



# Teaching Module VII

ESUR guidelines on use of CM in certain clinical situations





# ESUR guidelines on use of CM in certain clinical situations

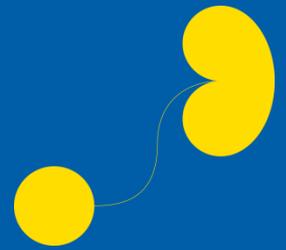
This slide deck was prepared by

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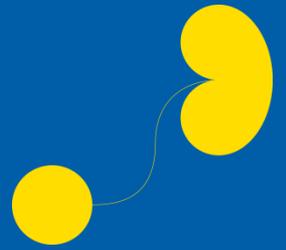
# Objectives

- Pregnancy and lactation
- Thyroid disease
- Diabetic patients on metformin
- Renal impairment

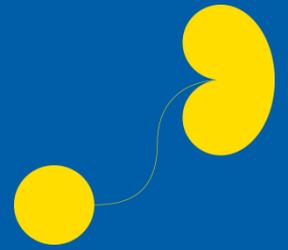


# Pregnancy

Is it indicated to give CM?



# Pregnancy

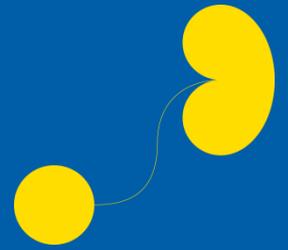


Is it indicated to give CM?

The radiation is more dangerous than the I-CM, e.g. abdominal CECT



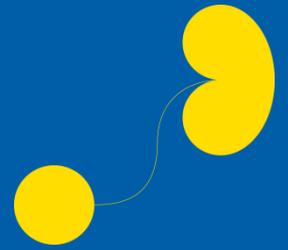
# Mutagenicity and Teratogenicity



No mutagenic or teratogenic effects were found in vivo with non-ionic I-CM or Gd-DTPA in animals.



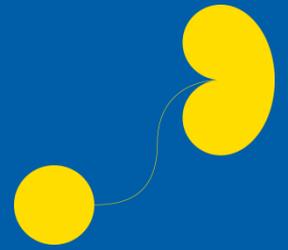
# Placental transfer



Current **I-CM** and **Gd-CM** which are water-soluble and have molecular weights in the range 500-850 Da are expected to transverse the placenta to some extent.



# Pregnancy

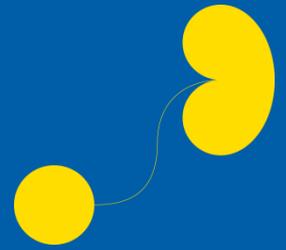


No harmful effects of I-CM were reported with the exception of **depression of the fetal thyroid**.  
No prospective trials.

Fetal thyroid function is essential for the normal development of the CNS.



# Gd-CM - Pregnancy

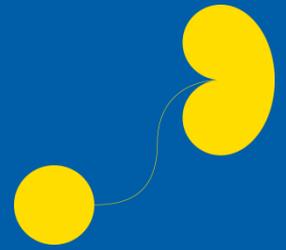


There are relatively few clinical reports of the effect on neonates of giving Gd-CM to the pregnant mother.

**No adverse effects on the infants were detected** in a total of **57 cases** reported when the pregnant mother had been given Gd-DTPA in doses of 0.1-0.2 mmol/kg.



# Gd-CM - Pregnancy



The ESUR guideline previously suggested that Gd-CM could be safely given to the pregnant female.

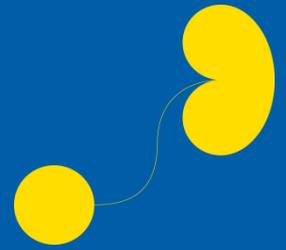
Recent data suggests potential for free gadolinium to be released from Gd-CM and to be deposited in bone and other tissues.

The **potential harmful effect of slow excretion of CM in the neonate** because of immature renal function, is important.

