Safety aspects of enhanced MDCT – Highlights from the presentation

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The ideal contrast medium

- It must be totally inert.
- It may not have any interaction with the organism at any level
- It must be excreted fast and completely.

The ideal contrast m…ium

- It must h…
- It…excreted fast and co…pletely.

It does not exist

However, the newer generations of contrast media are approaching that stage

Adverse reactions

- Acute: 0 – 60 min.
  - Renal e.g. Nephrotoxicity
  - Non-renal e.g. Larynxedema
- Late: 1 hour – 7 days
  - Skin reactions
- Very late: > 7 days
  - Thyrotoxicosis

Adverse reactions to I-CM

- Mild
  - Short, self-limiting and requires no treatment
  - Incidence: 1-15%
- Moderate
  - Response to adequate therapy
  - Incidence: 0.2-0.4%
- Severe
  - Requires instant therapy
  - Incidence: 0.01%
  - Death: 1:70,000 ???

Adverse reactions to I-CM

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  - Short, self-limiting and requires no treatment
  - Incidence: 1-15%
- Moderate
  - Respons
  - Incidenc
- Severe
  - Requires instant therapy
  - Incidence: 0.01%
  - Death: 1:70,000 ???

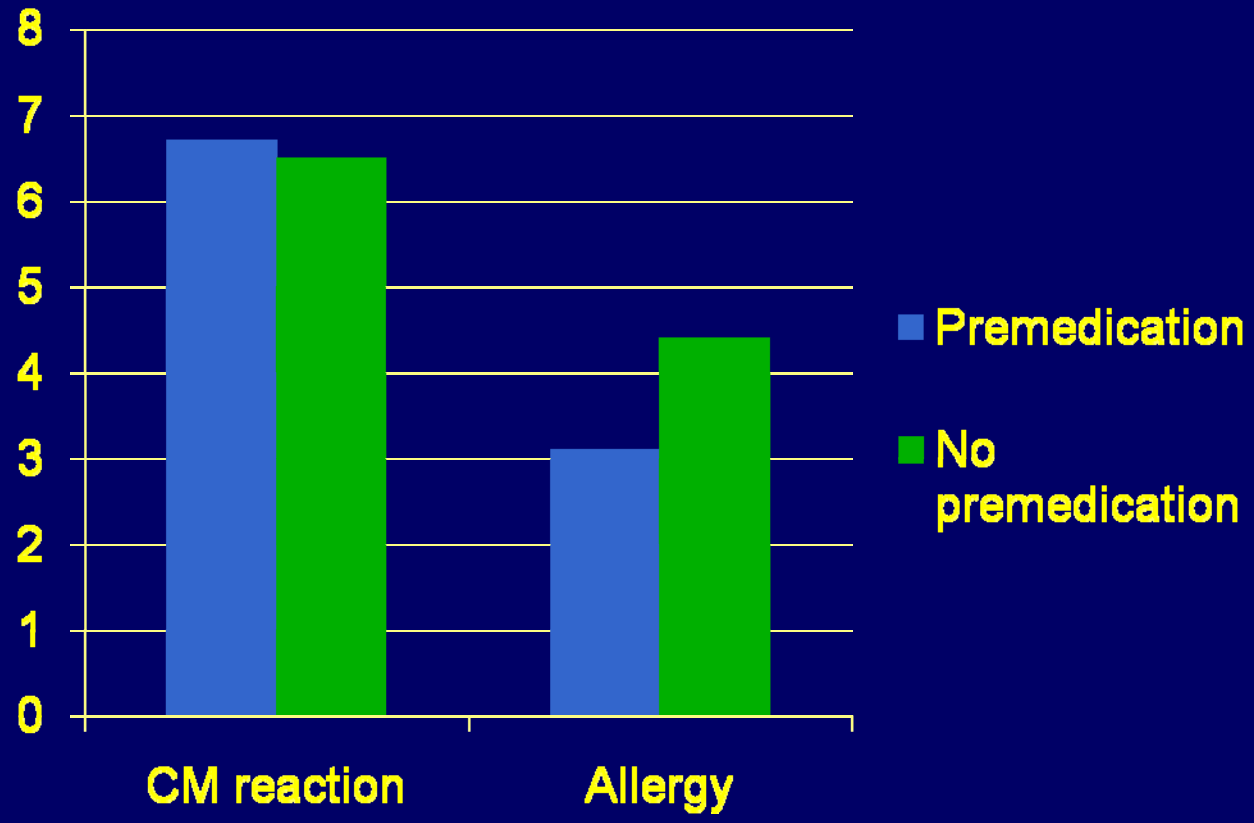
There is no evidence of a difference between the various non-ionic agents

Prevention

- Be calm.
- Be sure that drugs for first line treatment are present.

Premedication?

The incidence of acute adverse reactions was not altered by the use of premedication



Kopp et al Acta Radiol 2008

Premedication?

