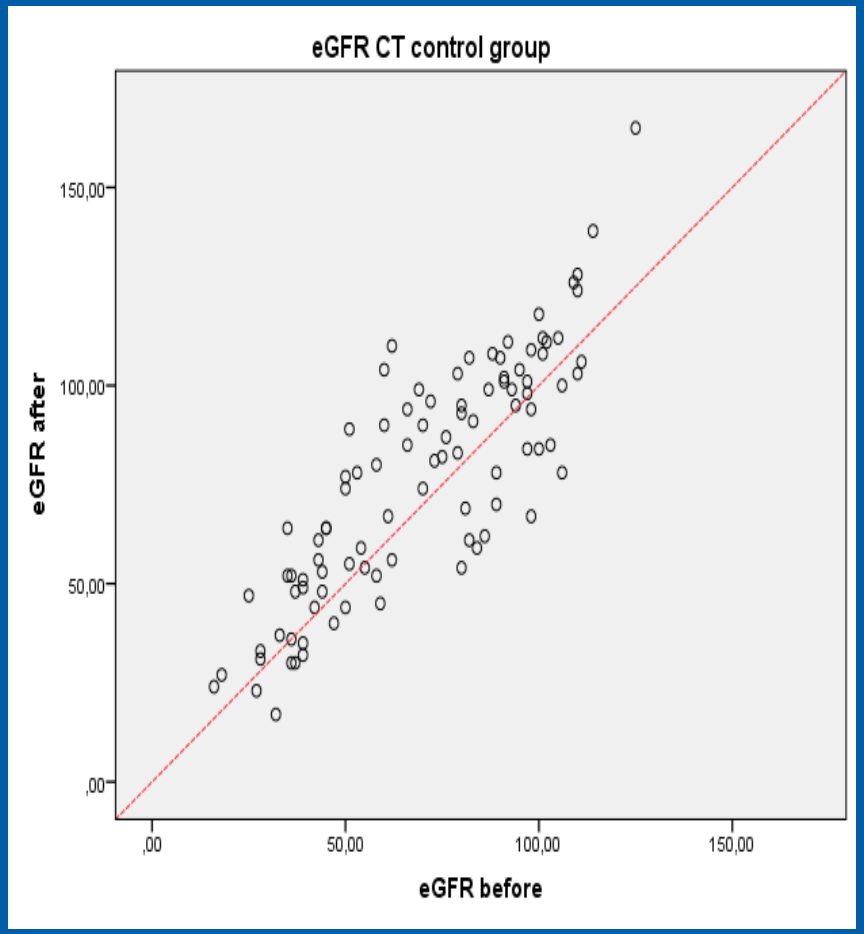
Newhouse et al. AJR 2008;191:376-382

Prospective study

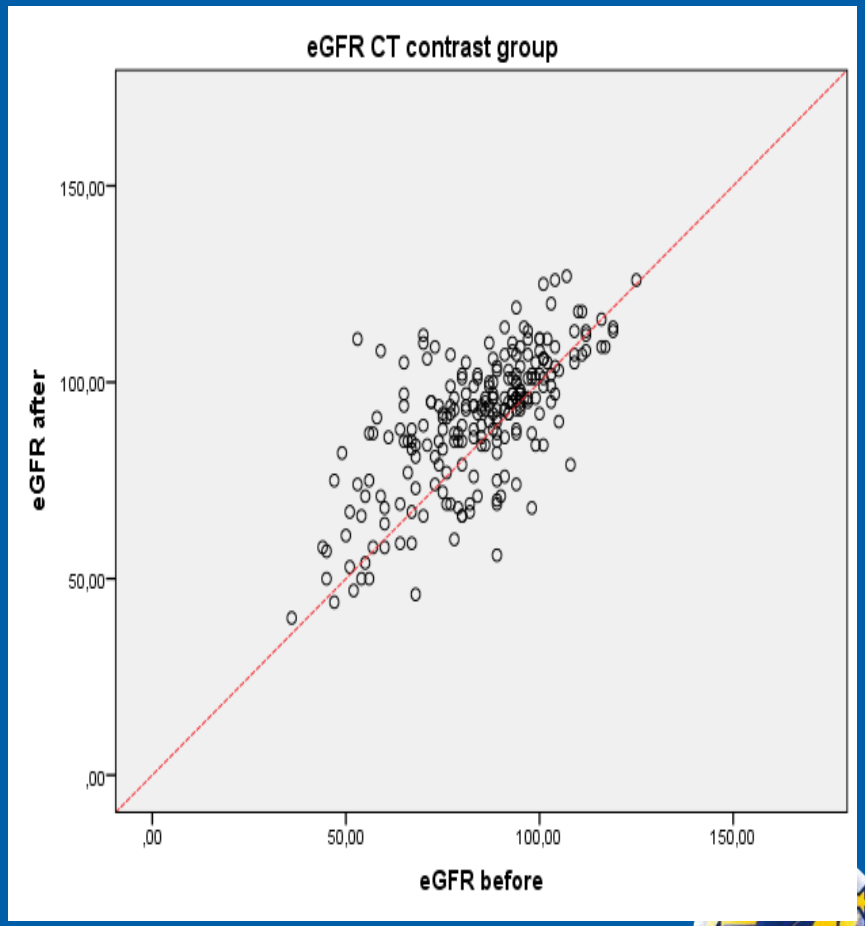
- 716 patients undergoing MRI and CT with and without CM.
- eGFR determined right before scanning and 72 hours after.

