Observational Study / Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	UVIA: Risk of anaphylactoid reactions of Iopromide after intra-arterial administration
Report version and date	v 1.0, 11 July 2019
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS25089
Active substance	Radiological / Low Osmolar non-ionic Contrast Medium (LOCM), (V08AB05) Iopromide
Medicinal product	Iopromide
Study Initiator and Funder	Bayer AG
Research question and objectives	To describe the risk of anaphylactoid reactions of Iopromide after intra-arterial administration and to put these results into perspective to intra-venous administration.
Country(-ies) of study	Not applicable
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG

Table of contents ..... Error! Bookmark not defined.

1. Abstract

Acronym/Title	UVIA: Risk of anaphylactoid reactions of Iopromide after intra-arterial administration
Report version and date **Author**	v 1.0, 11 July 2019 [redacted]
Keywords	Contrast Medium, Radiology, Iopromide, anaphylactoid reactions
Rationale and background	The safety profile of Iopromide and all other iodinated contrast media is well understood, there is a continuous discussion pertaining to the nature of anaphylactoid reactions which are unpredictable. Since anaphylactoid reactions are rare only a retrospective analysis on a large database bears the potential of answering this scientific question.
Research question and objectives	Evaluate the risk of anaphylactoid reactions of Iopromide after intra-arterial administration compared to intravenous administration.
Study design	The study was designed to investigate the risk of anaphylactoid reactions to Iopromide after intra-arterial versus intra-venous administration.
Setting	In this integrated analysis the data of four company sponsored non-interventional studies 'PMS I', 'Ultravist in CT', 'IMAGE' and 'TRUST' were pooled.
Subjects and study size, including dropouts	About 122,000 records of patients with intra-venous and approx. 28,000 patients with intra-arterial administration were expected for evaluation.
Variables and data sources	The primary variables to answer the study objectives were the number and percentage of anaphylactoid reactions which were documented by pooling data of four company sponsored non-interventional studies with iopromide.
Results	Anaphylactoid reactions were significantly more frequently recorded after i.v. than after i.a. administration, 0.7 % vs 0.2%, respectively ($p < 0.0001$). Adjusted Odds ratio (i.a. vs. i.v.) was

	0.23 (95 % C.I. 0.16 - 0.32) for all countries together. For China only: 0.22 (0.11 - 0.44); for all countries without China: 0.36 (0.25 - 0.53). The most frequent anaphylactoid reactions were skin reactions (erythema, urticaria, rash), reported in 508/133,331 patients (0.4%), followed by pruritus (n=294; 0.2%), cough/sneezing (n=151; 0.1%) and dyspnea/bronchospasm (n=105; <0.1%). Clinically relevant severe adverse reactions like anaphylactic shock, laryngeal edema and respiratory arrest were recorded once each (Table 5, Figure 2).
Discussion	This study showed anaphylactoid reactions to be significantly more frequent after i.v. than after i.a. administration, 0.7 % vs 0.2% (p<0.0001), respectively. This risk difference remained even after adjustment for potential confounders. Also the specific symptoms, i.e., erythema/urticarial/rash, pruritus, cough/sneezing and dyspnea/bronchospasm were more often seen after i.v. administration. To the best of our knowledge, this has not been shown before in a large cohort study, and confirms a hypothesis concerning the nature and patho-mechanisms of these reactions.
Marketing Authorization Holder(s)	Bayer AG

2. List of abbreviations

AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
EC	European Commission
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
GPV	Global Pharmacovigilance
GSL	Global Safety Leader
HEOR	Health Economics and Outcomes Research
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
N/A	Not Applicable
OS	Observational Study
OSP	Observational Study Protocol
OSR	Observational Study Report
PASS	Post-Authorization Safety Study
PBRER	Periodic benefit-risk evaluation report
PMCF study	Post Market Clinical Follow-up study
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

3. Investigators

Not applicable for retrospective pooled integrated analysis of four non-interventional studies.

4. Other responsible parties

The study was supported by the CRO Parexel.

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection / observation	Jan 2018	Sept 2018	
End of data collection / observation	July 2018	27 Feb 2019	
Registration in the EU PAS register	-	July 2018	
Final report of study results	Dec 2018	11 July 2019	

6. Rationale and background

The purpose of the study was to investigate the risk of anaphylactoid reactions to iopromide after i.a. administration compared to i.v. administration to evaluate the hypothesis that the incidence of these reactions depends on the route of administration and thus an earlier or later lung passage. As ICMs reach the lung earlier and at a higher concentration after i.v. compared to i.a. administration, the trigger on mast cells and basophils to release histamines and other vasoactive substances and consequently cause anaphylactoid reactions is assumed to be more pronounced (Schild).

7. Research question and objectives

Given the large amount of observational study patient data available to Bayer for Ultravist both after IV and after IA administration, can it be shown that the rate of anaphylactoid reactions varies according to the route of administration.

Therefore, the primary objective was to evaluate the risk of anaphylactoid reactions of Iopromide after intra-arterial administration compared to intravenous administration. This included the evaluation of specific patient group with higher or lower risk.

The following research questions were secondary objectives:

1. Assess the proportion of patients with anaphylactoid reactions after intra-arterial administration of Iopromide
2. Assess the proportion of patients with anaphylactoid reactions after intra-venous administration of Iopromide
3. Assess the impact of pretreatment with histamines and/or corticosteroids
4. Evaluate the general ADR profile in the analysis population.