- Only 23 - 46 % of risk patients received premedication
- Preference
- Asia – Corticosteroids
- USA – H1-blockers
- Europe – in between

Kopp et al Acta Radiol 2008

Fact

- Radiologist and trainee knowledge of immediate life-threatening contrast reaction is deficient e.g.:
  - 53% of questions were answered correctly
  - 43% knew the adrenaline dose
    - Incorrect doses were mainly too high doses
  - 45% knew the emergency telephone number
  - 45% of rooms contained not an immediately visible chart for contrast reaction management

Australasian Radiology 2003; 47: 363-367

When it occurs

- Instant treatment of severe acute reactions is often mandatory: HERE & NOW.
- The venous access used for the injection is often no longer present.
- The right procedure must be instituted.

Second line should be taken care of by a resuscitation team

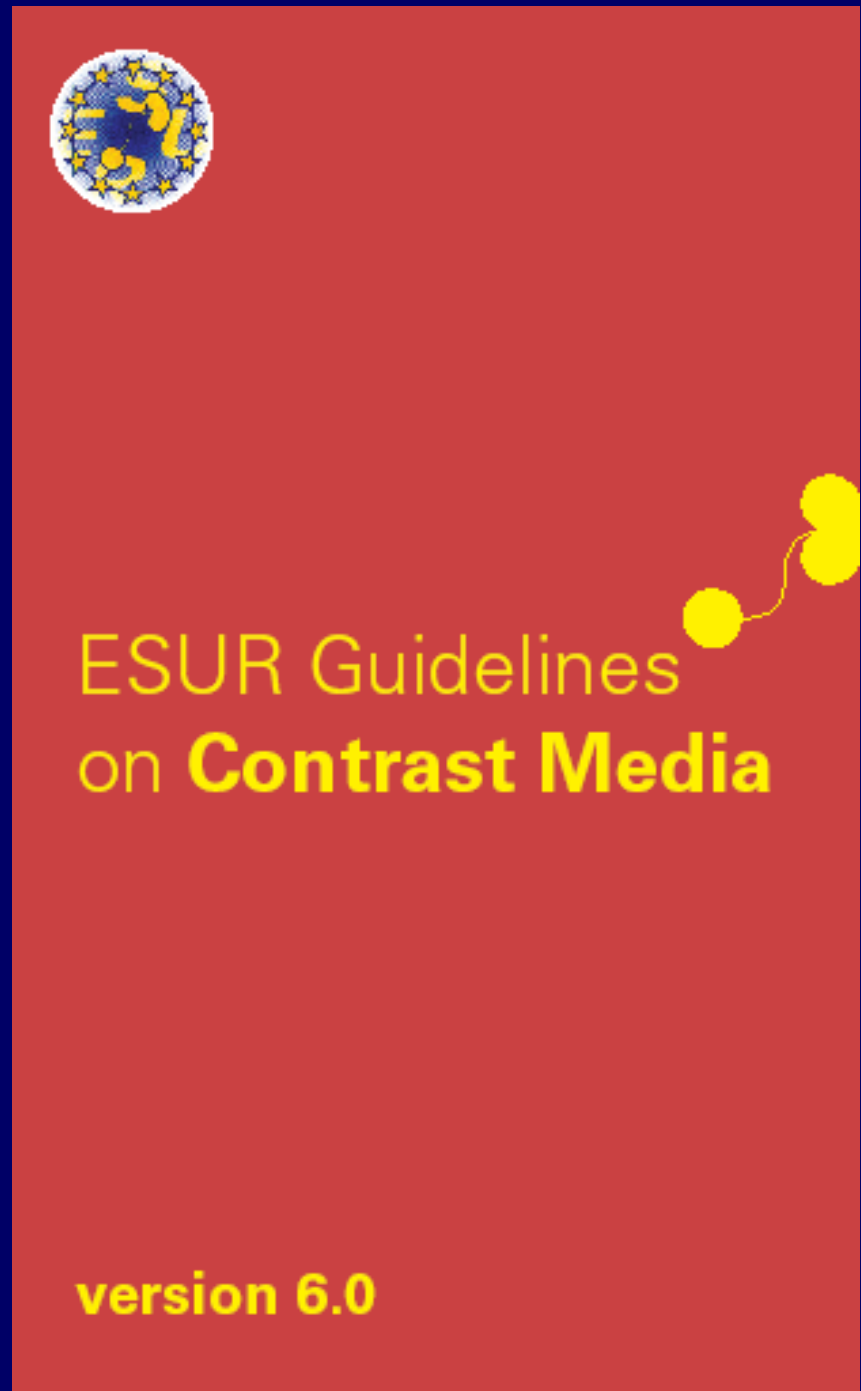
They are more experienced

Finally

- Remember training

- Experience in the management of adverse reactions can only come from regular, compulsory training.