The **use of Gd-CM in the pregnant female should be restrictive.**



# Gd-CM - Pregnancy



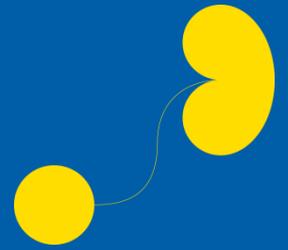
## Recommendations:

Gd-CM should only be given to pregnant women when there is a **very strong clinical indication**.

One of the more stable, **macrocyclic Gd-CM** should be used in the **lowest dose** consistent with a diagnostic result.



# Lactation

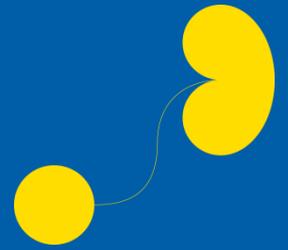


Is it indicated to give CM?

The baby gets very small amounts ( $< 0.5\%$ ) of I-CM – it may give a bad taste.



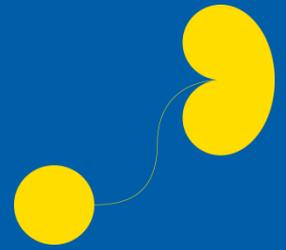
# Gd-CM – Lactation



The amount of Gd-CM reaching the neonatal gut is less than 1% of the recommended intravenous dose for an infant after the lactating mother has received a Gd-CM intravenously.



# Gd-CM – Lactation



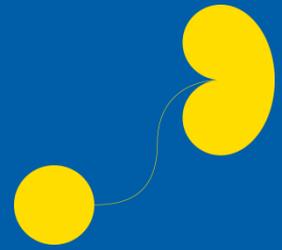
The previous ESUR guideline indicated that when Gd-CM were given intravascularly to the pregnant woman, breastfeeding could continue normally.

However, the information about the potential harmful effects of free gadolinium combined with immature neonatal renal function indicate that despite the very tiny amounts of Gd-CM likely to be absorbed into the blood by the breastfeed infant, it may be prudent to recommend that breast feeding is discontinued for 24 hours if the lactating mother receives high risk intravascular Gd-CM.



# Guideline

## 3.5. Pregnancy and lactation

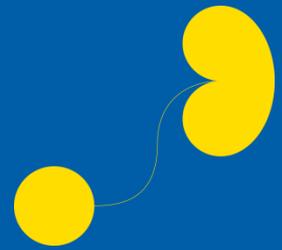


	Iodinated agents	Gadolinium agents
Pregnancy	<p>a) In exceptional circumstances, when radiographic examination is essential, iodinated contrast media may be given to the pregnant female.</p> <p>b) Following administration of iodinated agents to the mother during pregnancy, thyroid function should be <b>checked in the neonate during the first week.</b></p>	<p>a) When there is a very strong indication for enhanced MR, the smallest possible dose of the most stable gadolinium contrast agent (macrocyclic agents) may be given to the pregnant female.</p> <p>b) Following administration of gadolinium agents to the mother during pregnancy, <b>no neonatal tests are necessary.</b></p>
Lactation	Breast feeding may be continued normally when iodinated agents are given to the mother.	Breast feeding should be avoided for 24 hours after contrast medium.
Pregnant or lactating mother with renal impairment	See renal adverse reactions (see 2.1). No additional precautions are necessary for the fetus or neonate.	Do not administer gadolinium-based contrast agents.