8. Amendments and updates

Not applicable.

9. Research methods

9.1 Study design

The study design was a nested case-control design applied on a pool of four large observational studies.

9.2 Setting

In this integrated analysis the data of four company sponsored non-interventional studies with Iopromide in contrast-enhanced X-ray examination were pooled (for publications on these studies please refer to 'source studies' in reference list). The pool consisted of studies 'PMS I', 'Ultravist in CT', 'IMAGE', and 'TRUST'. In the year 2010, the three studies 'PMS I', 'Ultravist in CT' and 'IMAGE' were pooled and the general ADR profile was analyzed. The 'TRUST' study conducted purely in catheter labs in China enriches the intra-arterial administration group.

The four studies were all sponsored by Bayer or Schering. They comprise all available prospective observational studies with primary data collection performed with Iopromide.

These were:

- 'PMS I' was conducted in contrast-enhanced X-ray examination between June 1999 and November 2003 in 27 countries in Europe, Africa and Asia and comprised 74,717 patients (Kopp 2008) of which 65,452 patients received intra-venous and 8,368 patients intra-arterial administration.
- 'Ultravist in CT' was performed with focus on contrast-enhanced CT examination (intra-venous application) between November 2006 and December 2008 and included 15,168 patients in Germany, Iran, Romania and Saudi Arabia (Palkowitsch 2014).
- 'IMAGE' consists of 44,835 patients with contrast-enhanced X-ray examination and was conducted in 21 European and Asian countries from February 2008 to September 2009 (Palkowitsch 2012), 41,703 patients received intra-venous administration, and 2,782 patients with intra-arterial administration.

- 'TRUST' assessed the safety and tolerability of Iopromide in patients undergoing cardiac catheterization (intra-arterial administration). It was conducted from August 2010 to September 2011 in China and included 17,513 patients (Chen 2015).

The pooled integrated analysis was performed with the support of the CRO Parexel from November 2018 till February 2019.

9.3 Subjects

Four company-sponsored observational studies on iopromide were pooled and analyzed comprising a total of 152,233 patients. PMS I (n=74,717), IMAGE (n=44,835), TRUST (n=17,513) and Ultravist in CT (n=15,168). While PMS I and IMAGE included patients with i.v. and i.a. injection, TRUST only included i.a. patients and Ultravist in CT only i.v. patients (Table 2).

For these studies Institutional Review Board / Ethics Committee approvals and patient informed consents were obtained from participating countries. This voluntary Post-Authorization Safety Study (PASS) was registered at ClinicalTrials.gov (NCT03622801) and at ENCePP (EUPAS25089).

For the purpose of study pooling the data anonymization was increased to eliminate all potential links to patient charts. For example, the original site and patient identifiers were replaced by random numbers and all free text was eliminated. For adverse events, only MedDRA coded terms were stored.

Table 2 Essentials of pooled studies

Study name	Countries	Study Duration	Intravenous Injection (N=105,460)	Intra-arterial Injection (N=27,871)	Cases (N=822)	Controls (N=132,509)	Total (N=133,331)
PMS I	27 countries in Europe, Africa and Asia	6/1999 – 11/2003	55,470 (52.6%)	7,581 (27.2%)	353 (42.9%)	62,698 (47.3%)	63,051 (47.3%)
IMAGE	21 countries in Europe and Asia	2/2008 - 11/2009	35,903 (34.0%)	3,016 (10.8%)	343 (41.7%)	38,576 (29.1%)	38,919 (29.2%)
TRUST	China	8/2010- 11/2011	---	17,274 (62.0%)	16 (1.9%)	17,258 (13.0%)	17,274 (13.0%)
Ultravist in CT	Germany, Iran, Romania, Saudi Arabia	11/2006 – 12/2008	14,087 (13.4%)	---	110 (13.4%)	13,977 (10.5%)	14,087 (10.6%)

9.4 Variables

Cases were defined as patients with a typical and unequivocal anaphylactoid, i.e., allergy-like reaction: Anaphylactoid shock, angioedema, asthma, bronchospasm, conjunctivitis, cough, dysphagia, dyspnea, edema mucosal, erythema/exanthema/rash, hoarseness, lacrimation, laryngeal/pharyngeal/face edema, laryngeal/pharyngeal spasm, nasal stuffiness, pruritus/itching, respiratory arrest, rhinitis, sneezing, stridor, swelling (eyes/face), throat irritation, tongue edema, urticaria/hives/blisters, wheezing (He et al.).

All cases were considered as drug related, irrespective of the investigators' judgement, i.e. the most conservative approach for drug relationship to anaphylactoid event was chosen. Controls were defined as subjects in which no adverse event was reported. Unspecific reactions (e.g. headache, nausea) and possibly procedure-related reactions (e.g. drop in blood pressure, bradycardia,

tachycardia) were excluded from the cases and from the controls, to avoid misclassification and confounding by the procedure performed.

9.4.1 Target variables

The primary target variable were the number and proportion of patients an anaphylactoid reaction after i.a. vs i.v. administration of iopromide.

Secondary target variables pertained to assessing the impact of pretreatment with antihistamines/corticosteroids and to evaluate the profile of reactions within each route of administrations.

9.5 Data sources and measurement

The study was conducted by pooling data of four company sponsored non-interventional studies with iopromide.