For details



CIN

Contrast induced Nephropathy

Awareness of CIN

- Telephone or on-line survey involving 509 radiologists from 10 European countries.
  - Important factors
    - Renal impairment 97%
    - Dehydration 90%
    - Diabetes mellitus 89%
      - Age 26%
      - CM dose 30%
      - Congestive heart failure 46%

Reddan & Fishman EJR 2007

CIN

Definition:

CIN is a condition in which an impairment in renal function (an increase in serum creatinine by more than 25% or 44 µmol/l) occurs within 3 days following the intravascular administration of a contrast medium (CM) in the absence of an alternative etiology.

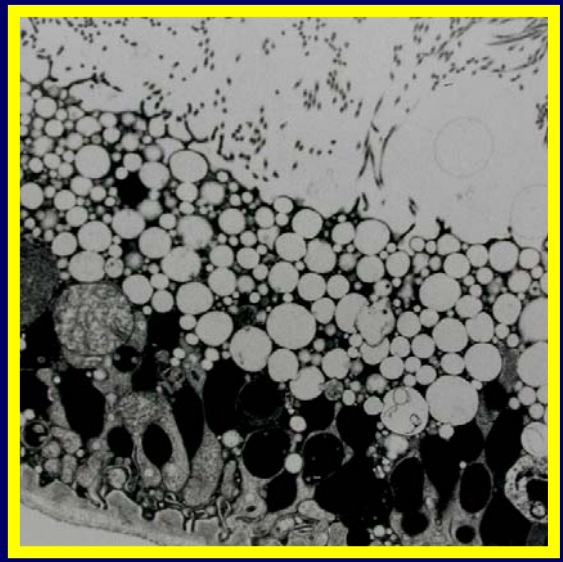
The kidney is the main route of elimination of CM

- Increase RVR
- Decrease GFR
- Diuresis
- Natriuresis
- Enzymuria
- Structural changes [Osmotic nephrosis]

Modulation of production of intrarenal vasoactive mediators

- ↑ Endothelin (vasoconstriction)
- ↑ Adenosine (vasoconstriction)
- ↓ NO (vasodilatation)
- ↓ Prostacycline (vasodilatation)

It represents the normal response of the kidney to CM exposure



RVR = Renal vascular resistance

GFR = Glomerular Filtration Rate

CM → Normal kidneys , No risk factors

↓

No clinical problem

Risk factors

↓

Renal impairment + DM
Dehydration
Congestive heart failure
Age over 70 years old
Administration of nephrotoxic drugs
Dose and type of CM

Incidence of CIN after IV injection in high risk patients

- **Range from 0 to 21%**
  - **Se Cr > 220 µmol/L 21%**
  - (Tepel et al, New England Journal of Medicine 2000; 343: 180-184)
  - **Se Cr > 176 µmol/L 0%**
  - (Thomsen et al. Invest Radiol 2008 – in press)
  - Precise true incidence is not clear

CIN

Clinical Course

- Although self limiting in most cases (resolve within 1-2 weeks)

There is a clinical concern

Clinical Importance of CIN

- CIN increases the incidence of non-renal complications and prolongs hospital stay
  - Sepsis
  - Bleeding
  - Stroke
  - Respiratory failure
  - Fifteen fold increase in major adverse cardiac events (MACE) post PCI

Rihal et al; Circulation 2002; 105: 2259-2265.
Bartholemew et al, Am J Cardiol 2004; 93: 1515-1519 Marenzi et al, JACC 2004; 44:1780-1785

Conclusion 1

Forget the Gd-CM for CT

"CIN and NSF"

Iodine CM

LOCM
less nephrotoxic than
HOCM

14 years ago

Pooled odds ratio for use of LOCM *vs.* HOCM

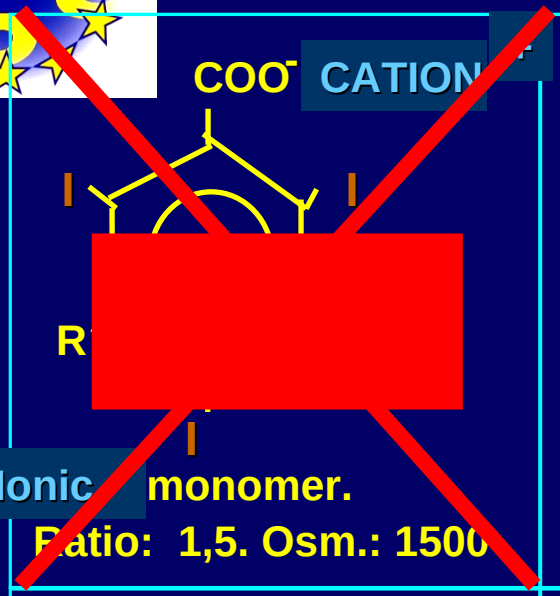
	No. studies	No. subjects	Pooled odds ratio (CI)
All patients	25	4589	0.61 (0.48, 0.77)
Normal renal function	20	2865	0.75 (0.52, 1.1)
SCr >120 μmol/l or GFR <70 ml/min	8	1418	0.5 (0.36, 0.7)