# Guideline

## 3.5. Pregnancy and lactation

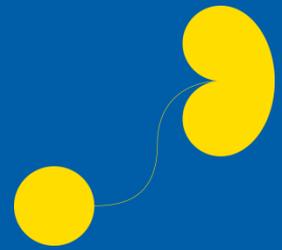


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Pregnancy	<p>a) In exceptional circumstances, when radiographic examination is essential, iodinated contrast media may be given to the pregnant female.</p> <p>b) Following administration of iodinated agents to the mother during pregnancy, thyroid function should be checked in the neonate during the first week.</p>	<p>a) When there is a very strong indication for enhanced MR, the smallest possible dose of the most stable gadolinium contrast agent (macrocytic agents) may be given to the pregnant female.</p> <p>b) Following administration of gadolinium agents to the mother during pregnancy, no neonatal tests are necessary.</p>
Lactation	Breast feeding may be continued normally when iodinated agents are given to the mother.	Breast feeding should be avoided for 24 hours after contrast medium.
Pregnant or lactating mother with renal impairment	See renal adverse reactions (see 2.1). No additional precautions are necessary for the fetus or neonate.	Do not administer gadolinium-based contrast agents.



# Guideline

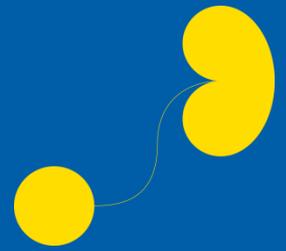
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# Thyrotoxicosis – a very late adverse reaction



## Graves' disease

- Stimulation of antibodies that stimulate iodine uptake and the synthesis of thyroid hormones.

## Thyroid autonomy

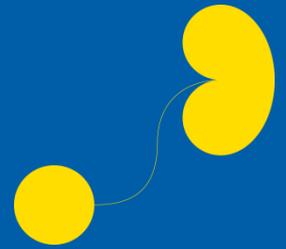
- No TSH control. Large amounts of free iodine cause production and secretion of thyroid hormones.



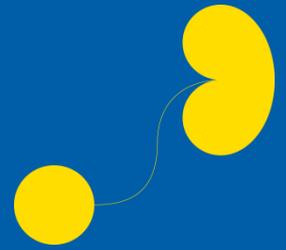
# Prevalence of iodine-induced hyperthyroidism

In iodine-deficient areas ~ 1.7%

In iodine-sufficient areas ~ very low



# Why of interest for a radiologist?



Iodine containing contrast media contains free iodine.

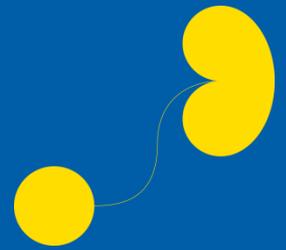
A 300 mgI/ml solution may contain  $< 50 \mu\text{gI/ml}$  right after production and  $< 90 \mu\text{gI/ml}$  after 3 to 5 years.

Normally, they contain less (1/5 -1/10) than the previously mentioned figures.

A 200 ml bottle of 300 mgI/ml gives 7,000  $\mu\text{g}$  free iodine ~ 45 times the recommended daily dose.



# Thyrotoxicosis after CM



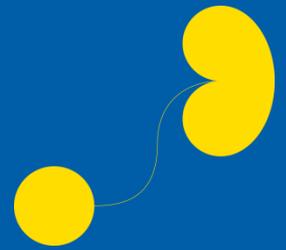
It is a very late reaction.

IT CAN BE SEEN UP TO **3 MONTHS AFTER** THE INJECTION OF THE CONTRAST MEDIUM.

Then the patient is no longer in contact with the department of radiology – the **possible link to the contrast application is often overlooked.**



# Isotope imaging and radioactive treatment



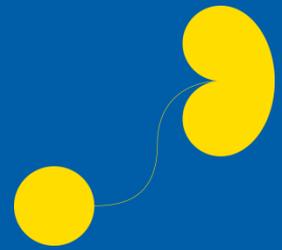
## Recommendation

- Isotope imaging of the thyroid should be **avoided** for **two months** after iodinated contrast medium injection.
- No **radioactive treatment** of thyroid gland within the next **2 months** and/or don't give I-CM to patients planned for radioactive treatment within the next two months (*The iodine deposits are full*).



