Confidence in renal safety

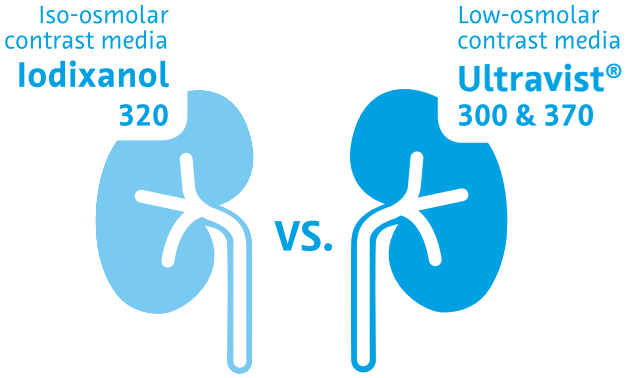
Clear Direction. From Diagnosis to Care.

Ultravist®
Iopromide

Confidence in renal safety with Ultravist®

- Ultravist® has a well proven general and renal safety profile including data from Asian populations.[1,2]
- The different concentrations available do not differ in their safety profile.[2]
- For renal safety, comparative studies with Ultravist® and meta-analysis of LOCM including Ultravist® showed no significant differences for patients with normal renal function as well as high-risk patients.[1, 3-8]

Comprehensive scientific and clinical evidence shows ...



... no significant difference in renal safety

Scientific Evidence Ultravist® vs. Iodixanol

INDIVIDUAL COMPARISION Ultravist® VS IODIXANOL*		
Chen et al. (2012)	Iodixanol 320 (N=284) Ultravist® 370 (N=278)	***NON-INFERIOR*** (p<0.001)
Bolognese et al. (2012)	Iodixanol 320 (N=236) Ultravist® 370 (N=239)	***NON-INFERIOR*** (p<0.0002)
Shin et al. (2011)	Iodixanol 320 (N=215) Ultravist® 300 (N=205)	***NO SIGNIFICANT DIFFERENCE*** (p=0.394)
Juergens et al. (2009)	Iodixanol 320 (N=91) Ultravist® 370 (N=100)	***NO SIGNIFICANT DIFFERENCE*** (p=0.56)
META-ANALYSES LOCM VS IODIXANOL		
Han et al. (2018)	Diabetic patients, 12 trials Iodixanol 320 (N=575) LOCM (N=525)	***NO SIGNIFICANT DIFFERENCE*** Subgroup analysis: Significant difference between Iohexol vs Iodixanol
From et al. (2010)	36 trials Iodixanol 320 (N=3,672) LOCM (N=3,494)	***NO SIGNIFICANT DIFFERENCE*** Subgroup analysis: Significant difference between Iohexol vs Iodixanol
Heinrich et al. (2009)	25 trials Iodixanol (N=1,701) LOCM (N=1,569)	***NO SIGNIFICANT DIFFERENCE*** Subgroup analysis: Significant difference between Iohexol vs Iodixanol

Fig 1: Overview of scientific evidence Iodixanol vs. Ultravist®

Recent scientific research with Ultravist® has led to a better understanding of renal safety and should be highly relevant for radiologists.[9]

AMACING investigations provide new insights into renal safety [9,10,12,13]

The recent AMACING trial, conducted with Ultravist®, was the first randomized trial prospectively comparing prophylactic i.v. hydration against non-hydration in renal impaired patients.[9] The data showed that: [9,10,12,13]

- Assuming optimal contrast administration, withholding i.v. hydration for patients with an eGFR 30-59ml/min/1.73m² (CKD 3) is safe.
- The incidence of post contrast acute kidney injury (PC-AKI)** showed no difference in both the prophylaxis and no-prophylaxis study arm (2.6% - 2.7%).
- I.v. hydration was not without risk by itself as 5.5% patients had complications associated with the prophylactic treatment.

AMACING trial demonstrated low post contrast acute kidney injury (PC-AKI) rate in both study arms[9,10]