Barrett & Carlisle (1993)

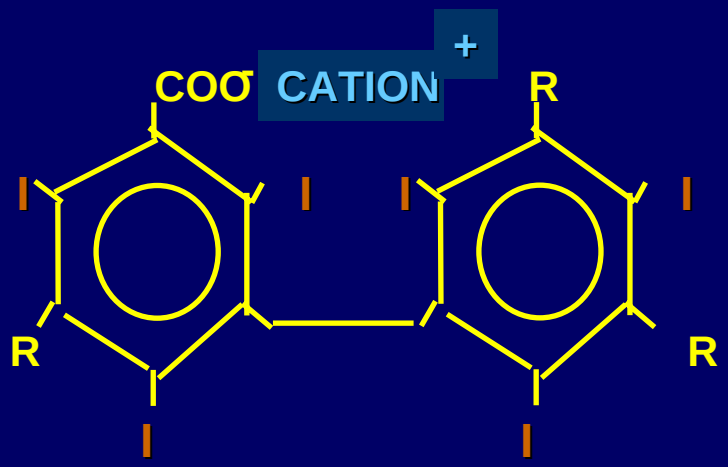
Conclusion 2

Forget the HOCM for CT

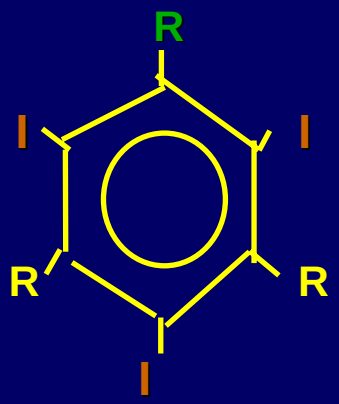
Classification



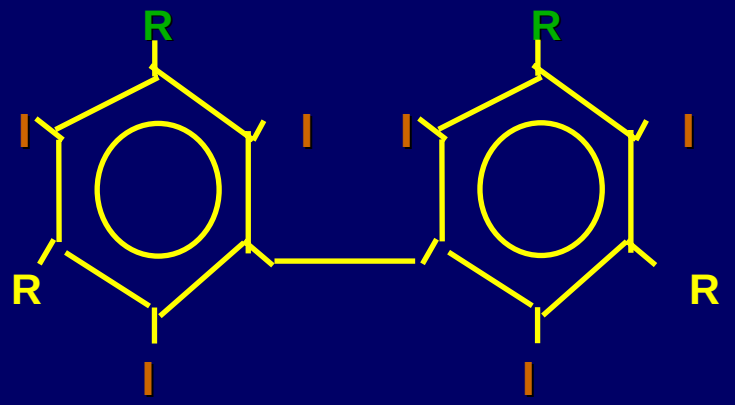
Ionic monomer.
Ratio: 1,5. Osm.: 1500



Ionic dimer.
Ratio: 3,0.
Osm.: 600.