Azzouz et al. Eur J Radiol 2014

eGFR before (X-axis) and after (Y-axis) CT-scanning



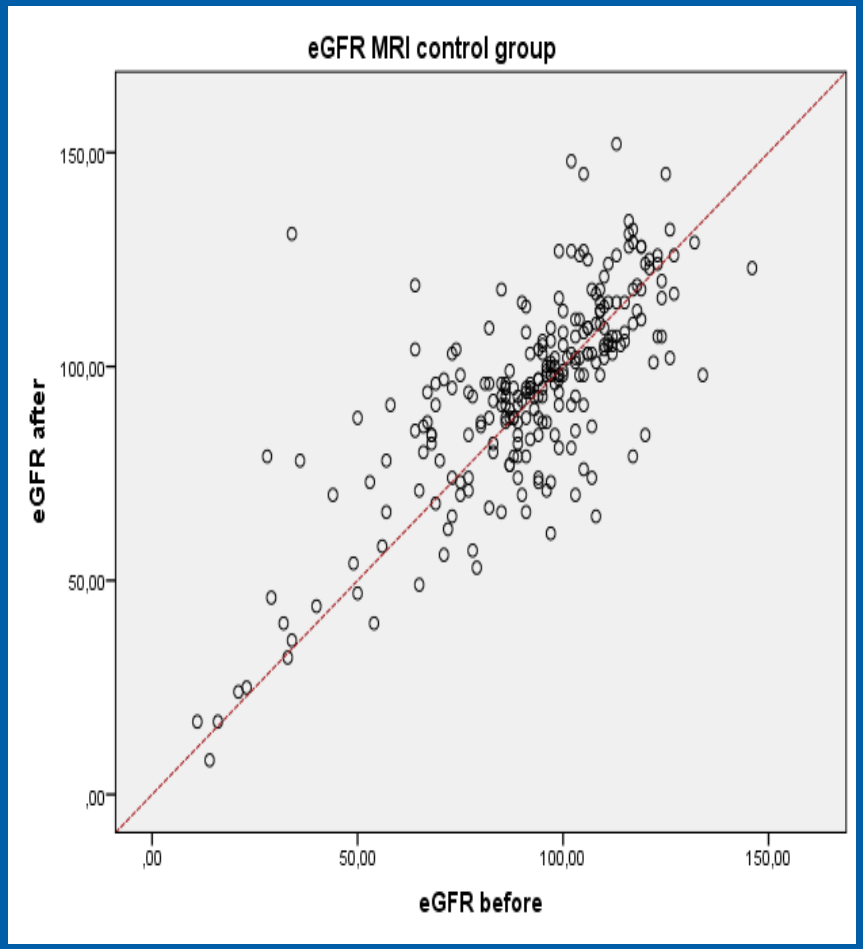
No Contrast



Contrast

Azzouz et al. Eur J Radiol 2014

eGFR before (X-axis) and after (Y-axis) MR-scanning



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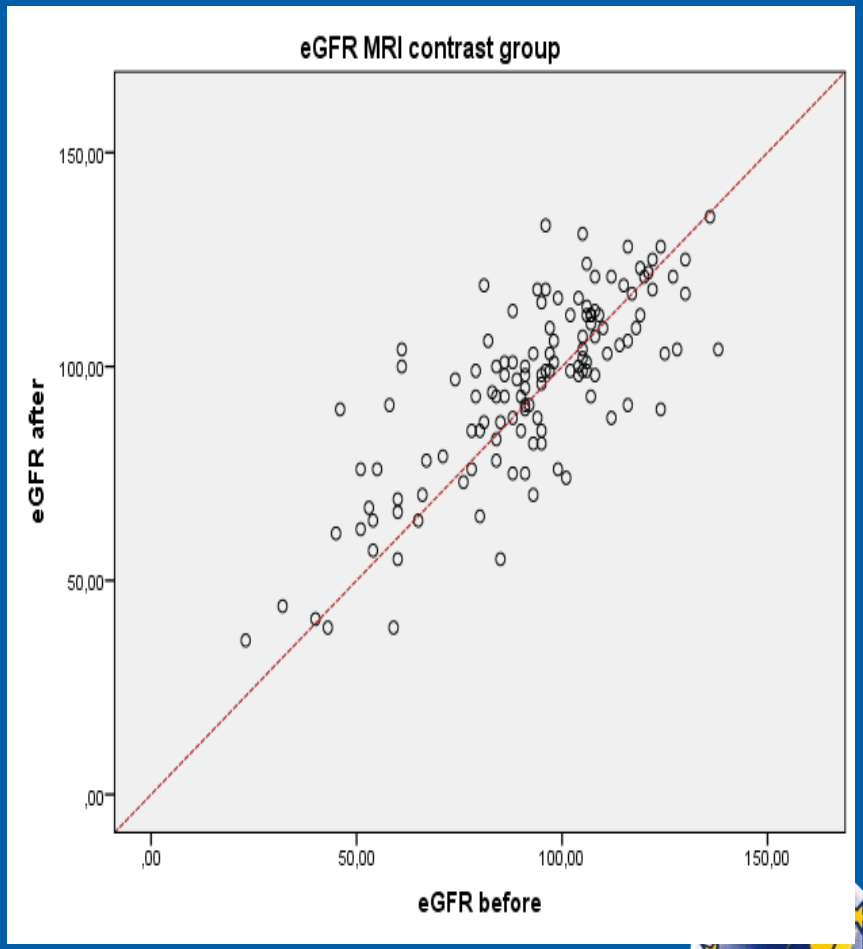

Contrast

Azzouz et al. Eur J Radiol 2014

- eGFR varied independently of whether the patient had received CM or not

Azzouz et al. Eur J Radiol 2014

Enhanced and unenhanced CT or MRI and P-Creatinine or eGFR

	Contrast-enhanced MRI group (n= 129)	MRI control group (n= 253)	P [95% CI]	Contrast-enhanced CT group (n= 237)	CT control group (n=97)	P [95% CI]
CIN (S-Cr ≥ 44 µmol/L)	0	2 (0.8%)	.552	0	1 (1.0%)	.288
CIN (S-Cr ≥ 25%)	13 (10.1%)	33 (13.0%)	.506	13 (5.5%)	8 (8.4%)	.325

Azzouz et al. Eur J Radiol 2014

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Azzouz et al. Eur J Radiol 2014