A pool of three of the four studies were prepared in 2010 (Palkowitsch et al. 2014). It contained the studies 'PMS I', 'Ultravist in CT' and 'IMAGE'. The 'TRUST' study was added to the existing pool. Variables were mapped to the corresponding variables in the existing pool. Categories (technically displayed in code lists) were modified as necessary. A Data Management Report (DMR) was prepared which describes rules and decisions which were made during the preparation of the mapping. No data correction was performed.

During data integration, the MedDRA coding of adverse event was updated to the same most current MedDRA version, which was version 21.0.

Procedures for the anonymization of the database were implemented e.g. patient identifies from the original studies were replaced by randomly generated identifiers, birth dates were replaced by year only, patient initials, investigator site identifiers and verbatim texts for adverse events were eliminated. The data changes are listed in a self-evident correction list that is attached to the Data Management Report.

9.6 Bias

This was an integrated analysis on pooled data from four non-controlled, multi-center, observational cohort studies. The four studies were conducted in different years and in different countries and geographic regions all over the world. Nearly 45% of the pooled patients were enrolled in Europe and a group of 45% of the observed patients were enrolled in China. Geographical and cultural differences in the reporting of adverse events were possible.

Since i.a. administrations of contrast agents can result in procedure related adverse reactions (e.g. blood pressure drop, arrhythmia, dizziness, nausea) some of which can also be symptoms of anaphylactoid reactions, the case definition in the present study is restricted to typical and unequivocal cases of anaphylactoid reactions which cannot be caused by the catheterization procedure. This restriction to typical anaphylactoid reactions removed confounding by indication and should yield a valid odds ratio estimate in the nested case-control analysis.

Statistical adjustment for country / geographic region may be limited by the fact that more than half of exposures in i.a. administration stems from one study only conducted in one country (China). Thus sensitive analyses were conducted to assess the impact of China.

Since the observation time of the patients in the observational studies used in this analysis was 30-60 minutes after the procedure, late-onset anaphylactoid reactions occurring hours or days after injection were not captured.

9.7 Study size

About 122,000 records of patients with intra-venous and approx. 28,000 patients with intra-arterial administration were expected for evaluation. The sample size was determined by the available data from the four studies that were analyzed.

In the previous pooled analysis of three non-interventional studies with Iopromide (Palkowitsch et al. 2014) the incidence of drug-related erythema, urticarial and rash was 0.3%. Using this result as the assumption for the integrated analysis, the 95% confidence interval of this specific ADR in the entire pool of about 150,000 patients was [0.27%; 0.33%]. Assuming an equal incidence rate for both administration groups, the 95% CI would be [0.27%; 0.33%] for patients with intra-venous administration, and [0.24%; 0.37%] for patients with intra-arterial administration which would be considered sufficiently precise.

9.8 Data transformation

During the mapping of the four studies, categories of variables were harmonized. For example, categories which described the same concomitant disease but with different terms were mapped to the same category. All data transformations were described in the Data Management Report.

9.9 Statistical methods

Statistical analyses were of exploratory and descriptive nature only. No confirmatory hypothesis tests were performed. In case that statistical test was performed p-values have to be interpreted as a metric for uncertainty. Therefore no adjustment for multiplicity was necessary.

The analysis population consisted of all patients of the study pool which received an injection (intra-arterial or intra-venous) with Iopromide of the iodine concentrations of 300 mg/mL or 370 mg/mL at the discretion of the Radiologist, and without missing information about age or sex. A disposition table was prepared to describe the number of patients which were not valid for analysis.

All statistical details including calculated variables and proposed format and content of tables, listings and figures were detailed in the Statistical Analysis Plan (SAP). The SAP was finalized before the analysis started.

9.9.1 Main summary measures

All variables were analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables were described by absolute value and as change from baseline, if applicable. Results were presented by type of Iopromide administration (intra-arterially and intravenously).

Background data such as subject demographics, specific concomitant diseases, specific risk factors like previous moderate or severe acute reaction to an iodine-base contrast agent, unstable asthma, atopy requiring medical treatment, pre-medication, examination region, type of examination and indication for the application of Iopromide were described by means of summary statistics.

Concentration of Iopromide was summarized and total dose of Iopromide applied was calculated for each patient (ml and g iodine).

9.9.2 Main statistical methods

In order to address the primary objective, cases of anaphylactoid reactions and controls were identified as described in section 9.4.The exposure variable of interest is defined as i.a. administration vs. i.v. administration of Iopromide. A crude odds ratio with 95 % CI of the risk of anaphylactoid reactions for i.a. vs. i.v. administration was calculated in the case-control analysis.

Furthermore, unconditional, univariate logistic regression models were computed to identify relevant covariates (e.g. history of allergy, premedication etc.) and potential confounder. A covariate was considered as important when its effect, represented by a descriptive p-value, was below 0.1. Age and sex were always included as a covariate. Subsequently, the covariates identified in the univariate regression models were brought together in a multivariate logistic regression model in order to identify the individual effect on the occurrence of anaphylactoid reactions. No matching on confounders were performed in the case-control analysis.

The topics of the secondary objectives were evaluated by means of frequency and summary tables.

9.9.3 Missing values

In general, subjects with missing data in variables needed for a specific model for the analysis of the primary variable were excluded for this model only. Subjects with missing age or sex were excluded from all analyses. No imputation was done.

9.9.4 Sensitivity analyses

The primary analysis showed a strong influence of China as geographical region. Therefore, additional logistics regressions were performed on the integrated data without Chinese patients as well as only on Chinese patients to assess the impact of this region.