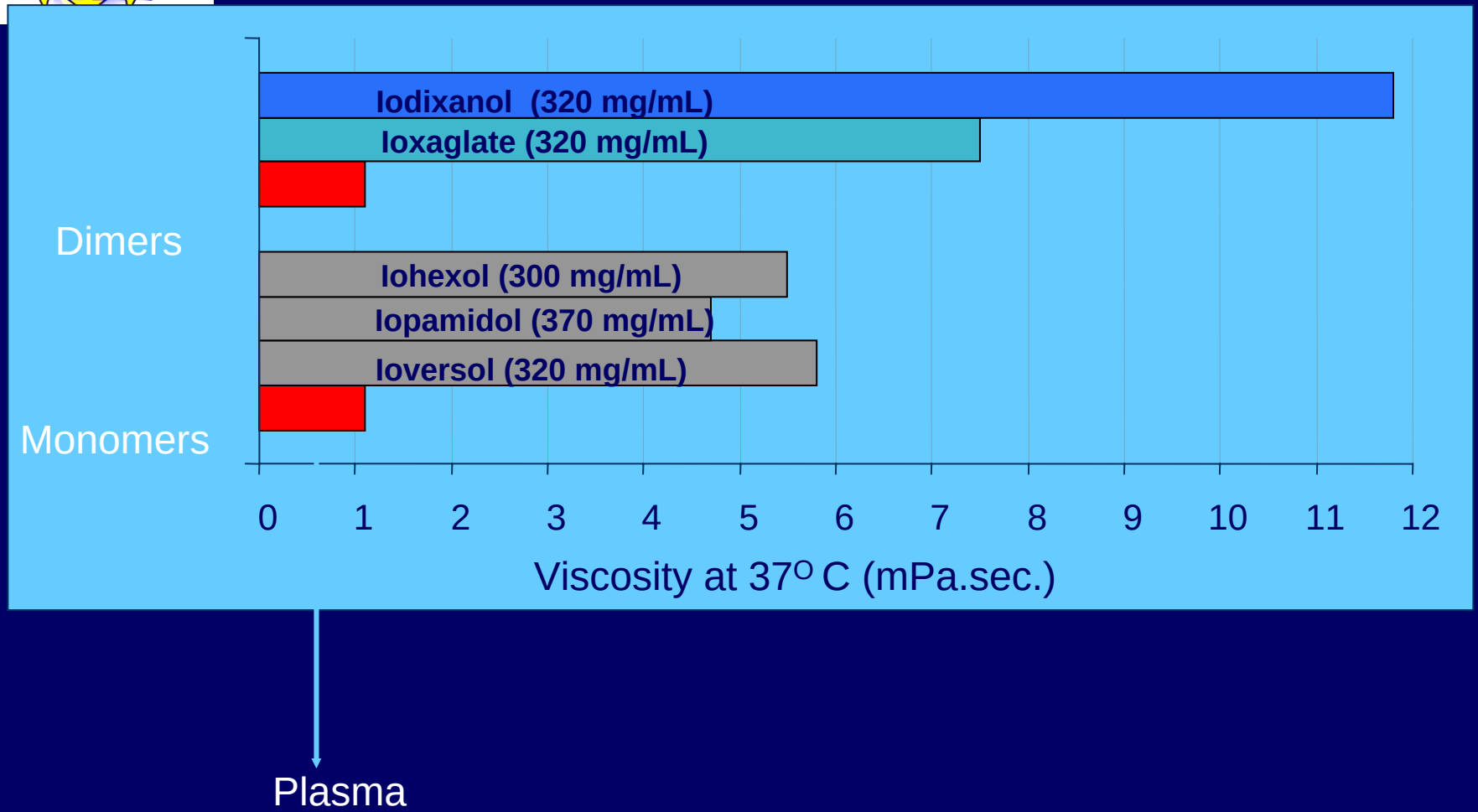


Non-ionic monomer.
Ratio: 3,0. Osm.: 520-750



Non-ionic dimer.
Ratio: 6,0.
Osm.: 280.

Viscosity of Low- or Iso-Osmolar Agents

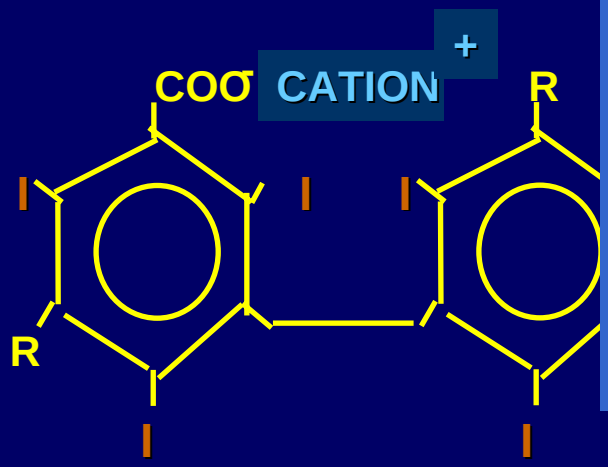


And many other factors

- Hydrophilicity
- Chemotoxicity
- Other substances

Classification

Ionic monomer.
Ratio: 1,5. Osm.: 1500



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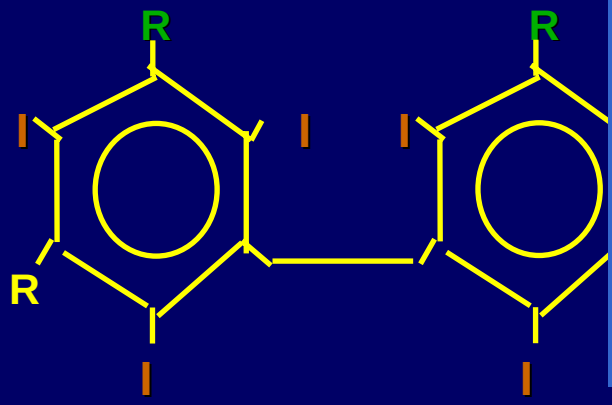
Osm.: 600.

8



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Non-ionic monomer.
Ratio: 3,0. Osm.: 520-750

Analogy

- For many years we have gathered all Gd-CM into one class despite differences in f. ex. stability and osmolality.
- To day we know that it was a great mistake.
- It may also be a mistake for Iodine-CM.
- Each iodine based compound should be evaluated individually due to the differences in viscosity, osmolality, chemotoxicity, hydrophilicity et c.

MDCT

- We have access to 10 compounds with various specifications.
- What is available regarding CIN, CT and those 10 compounds?