# Guideline

## 1.3. Very late adverse reactions



### Thyrototoxicosis

At risk

- Patients with untreated Graves' disease
- Patients with multinodular goiter and thyroid autonomy, especially if they are elderly and/or live in areas of dietary iodine deficiency

Not at risk

Patients with normal thyroid function

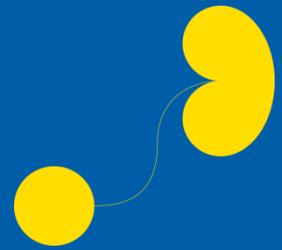
Recommendations

- **Iodinated contrast media should not be given to patients with manifest hyperthyroidism.**
- Prophylaxis is generally not necessary.
- In selected high-risk patients, prophylactic treatment may be given by an endocrinologist; this is more relevant in areas of dietary iodine deficiency.
- Patients at risk should be closely monitored by endocrinologists after iodinated contrast medium injection.
- Intravenous cholangiographic contrast media should not be given to patients at risk.



# Guideline

## 1.3. Very late adverse reactions



### Thyrototoxicosis

- |         |  |
|---------|--|
| At risk | <ul style="list-style-type: none"><li>• Patients with untreated Graves' disease</li><li>• Patients with multinodular goiter and thyroid autonomy, especially if they are elderly and/or live in areas of dietary iodine deficiency</li></ul> |
|---------|--|

Not at risk

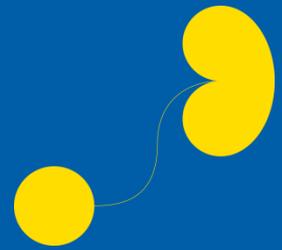
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# Guideline

## 1.3. Very late adverse reactions



### Thyrotoxicosis

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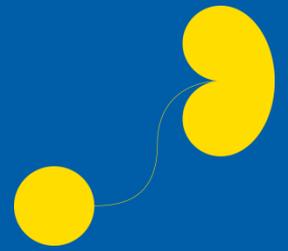
Not at risk

Patients with normal thyroid function

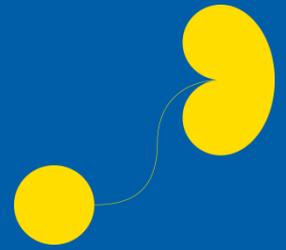
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# Metformin



# Biguanides

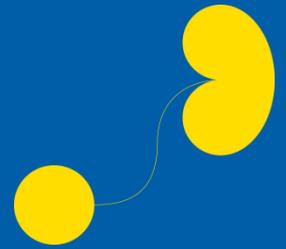


**The biguanides are used in non-insulin dependent diabetes mellitus in three ways:**

- As primary treatment in obese patients inadequately controlled by diet
- As adjunct therapy when sulphonurea alone fails
- Sometimes in combination with insulin
  
- Now also available as a “retard” product



# Renal handling

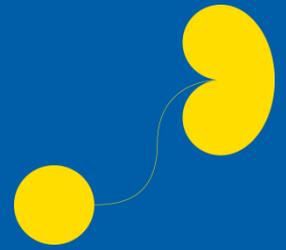


**Biguanides differ in their routes of elimination.**

- Phenformin and buformin undergo hepatic metabolism and renal excretion.
- Metformin is excreted unchanged in the urine.



# Renal handling

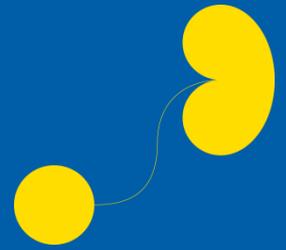


**Biguanides do not cause renal failure.**

**Metformin accumulation sufficient to produce lactic acidosis can occur only in the presence of renal failure (and rarely hepatic failure) and it occurs slowly.**



