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Iobitridol

Does iodine concentration influence diagnosis?

Comparative assessment of image quality for coronary CT angiography with iobitridol and two contrast agents with higher iodine concentrations: iopromide and iomeprol. A multicenter randomized double-blind trial. Achenbach, S., Paul, J.F., Laurent, F. et al. Eur Radiol (2016). doi:10.1007/s00330-016-4437-9.

OBJECTIVE | METHODOLOGY | ENDPOINTS | POPULATION | RESULTS | CONCLUSION

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OBJECTIVE

- To demonstrate non-inferiority in diagnostic efficacy of iobitridol (**Xenetix® 350**) for coronary CT angiography (CTA) compared to higher iodine content contrast media in terms of rate of patients with CT scans evaluable for the presence of coronary artery stenoses.

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METHODOLOGY

A non-inferiority, multicenter, randomized, double-blind, clinical trial

- Performed in 23 centers from 5 countries
- 468 patients clinically indicated for coronary CTA were included (58% male; mean age 57.8± 12.4 years)
- Randomized on a 1:1:1 ratio for injection of **Xenetix® 350**, Iopromide 370 or Iomeprol 400

Contrast Media administration

- Volume and delivery rate of CM was consistent for the three CM but varied according to patient body weight (BW)
- 60 ml injected at 4 ml/s for a BW <60 kg, 75 ml at 5 ml/s for a BW comprised between 60 and 80 kg, 90 ml at 6 ml/s for a BW>80 kg

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ENDPOINTS

Primary endpoint (offsite blinded reading)

- Rate of patients with evaluable CT scans allowing to identify or rule out coronary artery stenoses in all segments of the coronary tree with a reference diameter of 1.5 mm or more, using a 18 segment (SCCT) model and a 5-point scale

Secondary endpoints (offsite/onsite reading)

- Image quality score by averaging segment quality scores
- Arterial attenuation, signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR)
- Diagnostic efficacy (number of significant stenosis identified)
- Clinical safety

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POPULATION

	Xenetix® 350 (N=155)	Iopromide 370 (N=160)	Iomeprol 400 (N=153)	Total (N=468)
Age (years)	57.9±12.2	58.7±11.6	56.9±13.4	57.8±12.4
Male gender	90 (58.1%)	92 (57.5%)	88 (57.5%)	270 (57.7%)
Body weight (kg)	78.7±15.4	76.6±16.9	77.3±14.0	77.5±15.5

- No differences were noted in terms of requirement of beta-blockers for the CTA procedure, calcium score and radiation dose.
- No significant differences between the three groups in terms of demographics, clinical symptoms, risk factors and pre-CTA heart rate.

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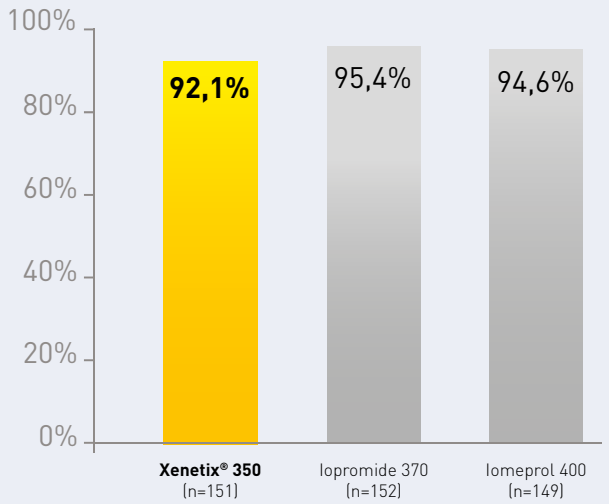
RESULTS
Primary endpoint (1/2)

Rate of patients with evaluable CT scans

- The rate of patients with fully evaluable CT scans was similar in the 3 groups
- Non-inferiority of **Xenetix® 350** versus the best of the two comparators, Iopromide 370, 95%CI [-8.8%; 2.1%] was demonstrated