The sad story

- Too little

- The overwhelming CIN-literature deals with angiography, not CT

Incidence of CIN after IV injection in high risk patients

- Number of studies on IV injection is limited; over the last 40 years, only 40 for IV injection in comparison to >3000 after IA injection”

Katzberg & Barrett, Radiology 2007; 243: 622-628

Average Baseline eGFR 52ml/min

Endpoint	Iopromide-370 (n=56)	Iodixanol-320 (n=61)	Fisher's exact test p-value
SCr increase ≥ 44 µmol/L	10 (18.5%)	3/61 (5.1)	0.037
The Nephric definition of CIN			
	Intravenous injection (CT) 37 gI per patient		

Nguyen, Radiology 2008

IMPACT

Endpoint	Iopamidol-370 (n=77)	Iodixanol-320 (n=76)	Fisher's exact test p-value
SCr increase ≥ 44 µmol/L	0	2 (2.6%)	0.2
The Nephric definition of CIN			
	Intravenous injection (CT) 40 gI per patient		

Barrett, Invest Radiol 2006

ACTIVE

Endpoint	Iomeron-400 (n=76)	Iodixanol-320 (n=72)	Fisher's exact test p-value
SCr increase ≥ 44 µmol/L	0	5 (6.9%)	0.025
The Nephric definition of CIN			
	Intravenous injection (CT) 40 gI per patient		

Thomsen, Invest Radiol 2008

PREDICT

All have diabetes and eGFR between 20 and 59 ml/min (CKD 3 & 4)

Endpoint	Iopamidol-370 (n=125)	Iodixanol-320 (n=123)	Fisher's exact test p-value
SCr increase ≥ 25%	7 (5.6%)0	6 (4.9%)	0.2
Definition different from IMPACT and ACTIVE			
	Intravenous injection (CT) Min 65 ml.		

Kuhn, ECR 2008

CIN with Head-to-Head Comparisons Risk Patients Receiving I.V. Contrast Material

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
TOTAL	**21/400 (5.25%)**	**21/393 (5.34%)**	NO DIFFERENCE

IMPACT + ACTIVE

High-risk patients: MDRD clearance 15 - 40 ml/min

Endpoint	Iomeron-400 Iopamidol-370 (n=72)	Iodixanol-320 (n=59)	Fisher's exact test p-value
SCr increase ≥ 44 µmol/L	0	6 (10.2%)	0.0059
The Nephric definition of CIN			
	Intravenous injection (CT) 40 gI per patient		

Thomsen, In press

ACTIVE + IMPACT + PREDICT

- Include only patients with stable renal function prior to CM-administration determined by at least S-cr/eGFR measurements

- Patients enrolled are not on the fast downslope, which may be the case if you have only one S-Cr pre and post.

Conclusion 3

No documented advantage of the available dimer in CT both in moderate and high-risk patients (CKD 3, 4 & 5)

According to randomized, prospective studies !!!!!!

Arteriography

LOCM (n)	IOCM (n)	S-Cr	DM	Statistical result	Ref.
48	54	273	35%	No dif.	Chalmer (1999)
65	64	132	100%	Iodixanol > Iohexol	Aspelin (2003)
125	134	176	52%	No dif.	Rudnick (2005)
204	210	128	41%	No dif.	Solomon (2006)
135	140	118	48%	Iodinaxol > ioxaglate ?	Jo (2006)
74	71	161	46%	No dif	Mehran (2006)
48	51	N/A	100%	No dif.	Hardiek (2006)

CONTRAST

37 % had diabetes; 99% eGFR between 20 and 59 ml/min (CHD 3 & 4), 1 % below

Endpoint	Iopamidol-350 (n=162)	Iodixanol-320 (n=162)	p-value
SCr increase ≥ 25% or ≥0.5 mg/dl	27.7%	22.2%	0.25
Definition different from NEPHRIC			
	Intraarterial 365 ml IOD ± 158 ; IOM ±170 ml		

Wessely ACR 2008

CONTRAST

37 % had diabetes; 99% eGFR between 20 and 59 ml/min (CHD 3 & 4), 1 % below

Endpoint	Iomeprol-350 (n=162)	Iodixanol-320 (n=162)	p-value
SCr increase ≥ 1 mg/dl Severe CIN	3.7 %	6.2%	0.30
DIALYSIS	0.6%	1.9%	0.31
	Intraarterial 365 ml IOD ± 158 ; IOM ±170 ml		

Wessely ACR 2008

Arteriography

- Only in 1 out of 8 prospective randomized arteriographic studies there is a statistical significant difference in CIN-rate between IOCM and some of the LOCM.

Conclusion 4

Below 800 mOsm, the osmolality is not a very important factor in CIN

Recent Review

- Never-the-less:
- The NEPHRIC study influenced the recommendations of several guidelines, despite the fact that the result have never been confirmed in a larger series.

