

Skin tests in patients with hypersensitivity reaction to iodinated contrast media: A meta-analysis

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Abstract

Background: Patients with a previous history of hypersensitivity reaction (HSR) to iodinated contrast media (ICM) are at high risk for the development of HSR to ICM. Many studies have tried to evaluate the diagnostic potential of skin tests in this population but have not yet reached a common conclusion. We investigated the role of skin tests in patients with HSR to ICM in terms of positive rate, cross-reactivity rate, and tolerability to skin test-negative ICM according to the type of HSR.

Methods: We performed literature searches of the MEDLINE and EMBASE databases and included studies where skin tests were performed in patients with HSR to ICM, with extractable outcomes. Outcomes were pooled using a random-effects model.

Results: Twenty-one studies were included. Pooled per-patient positive rates of skin tests were 17% (95%CI, 10-26%) in patients with immediate HSR, and up to 52% (95%CI, 31-72%) when confined to severe immediate HSR. Among patients with non-immediate HSR, the positive rate was 26% (95%CI, 15-41%). The pooled per-patient cross-reactivity rate was higher in non-immediate HSR (68%; 95%CI, 48-83%) than in immediate HSR (39%; 95%CI, 29-50%). Median per-test cross-reactivity rates between pairs of ICM were 7% (IQR, 6-9%) in immediate HSR and 38% (IQR, 22-51%) in non-immediate HSR. Pooled per-patient

recurrence rates of HSR to skin test-negative ICM were 7% (95%CI, 4-14%) in immediate HSR, and 35% (95%CI, 19-55%) in non-immediate HSR.

Conclusion: Skin tests may be helpful in diagnosing and managing patients with HSR to ICM, especially in patients with severe immediate HSR.

Keywords: contrast media, hypersensitivity, skin test, systematic review, meta-analysis

Background

Iodinated contrast media (ICM) are one of the most commonly used pharmaceuticals in diagnostic medicine today, with approximately 75 million administrations conducted yearly worldwide (1). Although generally considered safe, ICM can cause either immediate (≤ 1 hour after exposure) or non-immediate (>1 hour after exposure) hypersensitivity reaction (HSR), which is a concern considering its vast use. Fortunately, the incidence of immediate HSRs has declined with the introduction of non-ionic ICM, but still 0.7– 3.1% of patients have been reported to experience mild immediate HSRs and 0.02-0.04% severe immediate HSRs which can be life-threatening (2).

The best way to prevent HSR to ICM is avoiding the causative agent, as recommended for drug hypersensitivity in general. If ICM administration cannot be avoided, ICM use with corticosteroid and anti-histamine premedication may be attempted for patients at risk of developing HSR to ICM (3, 4). However, premedication alone may not be sufficient for HSR prevention, particularly in patients with severe HSR to ICM (5-7). To complement for this, the addition of skin tests may be useful in identifying patients sensitized to ICM and in guiding selection of an alternative non-cross-reactive ICM (8).

We, therefore, systematically reviewed and meta-analyzed studies on skin tests performed for the evaluation and management of patients at risk of HSR to ICM in terms of

positive rate, cross-reactivity rate, and tolerability to skin test-negative ICM.

Methods

Search strategy

Two of the authors independently performed a literature search of the MEDLINE and EMBASE databases to identify relevant publications using keywords related to contrast media and skin tests from January 1980 until June 2014. This search was further supplemented by screening bibliographies of the retrieved articles and review articles.

Selection of studies

We applied the following criteria to determine eligibility: (1) Study populations consisting of at least four or more patients suspected of having had previous HSR after administration of ICM; (2) Skin tests of at least one kind, among the skin prick test (SPT), intradermal test (IDT), and patch test (PT); (3) Data described in sufficient detail to extract outcomes.

Studies were excluded if the protocol of the skin test was not described at all or was not in accordance with current skin testing guidelines (9, 10). If study populations were overlapping, the study having enrolled the largest number of patients was included. We contacted all authors in case the identified abstracts were presented only for a conference without available full-text publications. When necessary, we contacted the author for additional unpublished data related to the full-text article.