Patients with fully evaluable CT scans



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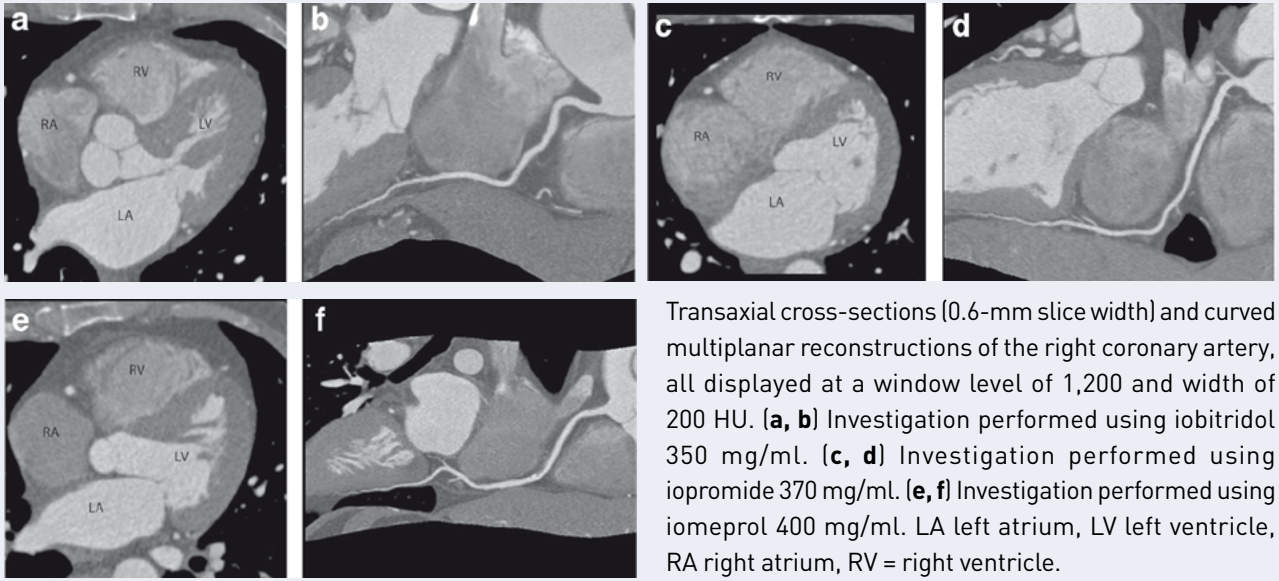
RESULTS
Primary endpoint (2/2)



Transaxial cross-sections (0.6-mm slice width) and curved multiplanar reconstructions of the right coronary artery, all displayed at a window level of 1,200 and width of 200 HU. (**a, b**) Investigation performed using iobitridol 350 mg/ml. (**c, d**) Investigation performed using iopromide 370 mg/ml. (**e, f**) Investigation performed using iomeprol 400 mg/ml. LA left atrium, LV left ventricle, RA right atrium, RV = right ventricle.

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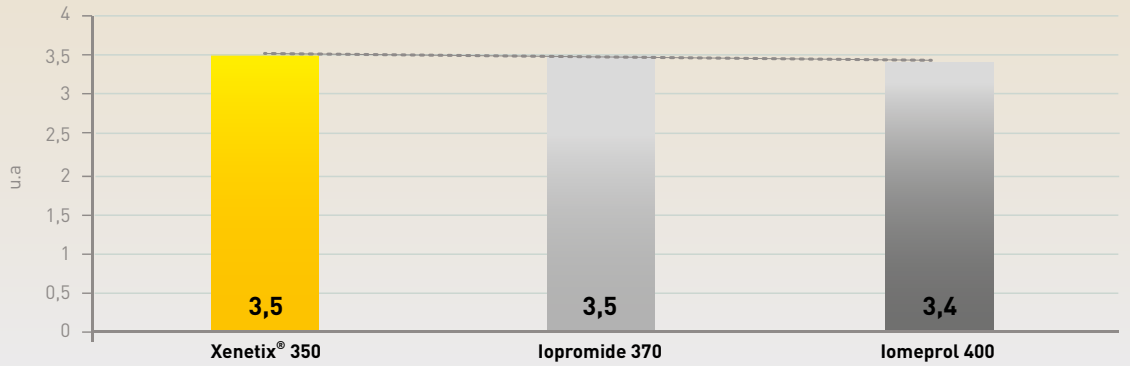
RESULTS
Secondary endpoints (1/3)

Similar image quality with a lower iodine content

- Non-inferiority of **Xenetix® 350** for image quality per segment (p>0,05)
- **Xenetix® 350** provides excellent image quality to identify or rule out coronary artery stenoses in all segments of the coronary tree (73.3%)

Average image quality



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RESULTS
Secondary endpoints (2/3)

Lower intravascular attenuation with lower iodine concentrations

Xenetix® 350	Iopromide 370	Iomeprol 400
426.3 ± 92.9	449.8 ± 88.1	466.4 ± 104.6

All values are expressed as Hounsfield Units (HU) with mean and standard deviation.