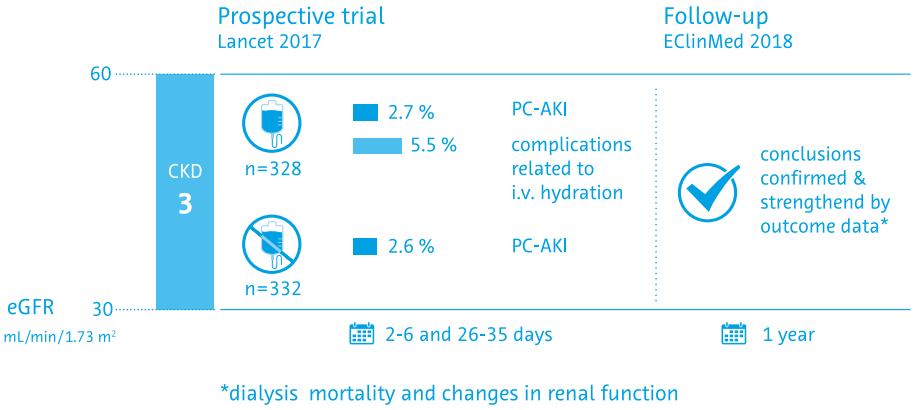


Fig 2: Renal results of the AMACING trial and one year follow-up

The authors concluded that CKD 3 patients do not benefit from prophylactic i.v. hydration and should no longer be considered high-risk.[9,10] These conclusions were confirmed in a one year follow-up.[10]

** Formerly termed contrast induced nephropathy (CIN)

Prevalence of CKD stages

- On a global scale, CKD 3 represents by far the largest group of patients with renal impairment.[11]

CKD stages and prevalences[11]

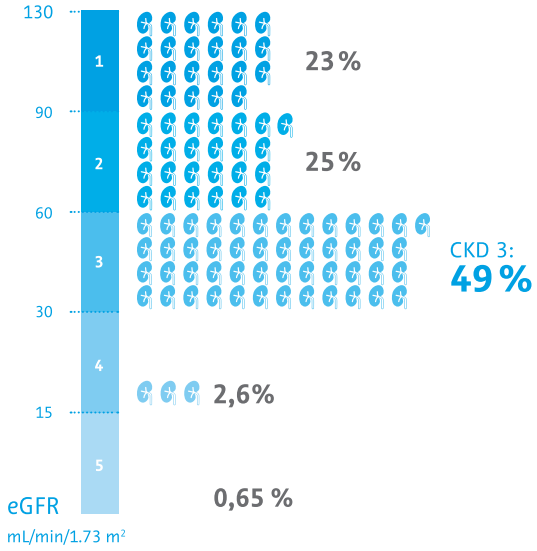


Fig 3: Global prevalences and their percentage distribution of the chronic kidney disease stages

The AMACING trial, conducted with Ultravist® and published in The Lancet, provided better understanding of renal safety and high-risk patients.[9]

AMACING – comprehensive data set on renal safety

For CKD 3 patients, a one year follow-up showed still no difference regarding renal safety between hydrated and non-hydrated patients.[10]

AMACING conclusions lead to a better understanding of renal safety[9,10,13]

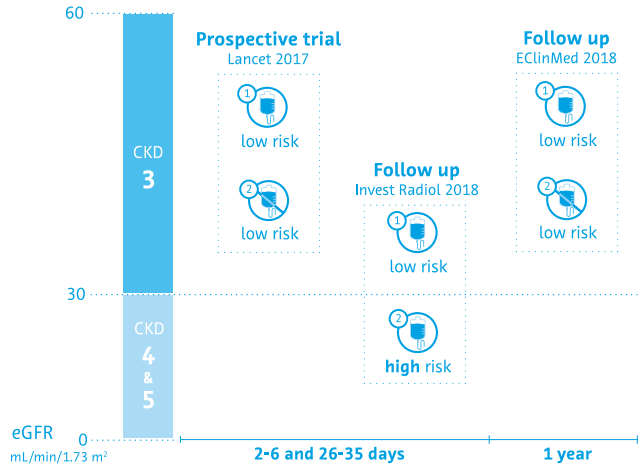


Fig 4: Overview of the AMACING trial and follow-up analyses

Looking at high-risk patients with an eGFR below 30 ml/min/1.73 m² (CKD 4 and 5):

- The data confirmed their significantly higher risk of post contrast acute kidney injury (PC-AKI).[12,13]
- Patients with CKD 4 and 5 need specific care. Benefits and risks of prophylaxis must be carefully weighed individually.[12]

Fewer patients classified as renal high-risk patients[14]

- The AMACING trial, conducted with Ultravist®, supported the re-definition of renal high-risk patients in the ESUR guidelines.[14] In ESUR 10, the threshold for the definition of renal high-risk changed from:
  - eGFR < 45 ml/min/1.73 m² to **eGFR < 30 ml/min/1.73 m²** before i.v. or i.a. contrast media administration with second pass renal exposure
  - eGFR < 60 ml/min/1.73 m² to **eGFR < 45 ml/min/1.73 m²** before i.a. contrast media administration with **first pass renal exposure or in ICU patients**
- This is in line with the ACR guidelines which also consider only patients with an eGFR below 30 ml/min/1.73 m² (CKD 4 and 5) with second pass renal exposure as high risk.[15]