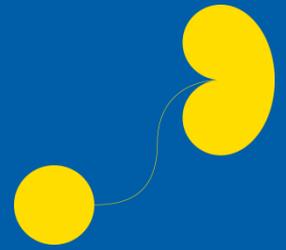
# Renal handling



**In patients with renal failure, metformin may accumulate in body tissues and produce lactic acidosis.**



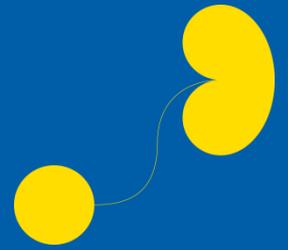
# Renal handling



**Renal insufficiency with failure to clear metformin leads to accumulation of the drug and the potential for development for fatal lactic acidosis.**



# Lactic acidosis

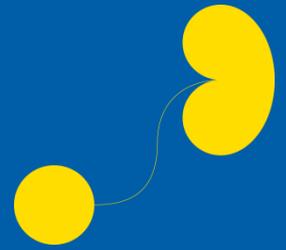


Lactic acidosis is generally defined as a metabolic acidosis due to the accumulation of lactic acid in the blood in excess of 5 mmol with an accompanying blood pH of less than 7.25.

Acute renal failure is a prominent causal factor.



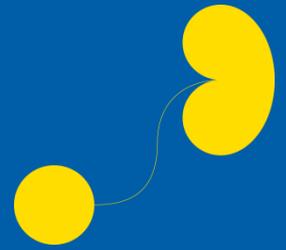
# Metformin



About 20-25% of diabetics with serum creatinine less than  $150 \mu\text{mol/l}$  (a common cutoff level for receiving metformin) have an eGFR between 30 and  $59 \text{ ml/min/1.73 m}^2$  (chronic kidney disease, CKD, stage 3).



# Metformin

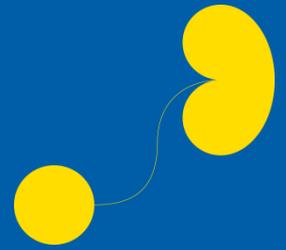


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The incidence of contrast-medium nephrotoxicity is higher in diabetics with renal impairment than in non-diabetics with the same degree of renal impairment.



# Metformin



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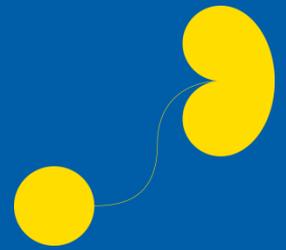
The incidence of contrast-medium nephrotoxicity is higher in diabetics with renal impairment than in non-diabetics with the same degree of renal impairment.

Since metformin clearance is reduced by 74-78% in moderate or severe renal impairment, the potential for metformin retention and lactic acidosis is higher in CKD-3 patients.



# Guideline

## 2.1 Renal adverse reactions to iodinated contrast media



### Risk of iodinated contrast media in patients taking metformin

Lactic acidosis	Metformin is excreted unchanged in the urine. In the presence of renal failure, either pre-existing or induced by iodinated contrast medium, metformin may accumulate in sufficient amounts to cause lactic acidosis.
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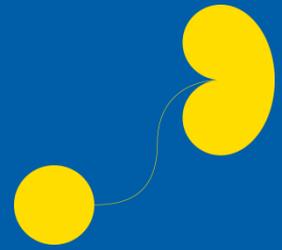
Note Metformin does not cause renal failure.



# Guideline

## 2.1.1. Time of referral

Elective Examination



### 2) Identify diabetic patients taking metformin

Depending on eGFR/serum creatinine level, metformin will have to be stopped either before or at the time of contrast medium administration.



# Guideline

## 2.1.1. Time of referral

### Emergency Examination

1. Identify diabetic patients taking metformin

Measure eGFR (or serum creatinine) if the procedure can be deferred until the result is available without harm to the patient.

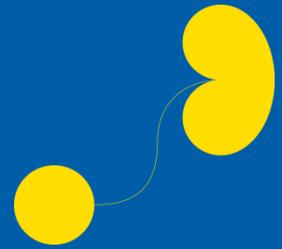
In extreme emergency, if eGFR (or serum creatinine) measurement cannot be obtained, follow the protocol for patients with eGFR less than 60 ml/min/1.73 m<sup>2</sup> (or raised serum creatinine) as closely as clinical circumstances permit.