- Average post-contrast arterial vascular attenuation shows a trend towards higher attenuation with higher iodine concentrations

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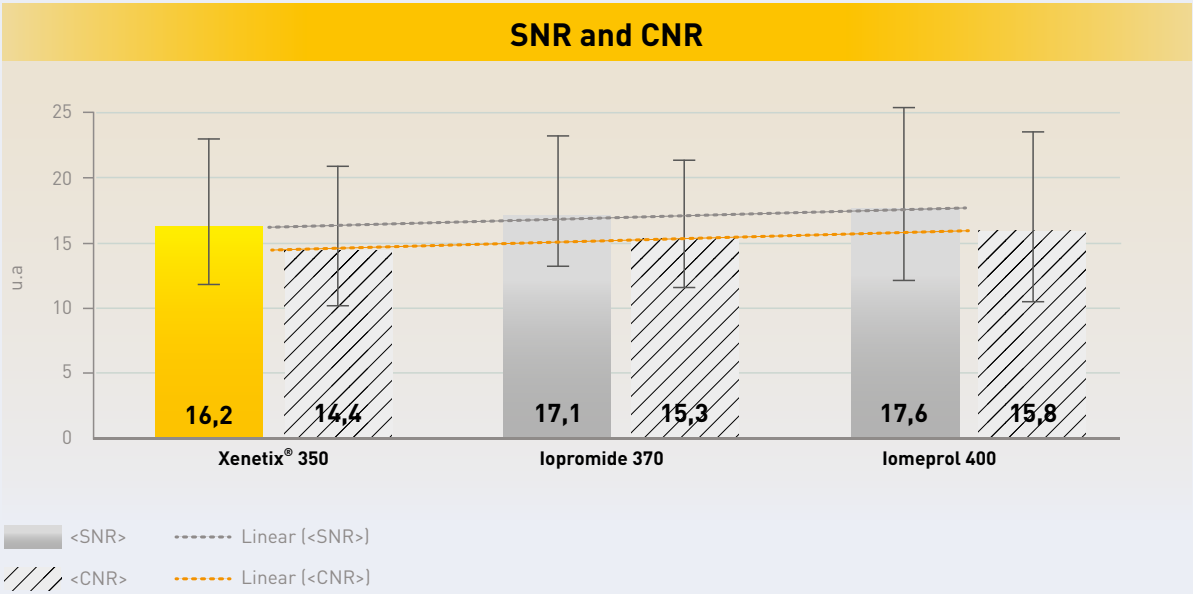
RESULTS
Secondary endpoints (2/3)

Similar values for SNR and CNR which reflect image quality and sharpness

- **Xenetix® 350** yielded similar values as Iopromide 370 and Iomeprol 400 when considering average SNR and CNR values
- No statistical difference between groups for measurements of noise in the ascending aorta (p=0.311)



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RESULTS
Secondary endpoints (3/3)

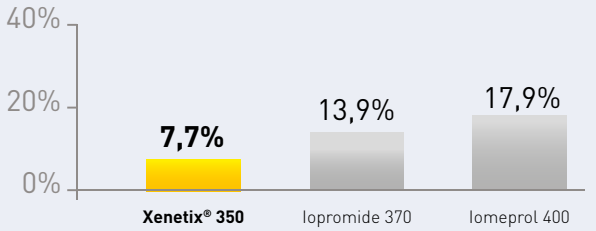
Optimum stenosis assessment

- No difference was observed regarding the number of significant stenoses identified between groups (p = 0.580)

Excellent safety profile

- **Xenetix® 350** was associated with the lowest incidence of related AEs (2 patients).
- No severe nor moderate AEs post CM-injection were reported with **Xenetix® 350**

Patients experiencing post CM-injection AEs



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CONCLUSION

Xenetix® 350 was not inferior to contrast media with higher iodine concentrations (Iopromide 370 and Iomeprol 400) in terms of image quality for coronary stenosis assessment.

Xenetix® 350, a Low Osmolar Contrast Medium, allows improving image quality while minimizing the amount of iodine injected, and the potential risk of adverse reactions, as supported by its excellent safety profile.