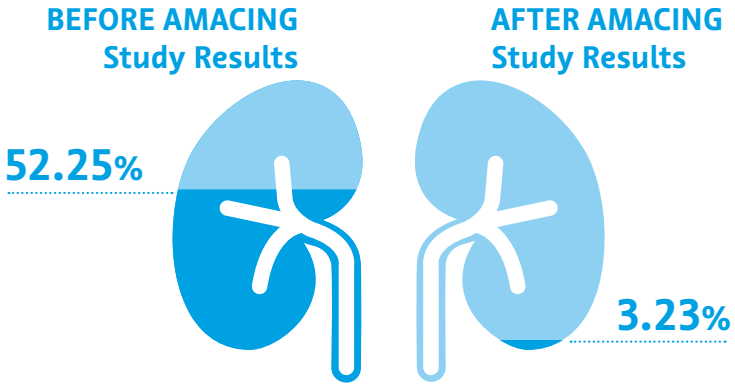


Fig 5: Comparison of patients who require i.v. hydration before and after applying the results of the AMACING study based on global prevalence of chronic kidney disease stages.[11]

U can have confidence in Ultravist®

- 30+ years on the market[16]
- 250+ million scans[16]
- 150k+ patients in studies[17,18]
- 100+ countries[16]

Over 250 million scans to date and 16 million examinations per year, as well as a well proven safety profile backed by 150.000 patients in observational studies[17,18], allow you to have confidence in Ultravist®.

The AMACING Trial, conducted with Ultravist®, and published in The Lancet provides important insights into renal safety.

Literature

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* CIN definitions of comparison studies

Study	CIN Definition
Chen et al. (2012)	SCr of ≥ 50 % from baseline at 72 h p.a.
Bolognese et al. (2012)	SCr ≥ 25 % from baseline till 72 h p.a.
Shin et al. (2011)	≥ 25 % or 0.5 mg/dl from baseline at 24 h or 48 h
Juergens et al. (2009)	≥ 25 % or 0.5 mg/dl from baseline at 48 h