Do not forget the natural fluctuations in eGFR

J Comput Assist Tomogr • Volume 33, Number 3, May/June 2009

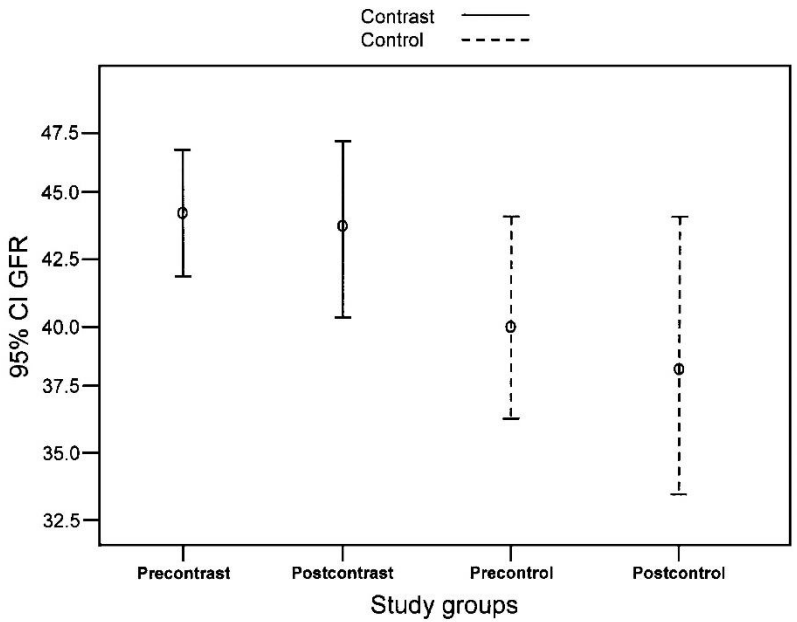


FIGURE 2. Error plot showing change in eGFR with CIs after contrast in the contrast group and without contrast in the control group.

44.33 mL/min (SD, 10.33; range, 14–77 mL/min). Estimated

Within 3.5 days

Bansal et al. J Comput Assist Tomogr 2009; 33: 455-459

Retrospective study I

- All enhanced and unenhanced abdominal, pelvic and thoracic CT scans from 2000 through 2010 at a single faculty.
- P-Creatinine:
  - Post-scan determination 24-72 h after imaging
  - Pre-scan determination within 24 h of imaging

- CIN definition:
  - Absolute (<44 µmol/l)

McDonald et al. Radiology 2013; 267:108-118

Retrospective study I

- 157,140 scans among 53,439 unique patients associated with 1,510,001 P-Creatinine measurements.

- Incidence of CIN was not significantly different from “CIN” in the group that had no CM.

McDonald et al. Radiology 2013; 267:108-118

Retrospective study II

- 20242 unenhanced and enhanced CT examinations performed over a 10-year period in adult inpatients with sufficient P-Creatinine data were identified.

Davenport et al. Radiology 2013; 267: 94-105

Retrospective study II

- Patients with P-creatinine levels less than 132.6 µmol/l before CT were not at risk of CIN, and the risk increased with increasing s-creatinine levels.

- Despite a number of risk factors other than CM helped to predict renal dysfunction after administration of CM, CM administration remained an independent risk factor for patients with a P-creatinine above 141 µmol/l.

Davenport et al. Radiology 2013; 267: 94-105

Retrospective study III

- 12508 propensity score-matched patients with enhanced or unenhanced scans met the inclusion criteria:
  - a) CT-scanned from 2000 through 2010
  - b) P-Creatinine determined 24 h before and 24-72 h after CT
  - c) had necessary demographic variables for the Modification of Diet in Renal Disease (MDRD)) equation
- Patients on dialysis and who had additional contrast procedures within 14 days were excluded.

McDonald et al. Radiology 2014; 271:65-73

Retrospective III

- It could not be documented that administration of CM increased the risk of acute kidney insufficiency even in patients with substantially compromised renal function.