Patients can benefit from the technology development improving image quality while using contrast media with lower iodine concentrations such as **Xenetix® 350**.

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(*) For complete information please refer to the local Summary of Product Characteristics

(**) Indications, volumes and presentations may differ from country to country.

Xenetix® 350, solution for injection (350 mgI/ml) ; **Xenetix® 300**, solution for injection (300 mgI/ml) ; **Xenetix® 250**, solution for injection (250 mgI/ml) – **Composition per 100 ml** : **Xenetix® 350:** 76.78 g of iobitridol (corresponding to 35 g of iodine), **Xenetix® 300** : 65.81 g of iobitridol (corresponding to 30 g of iodine), **Xenetix® 250:** 54.84 g of iobitridol (corresponding to 25 g of iodine) - **Indications(**):** this product is for diagnostic use only. **Contrast agent for use in: Xenetix® 350** intravenous urography, whole body and cranial computed tomography, intravenous digital subtraction angiography, arteriography, angiocardiography, Sialography, Endoscopic retrograde cholangiopancreatography – **Xenetix® 300:** intravenous urography, whole body and head computed tomography, intravenous digital subtraction angiography, arteriography, angiocardiography, endoscopic retrograde cholangiopancreatography, arthrography, hysterosalpingography, herniography – **Xenetix® 250:** phlebography, whole body computed tomography, intra-arterial digital subtraction angiography, arteriography, endoscopic retrograde cholangiopancreatography – **Posology and method of administration(*):** the doses should be adapted to the examination and the territories intended to be opacified, as well as to the weight and renal function of the subject, particularly in children. –

Contraindications (*): hypersensitivity to iobitridol or any of the excipients, history of major immediate or delayed skin reaction (see undesirable effects) to **Xenetix®**, manifest thyrotoxicosis, hysterosalpingography during pregnancy. –

General comments for all iodinated contrast agents (*): There is a risk of allergic reactions regardless of the route of administration or the dose. In the absence of specific studies, myelography is not an indication for **Xenetix®**. All iodinated contrast media can cause minor or major reactions that can be life-threatening. They may occur immediately (within 60 minutes) or be delayed (within 7 days) and are often unpredictable. Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use - Before administering an iodinated contrast agent, it is important to ensure that the patient is not scheduled to undergo a scintigraphic examination or laboratory tests related to the thyroid or to receive radioactive iodine for therapeutic purposes. Administration of contrast agents via any route disrupts hormone concentrations and iodine uptake by the thyroid or by metastases of thyroid cancer, until urine iodine levels have returned to normal. Extravasation is a non-exceptional complication (0.04% to 0.9%) of intravenous injections of contrast media. More frequent with the high osmolar products, most of the injuries are minor, however severe injuries such as skin ulceration, tissue necrosis, and compartment syndrome may occur with any iodinated contrast medium. The risk and/or severity factors are patient-related (poor or fragile vascular conditions), and technique-related (use of a power injector, large volume). It is important to identify these factors, optimize the injection site and technique accordingly, and monitor the injection prior to, during and after the injection of **Xenetix®** –