SCr: Serum Creatinine; **p.a.:** post administration

Ultravist® (iopromide) Prescribing Information (Refer to package insert before prescribing) **Presentation:** Intravascular injections of nonionic iopromide in strengths of 300mg and 370mg of iodine/mL. Intravascular injections of nonionic iopromide in strengths of 300mg and 370mg of iodine/ml. **Indications:** For diagnostic use only. Delineation of the vascular and renal systems and of body cavities **Posology and administration:** ***Adults Intravenous urography:*** minimum doses: Ultravist 370: 0.8ml/kg body weight; Ultravist 300: 1ml/kg body weight. ***Children Intravenous urography:*** see package insert. ***Adults Computed tomography:*** Cranial CT: Ultravist 300: 1-max, 2ml/kg body weight; Ultravist 370:1-max, 1.5ml/kg body weight. Whole-body CT: Dosage and administration rate depend on investigation and scanner. ***Adults Angiography:*** depends on age, weight, cardiac output, general condition, clinical problem, examination technique and the nature and volume of the vascular region to be investigated. (see package insert). ***Paediatric population:*** young infants (age < 1 year) and especially newborns are susceptible to electrolyte imbalance and haemodynamic alterations. Care should be taken regarding the dose of contrast medium to be given, the technical performance of the radiologicalprocedure and the patient status. ***Renal impairment:*** to reduce the risk of additional contrast media-induced renal impairment in patients with pre-existing renal impairment, the minimum possible dose should be used (see package insert). ***Hepatic impairment:*** no dosage adjustment is necessary. ***Elderly:*** possibility of reduced renal function should be considered. **Contra-indications:** Uncontrolled thyrotoxicosis. **Warnings and precautions:** Can be associated with anaphylactoid/hypersensitivity reactions, ensure preparedness for institution of emergency measures. Allergy-like reactions from mild to severe possible, mostly within 30 min, but delayed reactions (hours to days) may occur. Particularly careful risk/benefit judgement required for patients with: known hypersensitivity to Ultravist or its excipients; previous reaction to any contrast medium or; history of bronchial asthma or allergic disorders (increased risk). Pre-medicate with corticosteroids if necessary. To minimise risk: administer Ultravist to recumbent patients; observe patients closely for 15 minutes and keep them in hospital for at least one hour after the last injection. Patients on beta-blockers may be resistant to the effects of beta agonists. If severe reaction occurs, patients withcardiovascular disease are more susceptible to serious or fatal outcomes. Caution in patients with: known/suspected hyperthyroidism or goitre, monitor thyroid function in neonates exposed via mother or during neonatal period. Caution in patients with cerebral arteriosclerosis, pulmonary emphysema, poor general health, renal insufficiency, dehydration, diabetes mellitus, multiple myeloma/ paraproteinaemia, repetitive and/ or large doses of Ultravist. Nephrotoxicity may occur or rarely acute renal failure. Ensure adequate hydration of patients; correct water or electrolyte imbalances before administration. With cardiac or severe coronary artery disease, increased risk of haemodynamic changes or arrhythmia. Intravascular injection may precipitate pulmonary oedema in patients with heart failure. Increased risk of neurological complications in patients with seizure historyor CNS disorders. Caution in patients with reduced seizure threshold. May aggravate the symptoms of myasthenia gravis. Flush intravascular catheters frequently with physiological saline (if possible with addition of heparin) and minimise procedure length to minimise procedure-related thromboembolism risk. Patients with phaeochromocytoma may be at increased risk of developing a hypertensive crisis. Minimise excitement, anxiety and pain. Do not use in myelography. Sensitivity testing is not recommended. **Interactions:** Consider interruption of biguanides treatment prior to Ultravist administration as a precaution against development of lactic acidosis. Prevalence of delayed reactions higher in patients who have received interleukin-2. Diagnosis and treatment of thyroid disorders with thyrotropic radioisotopes may be impeded for up to several weeks due to reduced radioisotope uptake. **Pregnancy and lactation:** Adequate and well-controlled studies in pregnant women have not been conducted. Safety for nursed infants has not been investigated. **Effects on ability to drive and use machines:** Driving or operating machinery is not advisable for 30 minutes after the last injection. **Undesirable effects:** Common: dizziness, headache, dysgeusia, blurred/disturbed vision, chest pain/ discomfort, hypertension, vasodilatation, vomiting, nausea, pain, injection site reactions (e.g. oedema, soft tissue injury post extravasation), feeling hot. Uncommon: Hypersensitivity/ anaphylactoid reactions (anaphylactoid shock, respiratory arrest, bronchospasm, laryngeal/pharyngeal/face oedema, tongue oedema, laryngeal/pharyngeal spasm, asthma, conjunctivitis, lacrimation, sneezing, cough, mucosal oedema, rhinitis, hoarseness, throat irritation, urticaria, pruritus, angioedema), vasovagal reactions, confusional state, restlessness, paraesthesia/ hypoaesthesia, somnolence, arrhythmia, hypotension, dyspnea, abdominal pain,oedema. Rare: Anxiety, cardiac arrest, myocardial ischemia, palpitations. Frequency not known: Thyrotoxic crisis, thyroid disorder, coma, cerebral ischaemia/infarction, stroke, brain oedemaa, convulsion, transient cortical blindness, loss of consciousness, agitation, amnesia, tremor, speech disorders, paresis/paralysis, hearing disorders, myocardial infarction, cardiac failure, bradycardia, tachycardia, cyanosis, shock, thromboembolic events,vasospasm, pulmonary edema, respiratory insufficiency, aspiration, dysphagia, salivary gland enlargement, diarrhoea, bullous conditions (e.g. Stevens-Johnson's or Lyell syndrome), rash, erythema, hyperhydrosis, compartment syndrome in case of extravasation, renal impairment, acute renal failure, malaise, chills, pallor, body temperature fluctuation. *These adverse reactions may have a fatal or life-threatening outcome and are considered the most serious adverse drug reactions. Prescribers should consult the SmPC in relation to other side effects. **Overdose:** Symptoms may include fluid and electrolyte imbalance, renal failure, cardivascular and pulmonary complications. Monitoring of fluids, electrolytes and renal function recommended in case of intravascular overdosage. Treatment of overdose should be directed towards the support of vital functions. Ultravist is dialysable. **Incompatibilities:** Because of possible precipitation, X-ray contrast media and prophylactic agents must not be injected as mixed solutions. **Special Precautions for Storage:** Protect from light and X-rays. **Date of revision of text:** April 2017. **Please note:** for current prescribing information refer to the package insert and/or contact your local Bayer HealthCare organization. **Bayer HealthCare Ltd.**14th Floor, Oxford House, Taikoo Place, 979 King's Road, Quarry Bay, Hong Kong.

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PP-ULT-HK-0065-1