McDonald et al. Radiology 2014; 271:65-73

Meta-analyses

- A meta-analysis of controlled studies examining the incidence of acute kidney insufficiency in patients CT-scanned with or without iodine-based CM.
- 1489 studies were identified
- only 13 (0.9%) fulfilled the inclusion criteria:
  - incidence of acute kidney insufficiency in patients exposed to intravenous CM was directly compared with the incidence of acute kidney insufficiency in unexposed patients through analyses of changes in P-Creatinine level or eGFR 48-72 hours following procedures of administration.

McDonald et al. Radiology 2013; 267:119-128

Meta-analyses

- Only 4 were prospective.

McDonald et al. Radiology 2013; 267:119-128

Meta-analyses

- CIN studies demonstrate a similar incidence of acute kidney insufficiency, dialysis and death between the CM-group and control groups.
- Regardless of intravenous CM-type, diagnostic criteria for acute kidney insufficiency or whether the patients had diabetes mellitus or renal insufficiency.

- The meta-analyses question the existence of CIN.

McDonald et al. Radiology 2013; 267:119-128

Retrospective studies

- Retrospective studies in this field are not optimal:

- 1. Why was the CM not administered? Was it because the patient had poor renal function or simply because the CT-scan was done to visualize a renal calculi for which purpose unenhanced CT-scans are sufficient in most cases.

Retrospective studies

- Retrospective studies in this field are not optimal:

- 2. Why was P-Creatinine levels determined between 24 and 72 hours after imaging? Was the patient in special circumstances that necessitated this determination? Blood samples are not taken for fun.

Retrospective studies

- Retrospective studies in this field are not optimal:

- 3. Were preventive measures used in the group undergoing enhanced CT? It is possible, but very unlikely in the control group.

Retrospective studies

- Retrospective studies in this field are not optimal:

- 4. Most of the patients undergoing CT are outpatients, but the majority in the retrospective studies are inpatients. In general, inpatients are more sick than outpatients.

Retrospective studies

- Retrospective studies in this field are not optimal:

- 5. It is probably impossible to conduct a prospective study of a size that is necessary to show CIN. It must also have a control group which is almost impossible.

2015

- Still only papers on no CIN coming from 2 American centers – they are both retropsective.

McDonald JS, Mayo Clinic Proc 2015

- Intravenous contrast material administration was not associated with an increased risk of AKI, emergent dialysis, and short-tern mortality in a cohort of patients with diminished renal function.

Davenport, AJR 2015; 204

- Contrast-induced AKI is rarer than previously thought, but there remains controversy about the incidence for patients with an estimated GFR of less than 45 ml/min/1.73m^2 are at highest risk.
- If contrast-induced AKI exists after IV contrast administration, patients with an estimated GFR of less than 30 ml/min/1.73m^2 are at highest risk.
- Until more definitive data are available, ICM should be defined in the same manner as other potential nephrotoxins using standardized criteria

Why not?

- In many studies over the years the authors have focused on the increase in P-creatinine and overlooked the patients who had a decrease

P-Creatinine

- The dark horse

Contrast-Induced Nephropathy

- Definition

- CIN is a condition in which a decrease in renal function occurs within 3 days of the intravascular administration of CM in the absence of an alternative etiology. An increase in P-Creatinine by more than 25% or 44 µmol/l (0.5 mg/dl) indicates CIN.

Clinical picture of CIN

- The diagnosis is based on an increase in P-Creatinine.
- Anuria may develop in severe cases.
- Dialysis is rarely required (< 1% of patients with CIN).

P-Creatinine and eGFR

- Neither P-Creatinine nor eGFR are perfect expressions of renal function.

- S-Creatinine levels are very variable.

Some of the factors that influence levels of P-Creatinine

- State of hydration
- Active secretion (increases with decreasing renal function)
- Food intake (e.g. beef)
- Muscular mass
- Drugs
- Physical activity
- Etc.