Special warnings and precautions for use (*): For at risk patients with:1) Intolerance to iodinated contrast agents: Prior the examination, at-risk patients should be identified by a precise screening of histories. During the procedure, the medical surveillance and permanent venous access must be maintained. After the examination the patient must be monitored for at least 30 minutes, since most serious adverse reactions occur within this time period and the patient must be informed of the possibility of delayed reactions (for up to seven days), 2) Severe cutaneous adverse reactions: At the time of initiation patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. Xenetix should be discontinued immediately upon suspicion of a severe hypersensitivity reaction. If the patient has developed a severe cutaneous adverse reaction with the use of **Xenetix®**, **Xenetix®** must not be re-administered in this patient at any time, 3) Renal insufficiency and/or hepatic insufficiency: Care should be taken in renal or hepatic impairment, diabetes or in patients with sickle cell disease, adequate hydration should be ensured in all patients before and after contrast media administration and particularly in patients with renal impairment or diabetes. 4) Asthma: Stabilisation of asthma is recommended before the injection of an iodinated contrast agent. Due to an increased risk of bronchospasm, special caution should be taken in patients do to suffered an asthmatic attack within eight days prior to the examination. 5) Dysthyroidism: After iodinated contrast agent injection, particularly in patients with a goitre or a history of dysthyroidism, there is a risk either of a flare-up of hyperthyroidism or development of hypothyroidism. There is also a risk of hypothyroidism in neonates who have received, or whose mother has received, an iodinated contrast agent. Therefore, thyroid function in such neonates should be evaluated and closely monitored to ensure thyroid function is normal. 6) Cardiovascular diseases: Careful weighing up of the risk-benefit ratio is necessary in these patients. 7) Central nervous system disorders: The benefit-to-risk ratio must be evaluated for each case: due to the risk of aggravation of neurological symptoms in patients with a transient ischaemic attack, acute cerebral infarct, recent intracranial haemorrhage, cerebral oedema, or idiopathic or secondary (tumour, scar) epilepsy and if the intra-arterial route is used in an alcoholic patient (acute or chronic alcoholism) and other drug-addicted subject. 8) Pheochromocytoma: Patients with pheochromocytoma may develop a hypertensive crisis after intravascular administration of a contrast agent and must be monitored prior to the examination. 9) Myasthenia: Administration of a contrast agent may worsen the symptoms of myasthenia gravis.10) Intensification of side effects: Adverse reactions related to iodinated contrast agent administration may be intensified in patients showing pronounced agitation, anxiety and pain. Appropriate management such as sedation may be necessary.

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Xenetix is part of UNIK, our solutions for Diagnostic Imaging

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Tailored interconnected solutions driving your journey to excellence

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Warnings and precautions for use specific to certain administration routes with appreciable systemic diffusion (*): - Products administered via the intra-uterine route (Xenetix® 300): Contraindication: Pregnancy for hysterosalpingography-Special precautions for use: In the interview and with appropriate tests, systematically check for possible pregnancy in women of childbearing age. Exposure of the female genital routes to x-rays must be subject to careful evaluation of the benefit-to-risk ratio. In the event of inflammation or acute pelvic infection, hysterosalpingography can only be performed after a careful assessment of the benefit-to-risk ratio. - Risk of acute pancreatitis in the context of endoscopic retrograde pancreatography **-Interaction with other medicinal products and other forms of interaction (*):** beta-blocker substances, diuretics, metformin, radiopharmaceuticals, interleukin 2
Fertility, pregnancy and lactation (*)
Undesirable effects(*): Uncommon (≥1/1000 to <1/100): nausea, feeling hot - Rare (≥1/10 000 to <1/1 000): hypersensitivity, presyncope, tremor, paresthesia, vertigo, tachycardia, bradycardia, hypotension, dyspnoea, cough, throat tightness, sneezing, vomiting, angioedema, urticaria, erythema, pruritus, facial oedema, malaise, chills, injection site pain - Very rare (<1/10 000): anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, thyroid disorder, coma, seizure, confusional state, visual pathway disorders, amnesia, photophobia, blindness transient, somnolence, agitation, headache, hypoacusis, cardiac arrest, myocardial, infarction (more frequent after intracoronary injection), arrhythmia, ventricular fibrillation, angina pectoris, torsades de pointes, coronary arteriospasm, circulatory collapse, respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, laryngeal oedema, abdominal pain, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, eczema, rash maculo-papular (all as delayed hypersensitivity reactions), acute kidney injury, anuria, injection site necrosis following extravasation, injection site inflammation following extravasation, injection site oedema, blood creatinine increased - Not known: transient neonatal hypothyroidism, dizziness, cyanosis, hypertension, drug reaction with eosinophilia and systemic symptoms (DRESS) - Compartment syndrome may be observed following extravasation
Overdose (*) – Pharmacodynamic properties (*): Pharmacotherapeutic group: Water-soluble, nephrotropic radiology contrast medium with low osmolarity; ATC code: V08AB11. **Presentation (**): Xenetix® 250:** 50 ml, 100 ml, 200 ml or 500 ml glass vials, **Xenetix® 300/350:** 20 ml, 50 ml, 60 ml, 75 ml, 100 ml, 150 ml, 200 ml or 500 ml **glass vials and 100 ml, 150 ml, 200 ml or 500 ml polypropylene bags. Marketing authorisation holder (*): Guerbet - BP 57400 - F-95943 Roissy CdG cedex – FRANCE. Information:** tel: 33 (0) 1 45 91 50 00. **Revision:** January 2021.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

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