9.9.5 Amendments to the statistical analysis plan

The SAP was amended one time. The first SAP was released on 15-NOV-2018. Version 2.0 was released on 30-NOV-2018. This was prior the start of the analysis. The SAP was updated to account the analysis population for missing information about patient's age or sex.

In addition, the analyses mentioned in section 9.9.4 were performed as post-hoc analyses.

9.10 Quality control

Data quality relied on the source data of the integrated observational studies. The data in these studies were captured by paper or electronic CRFs. No checks for multiple documented patients were done because multiple documentation was unlikely given the different years and regions where the studies were conducted.

CRO Parexel was responsible for data integrity and quality controls of the biometrical evaluation.

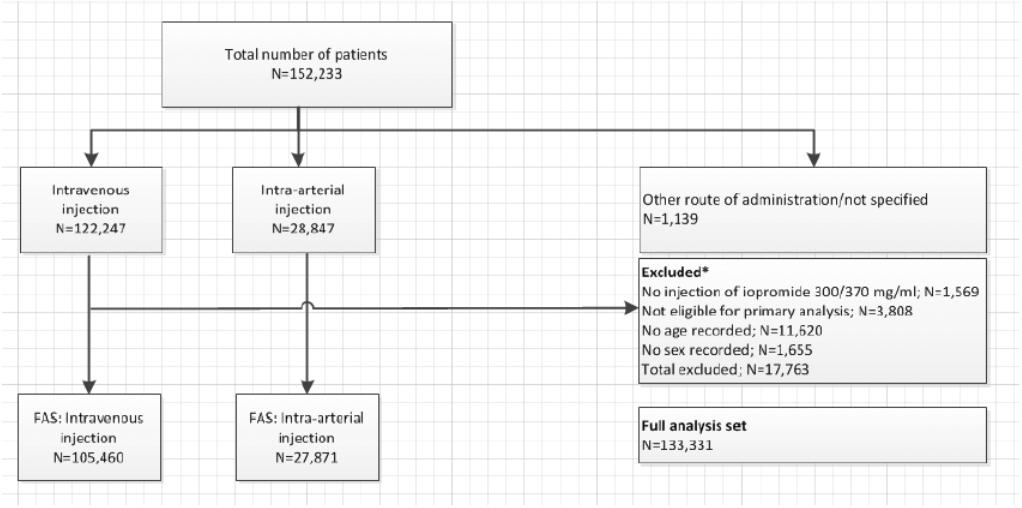
10. Results

The main results of this investigation have also been summarized in a scientific manuscript (Endrikat et al. 2019).

10.1 Participants

All participants stem from Bayer sponsored observational trials (Table 2). The below diagram shows the patient data flow into the FAS.

A total of 152,233 patients were pooled from four studies. After checking exclusion criteria, 133,331 patients comprised the full analysis set (FAS). There were 105,460 and 27,871 patients with i.v. and i.a. injection, respectively.



* Multiple reasons per patient were possible

10.2 Descriptive data

10.2.1 Distribution across regions

Almost half of the study population (48.1%) was from Europe, and one quarter each from China (27.6%) and other Asian countries (24.1%). While the majority of patients in the i.v. arm were from Europe (54.2%), the majority of patients in the i.a. arm were from Asia (including China) (74.9%) (Table 3).

Table 3 Geographical Regions

Region	Intravenous Injection (N=105,460)	Intra-arterial Injection (N=27,871)	Total (N=133,331)
Europe	57,195 (54.2%)	6,879 (24.7%)	64,074 (48.1%)
China	19,436 (18.4%)	17,339 (62.2%)	36,775 (27.6%)
Asia (excl. China)	28,541 (27.1%)	3,550 (12.7%)	32,091 (24.1%)
Africa	288 (0.3%)	103 (0.4%)	391 (0.3%)

10.2.2 Characteristics of study population

Table 4 shows the baseline characteristics of cases (n=822) and controls (132,509). Remarkable differences between the groups were recorded for geographic region (China, Asia), age, examination region (abdomen, heart, thorax, pelvis, kidneys), indication (tumor) and type of examination (CT, angiocardiography). No difference was seen for pre-medication, neither for corticosteroids nor for H1/H2 blocker (Table 4).

Table 4. Baseline characteristics of study population

	Cases N=822	Controls N=132,509
Geographic region		
Europe	**344 (41.8%)**	**63,730 (48.1%)**
China	**151 (18.4%)**	**36,624 (27.6%)**
Asia (w/o China)	**327 (39.8%)**	**31,764 (24.0%)**
Africa	**0**	**391 (0.3%)**
Concentration		
Iopromide-300	**553 (67.3%)**	**84,447 (63.7%)**
Iopromide-370	**269 (32.7%)**	**48,062 (36.3%)**
Sex		
Female	**408 (49.6%)**	**57,666 (43.5%)**
Male	**414 (50.4%)**	**74,843 (56.5%)**
Age (years)		
Mean (SD)	**50.9 (15.72)**	**56.0 (15.97)**
Min.-max.	**5-97**	**0-105**
Race		
Asian	**302 (36.7%)**	**49,320 (37.2%)**
White	**48 (5.8%)**	**6,121 (4.6%)**
Other	**8 (1.0%)**	**156 (0.1%)**
Black	**0**	**23 (<0.1%)**
Not specified	**464 (56.4%)**	**76,889 (58.0%)**
Concomitant Disease		
Patients with any disease	**374 (45.5%)**	**52,075 (39.3%)**
Hypertension arterial	**74 (9.0%)**	**16,633 (12.6%)**
Coronary heart disease	**49 (6.0%)**	**11,243 (8.5%)**
Diabetes mellitus	**68 (8.3%)**	**10,355 (7.8%)**
Reduced general condition	**45 (5.5%)**	**6,917 (5.2%)**
Specific contrast media risk factor	**114 (13.9%)**	**4,803 (3.6%)**
Allergy	**82 (10.0%)**	**3,484 (2.6%)**
Asthma bronchial	**15 (1.8%)**	**802 (0.6%)**
Contrast media reaction	**22 (2.7%)**	**699 (0.5%)**
Other	**154 (18.7%)**	**19,247 (14.5%)**