P-Creatinine - eGFR

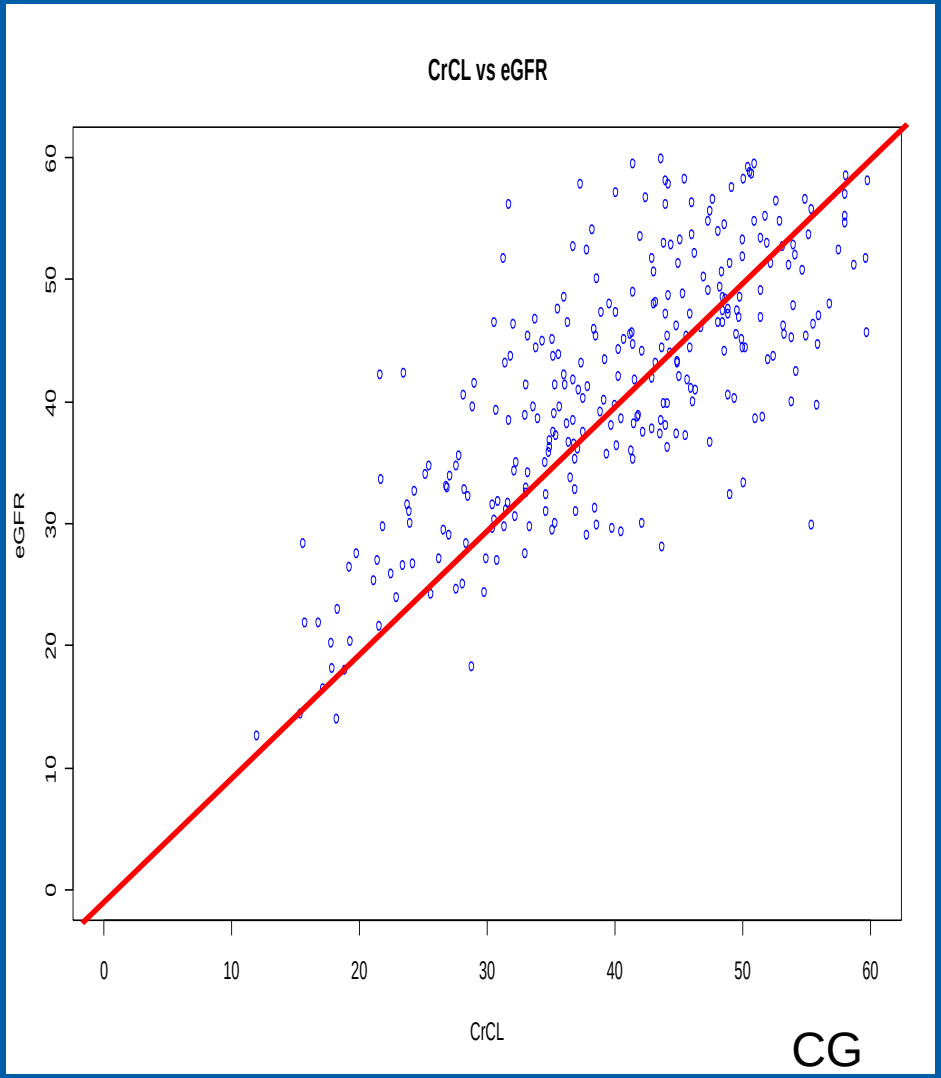
- Nevertheless, we have used P-creatinine for many years, but it is by no means optimal.

- We do not yet have another easy and cheap method.

Also the equations used for calculating eGFR vary

Correlation between CG and MDRD in 301 patients

MDRD



Also the equations used for calculating eGFR vary

- **The CKD-EPI formula gives the most accurate eGFR.**

Take-home points

- Risk of CIN at very low GFR is unknown
- No difference in nephrotoxic potential between the dimer and the monomers – both IA and IV.
- Risk of CIN has been overestimated.
  - It is too early to declare it none existing.
- P-Creatinine/eGFR is not optimal.

No risk or limited risk

- USA
- ACR states now (2015) that patients with a GFR above 30 ml/min 1.73 m^2 are not at ask of CIN

No risk or limited risk

- Europe
- ESUR has since 2011 considered that patients with a GFR above 45 ml/min 1.73 m^2 are not at risk of CIN


Thank you!