Thomsen & Morcos Eur Radiol 2006

Pharmacologic manipulation

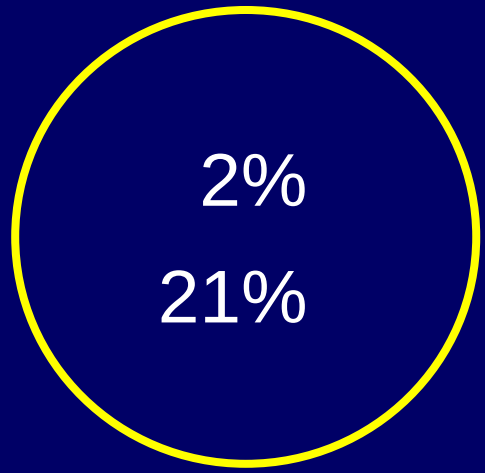
- Nearly nothing – all angiographic!!!!
- However, there are two interesting studies.

Acetylcysteine

- Patients with renal impairment [mean serum creatinine 211 µmol/l]
- Acetylcysteine (600mg) orally twice daily 24 hours before and continued for 24 hours after 75ml IV iopromide
- Hydration with 0.45% saline

CIN

Acetylcysteine + Hydration	2%
Hydration alone	21%



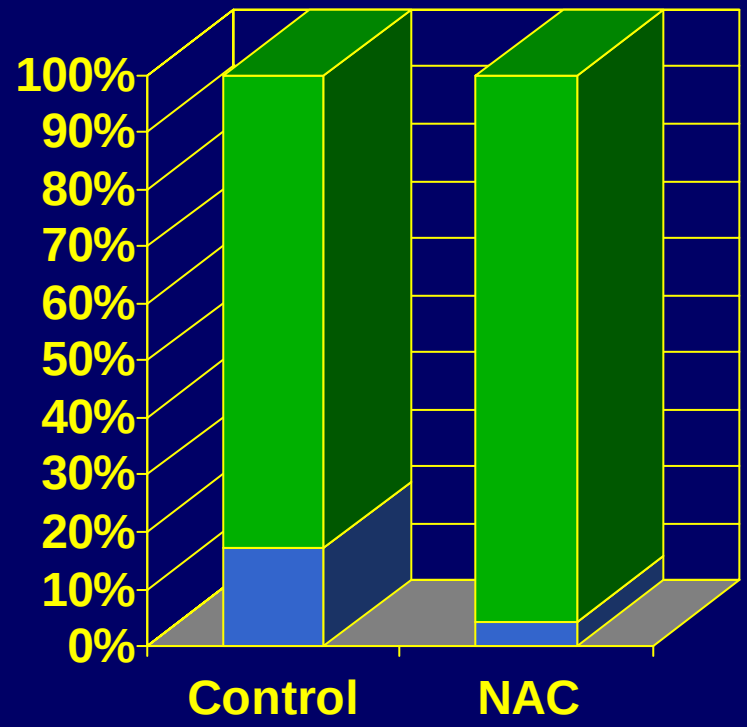
No difference regarding dialysis

Tepel et al, N Engl Med 2000; 343: 180-184

I.V. CM and acetylcysteine

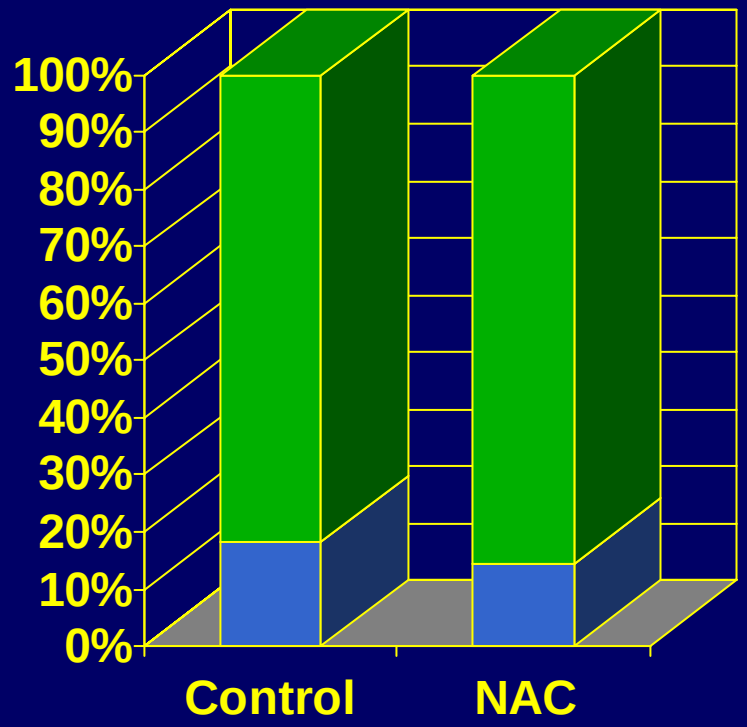
- Surprising result.,
- The same big difference is not confirmed in the ~40 other angiographic studies.
- The latest meta-analyses have not confirmed a renoprotective effect of NAC but severe inhomogeneity among the various studies.