	Cases N=822	Controls N=132,509
None specified	**448 (54.5%)**	**80,434 (60.7%)**
Pre-medication		
H1/H2 Blocker or Corticosteroids	**87 (10.6%)**	**13,807 (10.4%)**
Corticosteroids	**62 (7.5%)**	**10,488 (7.9%)**
H1/H2 Blocker	**25 (3.0%)**	**3,319 (2.5%)**
Other/not specified	**38 (4.6%)**	**6,023 (4.5%)**
Examination region		
Abdomen	**228 (27.7%)**	**25,033 (18.9%)**
Cardiac / Cardiac vessels	**46 (5.6%)**	**22,776 (17.2%)**
Thorax	**108 (13.1%)**	**12,962 (9.8%)**
Pelvis	**91 (11.1%)**	**7,631 (5.8%)**
Head / Brain	**45 (5.5%)**	**6,052 (4.6%)**
Kidney / Renal vessels	**51 (6.2%)**	**4,090 (3.1%)**
Neck	**20 (2.4%)**	**2,551 (1.9%)**
Blood vessels	**13 (1.6%)**	**1,733 (1.3%)**
Limbs	**1 (0.1%)**	**386 (0.3%)**
Joints	**0**	**43 (<0.1%)**
Other/not specified	**16 (1.9%)**	**922 (0.7%)**
Indication		
Tumor/Suspicion of tumor	**216 (26.3%)**	**24,857 (18.8%)**
Pain	**60 (7.3%)**	**6,969 (5.3%)**
Post-Therapy-Control	**47 (5.7%)**	**6,927 (5.2%)**
Staging	**36 (4.4%)**	**5,127 (3.9%)**
Inflammatory diseases	**36 (4.4%)**	**3,965 (3.0%)**
Infarct/Suspicion of infarct	**25 (3.0%)**	**3,361 (2.5%)**
Hemorrhage	**5 (0.6%)**	**832 (0.6%)**
Trauma	**1 (0.1%)**	**567 (0.4%)**
Other/not specified	**113 (13.7%)**	**23,500 (17.7%)**
Iodine dose (g)		
<=20	**133 (16.2%)**	**22668 (17.1%)**
>20-40	**561 (68.2%)**	**86581 (65.3%)**
>40-60	**108 (13.1%)**	**16548 (12.5%)**
>60	**16 (1.9%)**	**6135 (4.6%)**
Not specified	**4 (0.5%)**	**577 (0.4%)**
Type of examination		
CT	**673 (81.9%)**	**91,433 (69.0%)**
Angiocardiography	**20 (2.4%)**	**12,715 (9.6%)**
Urography	**60 (7.3%)**	**10,134 (7.6%)**
Angiography	**5 (0.6%)**	**1,794 (1.4%)**
Phlebography	**0**	**296 (0.2%)**
DSA	**0**	**221 (0.2%)**
Other/not specified	**64 (7.8%)**	**15,916 (12.0%)**

10.3 Outcome data

Table 5. Occurrence of anaphylactoid reactions

	i.v. injection (N=105,460)	i.a. injection (N=27,871)	Total (N=133,331)
All patients with any anaphylactoid reaction	766 (0.7%)	56 (0.2%)	822 (0.6%)
Erythema, urticaria, rash	481 (0.5%)	27 (<0.1%)	508 (0.4%)
Pruritus	277 (0.3%)	17 (<0.1%)	294 (0.2%)
Cough, sneezing	144 (0.1%)	7 (<0.1%)	151 (0.1%)
Dyspnea, bronchospasm	94 (<0.1%)	11 (<0.1%)	105 (<0.1%)
Face edema	4 (<0.1%)	0	4 (<0.1%)
Throat irritation	4 (<0.1%)	0	4 (<0.1%)
Dysphagia	3 (<0.1%)	0	3 (<0.1%)
Dysphonia	2 (<0.1%)	0	2 (<0.1%)
Eye swelling	2 (<0.1%)	0	2 (<0.1%)
Nasal congestion	2 (<0.1%)	0	2 (<0.1%)
Anaphylactic shock	0	1 (<0.1%)	1 (<0.1%)
Lacrimation	1 (<0.1%)	0	1 (<0.1%)
Laryngeal edema	1 (<0.1%)	0	1 (<0.1%)
Respiratory arrest	0	1 (<0.1%)	1 (<0.1%)
Rhinitis	1 (<0.1%)	0	1 (<0.1%)