# Guideline

## 2.1.2. Before the examination

### Elective Examination



Diabetic  
patients taking  
metformin

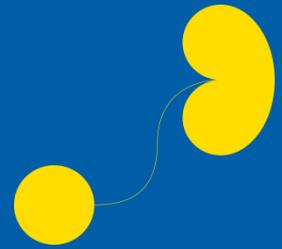
- Patients with eGFR equal to or greater than 60 ml/min/1.73 m<sup>2</sup> can continue to take metformin normally.
- Patients with eGFR is between 30 and 60 ml/min/1.73 m<sup>2</sup> :
  - A) Patients receiving intravenous contrast medium with eGFR equal to or greater than 45 ml/min/1.73 m<sup>2</sup> can continue to take metformin normally
  - B) Patients receiving intraarterial contrast medium and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m<sup>2</sup> should stop metformin 48 h before contrast medium and should only restart metformin 48 h after contrast medium if renal function has not deteriorated.
- Patients with eGFR less than 30 ml/min/1.73 m<sup>2</sup> or with an intercurrent illness causing reduced liver function or hypoxia. Metformin is contraindicated and iodinated contrast should be avoided.



# Guideline

## 2.1.2. Before the examination

### Emergency Examination



- If eGFR is greater than 60 ml/min/1.73 m<sup>2</sup> (or serum creatinine is normal), follow instructions for elective patients.
- If eGFR is between 30 and 60 ml/min/1.73 m<sup>2</sup> (or serum creatinine is raised) or unknown, weigh the risks and benefits of contrast medium administration and consider an alternate imaging method. If contrast medium is deemed essential take the following precautions:

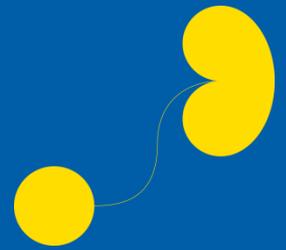
Diabetic patients taking metformin

- Metformin therapy should be stopped.
- The patient should be hydrated (e.g. at least 1 ml per hour per kg b.w. of intravenous normal saline up to 6 hours after contrast medium administration – In warm areas more fluid should be given).
- Monitor renal function (eGFR/serum creatinine), serum lactic acid and pH of blood.
- Look for symptoms of lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnea, lethargy, diarrhea and thirst). Blood test results indicative of lactic acidosis: pH  $\leq$  7.25 with plasma lactate  $\geq$  5 mmol/l.



# Guideline

## 2.1.3. Time of examination



In patients at increased risk of contrast medium induced nephropathy

- Use low- or iso-osmolar contrast media.
- Use the lowest dose of contrast medium consistent with a diagnostic result.

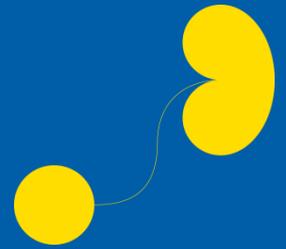
In patients with no increased risk of contrast medium induced nephropathy

- Use the lowest dose of contrast medium consistent with a diagnostic result.



# Guideline

## 2.1.3. Time of examination



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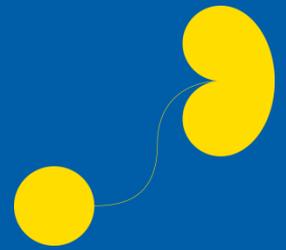
In patients with no increased risk of contrast medium induced nephropathy

- Use the lowest dose of contrast medium consistent with a diagnostic result.



# Guideline

## 2.1.4. After the examination



In patients with eGFR less than 60 ml/min/1.73 m<sup>2</sup> (or raised serum creatinine)

Continue hydration for at least 6 hours.