25% increase after 100 ml 300 mgI/ml intravenously



Se-creatinine

P = 0.026



Cystatin C

P = 0.59

Poletti et al. AJR 2007

NAG

- Newer studies
- No difference between S-Cr and Cystatin C
- Effect of NAC when Cystatin C used

- Inconsistent results continue

Conclusion 5

There is no evidence that any pharmacologic manipulation prior to enhanced CT protects the kidney against CIN

Hydration or inducing a diuresis

10 RCT published between 1992 and 2006:

- Both normal and decreased renal function
- Both intraarterial and intravenous routes of administration
- Variety of contrast media
- Study size: 18-1620
- Less than 2500 patients in total

What doesn't work

- Forced diuresus: adding mannitol or furosemide
- Rapid bolus: Isotonic saline (250-300 ml) at time of CM exposure
- Water alone: Oral hydration (unrestricted, no minimum) starting 12 hour before CM exposure

What works

- Hypotonic saline starting 12h before and continuing for 12 h after CM exposure at 1 ml/kg/h.
- Isotonic saline starting 4 h before and continuing for 12 h after CM exposure at 1 ml/kg/h.
- Oral hydration (1000 ml – 10 h) followed by hypotonic saline (300 ml/h) starting ½ h before and continuing for 6 h total.

Conclusion 6

Hydrate with saline

The history of CIN !!!!!!!!

- One day a preventive factor seems promising
- The next day the opposite is shown or no effect is shown.

1

Never base your decision on a single report

Look at the evidence

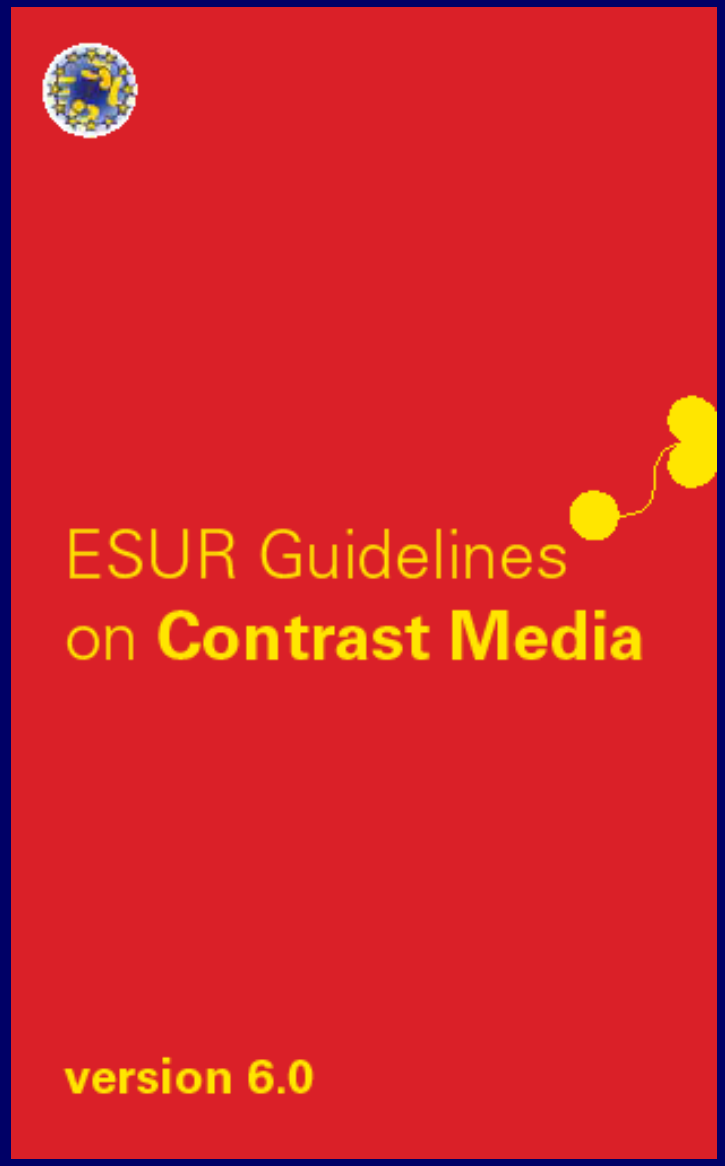
Take home point

- Follow the ESUR guidelines

www.esur.org

ESUR

- ESUR guidelines (version 1- 6) have been printed in > 100.000 copies and translated into 6 languages:
  - Japanese
  - Chinese
  - Russian
  - Spanish
  - Portuguese
  - Greek



www.esur.org

Thank you for your attention