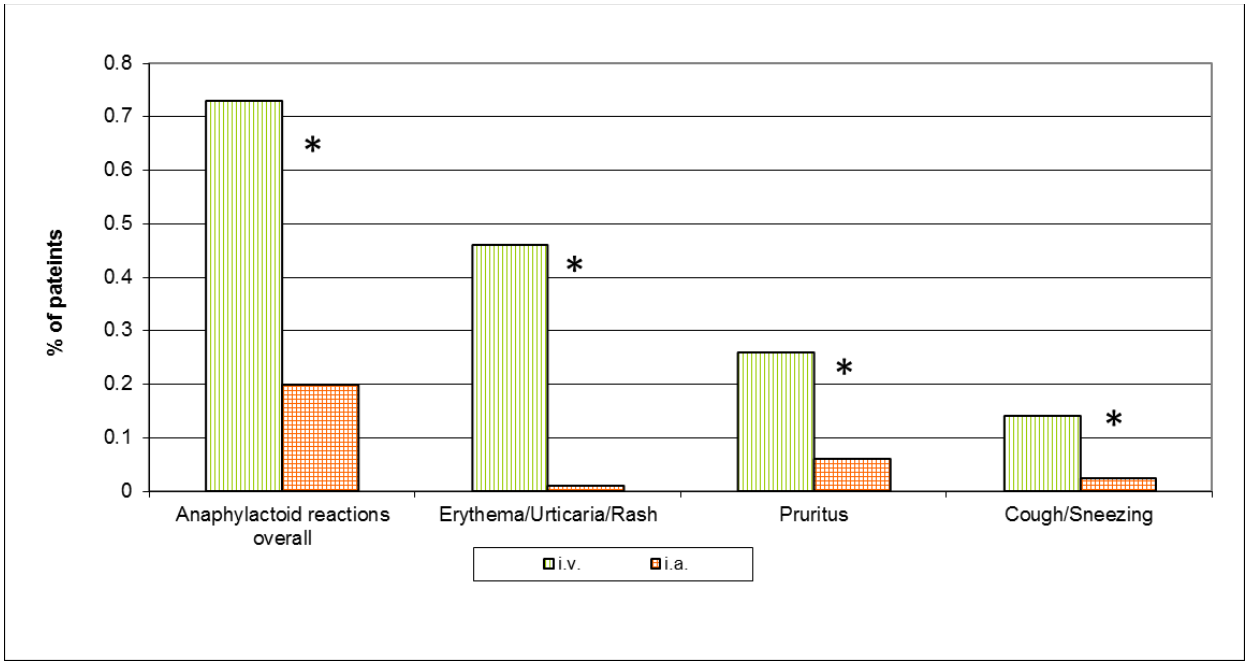


Figure 1 Occurrence of clinically most relevant anaphylactoid reactions (cut-off ≥0.1% in at least one study group)
* p-value <0.001)

10.4 Main results

Significant covariates for anaphylactoid reactions

10.4.1 Primary objective

The most striking effect was seen with respect to injection route: 93.2% of cases were seen after i.v. administration and 6.8% of the cases after i.a. while 79% and 21% of controls were in the i.v. and i.a. group, respectively (odds ratio 0.23 [95% CI: 0.16 - 0.32], p<0.001) for all countries together. For China only: 0.22 (0.11 - 0.44); for all countries without China: 0.36 (0.25 - 0.53). See Table 6.

10.4.2 Secondary objectives

In addition, age 18< 50 years (vs ≥65 years) (odds ratio 2.16 [1.78 - 2.62], p<0.001), allergy (odds ratio 3.61 [2.84 – 4.59], p <0.001), asthma (odds ratio 2.14 [1.26 – 3.62], p=0.005) and contrast media reaction in the past (odds ratio 4.31 [2.75 – 6.75], p<0.001) were identified as major risk factors for anaphylactoid reactions (Table 5).

Table 6. Risk of anaphylactoid reactions and odds ratios of significant covariates

	Cases N=822	Controls N=132,509	Odds ratio (World) (95% CI)	P-value	Odds ratio (China only) (95% CI)	P-value	Odds ratio (World w/o China) (95% CI)	P-value
Injection route (vs. i.v)								
i.v.	766 (93.2%)	104,694 (79.0%)						
i.a.	56 (6.8%)	27,815 (21.0%)	0.23 (0.16 - 0.32)	<0.001	0.22 (0.11 - 0.44)	<0.001	0.36 (0.25 - 0.53)	<0.001
Age (vs. >=65 years)								
>=65 years	164 (20.0%)	43,209 (32.6%)						
50-<65 years	307 (37.3%)	49,345 (37.2%)	1.67 (1.38 - 2.02)	<0.001	1.57 (0.99 - 2.49)	0.057	1.69 (1.37 - 2.09)	<0.001
18-<50 years	337 (41.0%)	36,989 (27.9%)	2.16 (1.78 - 2.62)	<0.001	2.09 (1.32 - 3.31)	0.002	2.19 (1.77 - 2.71)	<0.001
<18 years	14 (1.7%)	2,966 (2.2%)	1.14 (0.65 - 2.00)	0.646	1.72 (0.39 - 7.60)	0.474	1.13 (0.61 - 2.06)	0.702
Sex (vs male)								
Male	414 (50.4%)	74,843 (56.5%)						
Female	408 (49.6%)	57,666 (43.5%)	1.16 (1.01 - 1.34)	0.034	1.15 (0.83 - 1.59)	0.408	1.18 (1.01 - 1.37)	0.038
Arterial hypertension (vs. no)								
No	748 (91.0%)	115,876 (87.4%)						
Yes	74 (9.0%)	16,633 (12.6%)	1.10 (0.85 - 1.43)	0.466	0.38 (0.18 - 0.81)	0.011	1.53 (1.17 - 2.02)	0.002
Diabetes mellitus (vs. no)								
No	754 (91.7%)	122,154 (92.2%)						
Yes	68 (8.3%)	10,355 (7.8%)	1.54 (1.19 - 2.00)	0.001	1.02 (0.43 - 2.43)	0.958	1.56 (1.18 - 2.06)	0.002
Allergy (vs. no)								
No	740 (90.0%)	129,025 (97.4%)						
Yes	82 (10.0%)	3,484 (2.6%)	3.61 (2.84 - 4.59)	<0.001	9.51 (4.64 - 19.49)	<0.001	3.39 (2.62 - 4.38)	<0.001
Asthma bronchial (vs. no)								
No	807 (98.2%)	131,707 (99.4%)						
Yes	15 (1.8%)	802 (0.6%)	2.14 (1.26 - 3.62)	0.005	NA		2.22 (1.31 - 3.78)	0.003