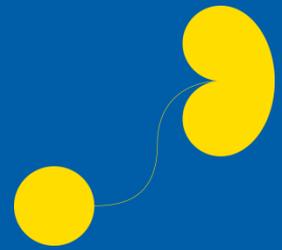
In diabetic patients taking metformin who have eGFR less than 60 ml/min/1.73 m<sup>2</sup>

Measure eGFR (or serum creatinine) at 48 hours after contrast medium administration. If it is not worsened, metformin can be restarted. Metformin is not approved in most countries in patients with abnormal renal function.



# Guideline

## 2.1.3. Time of examination



In patients with eGFR less than 60 ml/min/1.73 m<sup>2</sup> (or raised serum creatinine)

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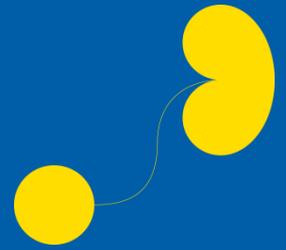
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# Renal impairment

## Your advice to the patient



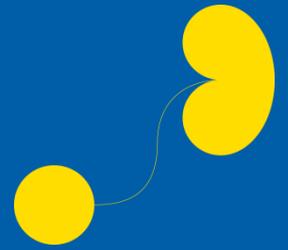
Nephrogenic systemic fibrosis

and

Contrast medium induced nephropathy



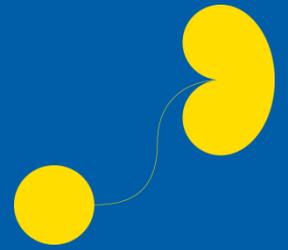
# Fact



We want to provide the patient with  
the best diagnostic service.



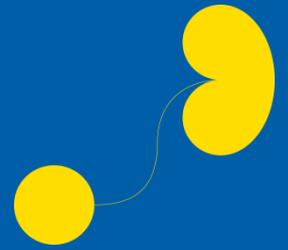
??



It is not only a question of the risk of CIN or NSF,  
but also the risk of **missing an important  
diagnosis**.



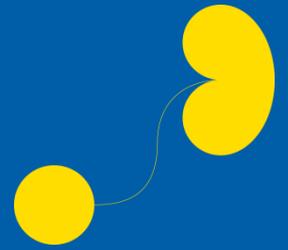
# Factors which must be taken into consideration



1. The diagnostic consequences of an inferior diagnostic work-up
2. Radiation, in particular in young patients
3. Prevalence of acute reactions
4. Prevalence of NSF and CIN
5. Associated morbidity and mortality with NSF and CIN



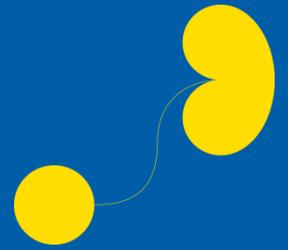
# Acute adverse reactions



**I-CA >> Gd-CA**



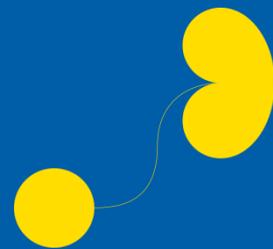
NSF



**What is the prevalence?**



# Incidence after a high-risk agent



Among patients with reduced renal function or on dialysis

**3 - 7 %\***

University of Copenhagen

University of Linda Loma

University of Wisconsin

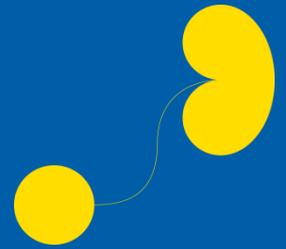
University of Glasgow

Connecticut

\* Based on registries – excludes the lower stages of NSF



# Incidence after a high-risk agent



Among patients with reduced renal function or on dialysis

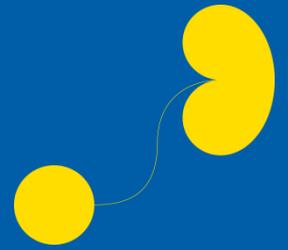
**18 %**

Based on inspection of skin and biopsy

All stages of NSF included



# NSF

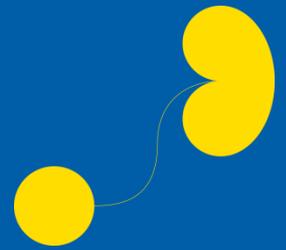


## Prevalence:

- Macrocyclic agents
  - Only three published unconfounded cases in the peer-reviewed literature following a large dose of Gadovist – **disagreement about whether the pathology is NSF**