Contrast media reaction								
No	800 (97.3%)	131,810 (99.5%)						
Yes	22 (2.7%)	699 (0.5%)	4.31 (2.75 - 6.75)	<0.001	NA		4.80 (3.06 - 7.54)	<0.001
Concomitant Disease: Other (vs. no)								
No	668 (81.3%)	113,262 (85.5%)						
Yes	154 (18.7%)	19,247 (14.5%)	1.42 (1.19 - 1.70)	<0.001	0.79 (0.49 - 1.26)	0.320	1.55 (1.28 - 1.89)	<0.001
Geographic region (vs Europe)								
Europe	344 (41.8%)	63,730 (48.1%)						
Asia (excl. China)	327 (39.8%)	31,764 (24.0%)	1.80 (1.54 - 2.11)	<0.001	NAP		1.78 (1.52 - 2.08)	<0.001
China	151 (18.4%)	36,624 (27.6%)	1.01 (0.82 - 1.25)	0.892	NAP		NAP	
Africa	0	391 (0.3%)	NA		NAP		NA	
Dose of iodine in CM (vs <=20 g)								
<=20 g	133 (16.2%)	22,668 (17.1%)						
>20-40 g	561 (68.2%)	86,581 (65.3%)	1.24 (1.01 - 1.51)	0.036	1.78 (0.62 - 5.06)	0.283	1.22 (0.99 - 1.50)	0.058
>40-60 g	108 (13.1%)	16,548 (12.5%)	1.28 (0.98 - 1.66)	0.068	3.66 (1.12 - 11.90)	0.031	1.22 (0.93 - 1.60)	0.146
>60 g	16 (1.9%)	6,135 (4.6%)	1.30 (0.73 - 2.30)	0.369	0.49 (0.05 - 4.62)	0.536	1.76 (0.98 - 3.18)	0.060
Iopromide concentration (vs Iopromide-300)								
Iopromide-300	553 (67.3%)	84,447 (63.7%)						
Iopromide-370	269 (32.7%)	48,062 (36.3%)	1.31 (1.12 - 1.54)	0.001	0.71 (0.49 - 1.04)	0.079	1.45 (1.22 - 1.73)	<0.001

NA: Not available Odds ratio was not computed because no cases were observed in the corresponding category.
NAP: Not applicable

10.4.3 Overall and details on anaphylactoid reactions

Anaphylactoid reactions were significantly more frequently recorded after i.v. than after i.a. administration, 0.7 % vs 0.2%, respectively (p <0.0001). The most frequent anaphylactoid reactions were skin reactions (erythema, urticaria, rash), reported in 508/133,331 patients (0.4%), followed by pruritus (n=294; 0.2%), cough/sneezing (n=151; 0.1%) and dyspnea/bronchospasm (n=105; <0.1%). Clinically relevant severe adverse reactions like anaphylactic shock, laryngeal edema and respiratory arrest were recorded once each (Table 6, Figure 1).

10.5 Other analyses

10.5.1 Impact of China

Since the TRUST study was carried out only in China and investigated exclusively patients with i.a. injection contributing 17,274 of 27,871 (62.0%) of patients with intra-arterial injection (Table 2). In total, 36,775 of 133,331 (27.6%) patients were recruited in China (Table 3) with 151 of 822 (18.4%) cases recorded in China while only 16 of 822 (1.9%) of those cases were recorded in the TRUST study (Table 3).

A sub-analysis for patients from China versus rest of the world showed the following: The Chinese odds ratio for i.a. administration was 0.22, very close to the whole cohort. Excluding Chinese patients, i.e. 27.6% of the total population and 62.2% of the i.a. population still resulted in an Odds ratio of 0.36 (p<0.001).

For allergy the Odds ratio for China only was nearly three times higher (9.51) compared to the world w/o China (3.39) or with the whole cohort (3.61). Neither contrast media reactions in the past nor asthma bronchial were documented for cases in China. (Table 4).

10.6 Adverse events/adverse reactions

Beyond the analyses belonging to the secondary objectives (Table 14.3.x), nor further AE analyses were done.

No new AEs where were found in UVIA study as the performed integrated analysis was based on already existing data pooled from four company sponsored non-interventional studies with Iopromide.

The UVIA analysis, however, did provide new numbers for the reported rate of ADRs observed in the observational data pool (Endrikat et al. 2019).

11. Discussion

11.1 Key results

This study showed all anaphylactoid reactions to be significantly more frequent after i.v. than after i.a. administration, 0.7 % vs 0.2% (p<0.0001), respectively. This risk difference remained even after adjustment for potential confounders. Adjusted Odds ratio (i.a. vs. i.v.) was 0.23 (95 % C.I. 0.16 -

0.32) for all countries together. For China only: 0.22 (0.11 - 0.44); for all countries without China: 0.36 (0.25 - 0.53).

Also the specific symptoms, i.e., erythema/urticarial/rash, pruritus, cough/sneezing and dyspnea/bronchospasm were more often seen after i.v. administration (Table 6, Figure 1). To the best of our knowledge, this has not been shown before in a large cohort study.

The overall incidence of anaphylactoid reactions was 822/133,331 (0.62%) (Table 5). This is well in the range reported by other studies, e.g. Zhang B et al. (0.16-0.21%) (20), Sadagari F et al. (0.48%) (18) and Kim et al. (0.02-0.05%) (21). A similar range is also seen in pediatric patients, as Dillman et al. reported a rate of 0.18% of acute allergy-like reactions in this population (7). Also the higher risk for anaphylactoid reactions for patients with history of allergy, bronchial asthma and previous ICM reactions is well established (22, 23).

An initial hint on a higher incidence of overall ADRs after i.v. iodine contrast media administration was given by Shenadi et al., Bush et al. and Kopp et al., all reporting higher overall ADR rates after i.v. administration compared to i.a. Interestingly, Bettmann et al. demonstrated the opposite, i.e., higher ADR rates after i.a. injections. Kopp et al. (who's dataset is part of this evaluation and trigger this study) found a statistically significant higher incidence of the overall ADR rate for i.v. administration (2.1%) versus i.a. (1.1%). Importantly, they excluded an impact of the ICM dose, which is generally higher in i.a. examinations. Furthermore, by excluding tolerance indicators (i.e., heat sensation and pain at the injection site) a faint hint of lower incidence of anaphylactoid reactions (e.g. skin reactions and dyspnea/bronchospasm) after i.a. injection was given, though not on the whole spectrum of anaphylactoid reactions.

11.2 Limitations

Some limitations need to be addressed: 1.) As this was a pooled analysis of four similarly designed studies of different sizes in different countries, any impact of study-specific reporting standards could not be completely excluded. 2.) A clear and scientifically proven explanation for some differences between the Chinese population vs. non-Chinese patients could not be provided. 3.) Adverse event reporting in observational studies is usually less stringent compared to prospective clinical trials, thus some underreporting may have occurred Hazell et al. 4) As intra-arterial administrations for coronary imaging are mainly done by cardiologists, an impact of different reporting habits of cardiologists and radiologists could not be excluded. However, case reporting standards, investigator trainings and general study standards were kept similar over all studies.

11.3 Interpretation

UVIA confirms, keeping in mind the limitations stated above, previous hypotheses about the nature of anaphylactoid reactions to ICM – these reactions may depend on the route of administration with the IA route having a significantly lower rate, which most likely points to a role of an earlier lung passage of the still highly concentrated agents (IV administration), probably related to a trigger on mast cells and basophils to release histamines and other vasoactive substances and consequently cause anaphylactoid reactions.

11.4 Generalizability

The study population was global and heterogeneous, so that generalizability of this results is assumed to be high to all patients world-wide. Experts assume to have fundamentally similar mechanism for the triggering of anaphylactoid reactions across the so-called LOCM class (the non-ionic monomers). Of the other agents only the non-ionic dimer iodixanol is also widely used in IV and IV administration. The agent and its class is known to have a higher rate of delayed skin reactions (different class of reactions, not investigated here).

12. Other information

N/A

13. Conclusion

This study confirmed the long-standing presumption of a lower risk for anaphylactoid reactions after i.a. administration versus i.v. administration in a sufficiently large cohort of Ultravist observational study patients.

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Source Studies

PMS I

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IMAGE

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Appendices

Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	**Final version and date**
Protocol	Version 1.0 19 JUL 2018
TFLs	Version 1.0 14 FEB 2019
SAP	Version 2.0 / 30 NOV 2018
DMP DMR	Version 1.0 27 FEB 2019

Annex 2 Additional information

N/A

Annex 3 Signature Pages

Signature Page – Study Medical Expert

Title	UVIA: Risk of anaphylactoid reactions of Iopromide after intra-arterial administration
Report version and date	Version 1.0 / 11 July 2019
IMPACT study number	19677
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS25089
Medicinal product / Active substance	Iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Study Conduct Responsible

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Signature Page – Study Data Manager

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Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Study Statistician

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IMPACT study number	19677
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS25089
Medicinal product / Active substance	Iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Study Epidemiologist

Title	UVIA: Risk of anaphylactoid reactions of Iopromide after intra-arterial administration
Report version and date	Version 1.0 / 11 July 2019
IMPACT study number	19677
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS25089
Medicinal product / Active substance	Iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – Study Safety Lead

Title	UVIA: Risk of anaphylactoid reactions of Iopromide after intra-arterial administration
Report version and date	Version 1.0 / 11 July 2019
IMPACT study number	19677
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS25089
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Print Name: [redacted]

Date, Signature: _____, _____