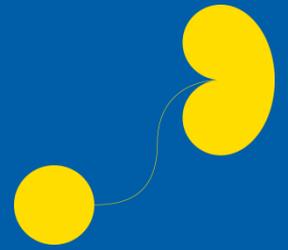
# NSF – morbidity & mortality



- NSF is associated with marked morbidity in the majority of cases.
- **24-month mortality** following examination was 48% and 20% in patients with and those without cutaneous changes of NSF, respectively.



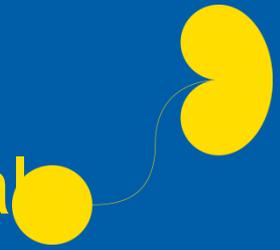
CIN



**What is the prevalence?**



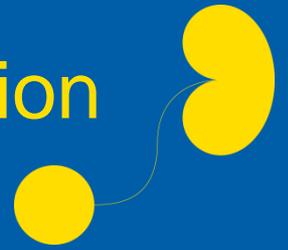
# CIN with head-to-head comparisons of risk patients receiving I.V. contrast material



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
Chuang (2009) (intravenous urography)	1/25 (iohexol)	1/25	25% ↑ SCr
<b>TOTAL</b>	22/425 (5.18%)	22/414 (5.31%)	NO DIFFERENCE



# Prevalence of CIN in CKD 5 after IV injection



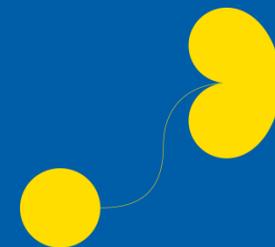
Unknown

Best guess: 10 - 15 %

**Very conservative guess**



# CIN is not only a temporary event



Adverse events in the follow-up period:

92 of 294 patients

CIN-group: 42%

Non-CIN-group: 26%

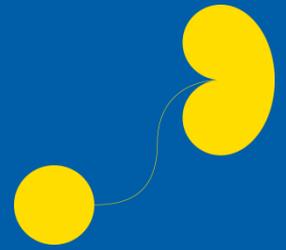
Major events

(death, stroke, myocardial infarction and ESRD requiring dialysis) in the follow-up period:

38 of 294 patients (13%)



# Conclusion

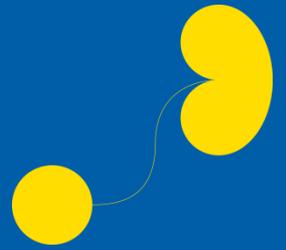


- All ICM have the potential of inducing CIN in patients with renal impairment.
- For patients with advanced renal impairment, it is crucially important to protect residual GFR to delay dialysis dependence.
- Protecting residual GFR in dialysis patients is also important.
  - Enhanced MRI with a low-risk NSF agent seems safer for a patient with severely reduced renal function or on replacement therapy with urine output than an enhanced CT with a non-ionic agent.

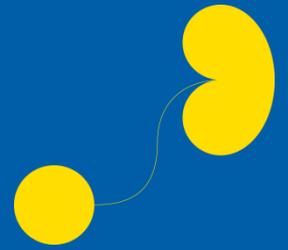


# Conclusion

- Only for dialysis patients with zero urine production, enhanced CT seems to be safer if it is diagnostically superior to MRI.



# Conclusion



It does not seem appropriate to deny a patient with reduced renal function a clinically well indicated enhanced MRI.