Definition of outcomes

The primary outcome of this meta-analysis was the per-patient positive rate of skin tests in patients with immediate or non-immediate HSR to ICM. The positive rate of IDT was

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further subdivided by reaction severity, tested ICM (culprit versus alternative), and time interval between reaction and testing (1-6 months versus > 6 months)(11). Secondary outcomes included per-patient cross-reactivity rates, per-test cross-reactivity rates between pairs of ICM in skin test-positive patients, and per-patient recurrence rates of HSR to alternate skin test-negative ICM.

Per-patient positive rates of skin tests were assessed collectively as well as separately for each type of skin test performed, i.e., SPT, IDT, and PT. Reading times of skin tests were confined to 20 minutes or less after testing (immediate reading) for immediate HSR and to 1 day or more after testing (delayed reading) for non-immediate HSR (9). Concentrations of ICM were limited to undiluted for SPT, 10^{-1} diluted for IDT, and undiluted for PT (12). Per-patient false positive rates in subjects tolerating ICM exposure were evaluated as control. We also looked for the presence of systemic reactions after skin testing. The severity of HSR described in individual studies was re-adjusted as follows (11, 13)(Additional file 1: Table S1): mild immediate HSR, generalized cutaneous and/or mucocutaneous symptoms; moderate immediate HSR, mild systemic symptoms; severe immediate HSR, life-threatening systemic symptoms or cardiac and/or respiratory arrest; mild non-immediate HSR, no treatment required; moderate non-immediate HSR, symptoms responding readily to appropriate treatment and not needing hospitalization; severe non-immediate HSR, life-threatening or requiring hospitalization.

Cross-reactivity was considered to be present when allergological tests, including skin tests or drug provocation tests, were positive to two or more ICM agents and it was evaluated in individual patients (per-patient cross-reactivity) or in the test results of total skin test-positive patients (per-test cross reactivity). The per-test cross-reactivity between pairs of ICM were individually assessed on a 12-by-12 table, in which rows and columns consisted of twelve ICM if complete data on the results of skin test and the list of the tested ICM were

clearly specified in the skin test-positive patients.

In regard to the per-patient recurrence rate of hypersensitivity reactions after challenge of skin test-negative ICM, it was considered to be tolerable when the reaction did not occur either to full dose challenge to ICM or to graded challenge/drug provocation test without premedication (14-16). In patients undergoing multiple challenges to different skin test-negative ICM, the patient was regarded tolerant only when all challenged ICM did not cause a reaction.

Data extraction and quality assessment

Data extraction using a standardized form and quality assessment were performed independently by two authors. We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool for quality assessment (17). All disagreements were harmonized by consensus.

Statistical analysis

Extracted outcomes were pooled by weighted averages using the DerSimonian-Laird random-effects model according to the type of hypersensitivity. Pooling of overall positive rates of skin tests was limited to studies that have included IDTs in ICM testing and included patients with all three severities of HSR (mild, moderate, and severe). Heterogeneity across the included studies was evaluated using I^2 statistics. I^2 was derived from the Cochran Q statistic with the following equation, $I^2 = 100\% \times (Q - df) / Q$. An I^2 statistic $> 50\%$ was regarded as indicating substantial heterogeneity (18).

To explore reasons for statistical heterogeneity, sensitivity analysis was performed by recalculating the pooled positive rates of skin tests based on a fixed-effects model and the characteristics of the studies. The potential for publication bias was evaluated visually using

funnel plots. All meta-analyses were performed using MetaAnalyst 3.1 software (version 3.1, Tuft Medical Center, Boston, BA, USA)(19).

Results

Literature search

Our initial search identified 2020 references. Of these references, twenty one studies (11, 20-39) were finally included in our analysis (Figure 1)(Additional file 2, 3: Table S2, S3) (E1, R2).

Characteristics and quality assessment of the included studies

The number of the study populations in the included studies ranged from 4 to 122 in immediate HSR (11, 20-32) and from 10 to 161 in non-immediate HSR (Table 1)(11, 21, 23, 24, 26, 33-39). All studies were performed in Europe and Asia. The protocols of skin tests were similar across the included studies (Additional file 4, 5: Table S4, S5).

When assessed by the QUADAS-2 tool, the included studies appeared to have relatively low risk of bias in patient selection and index test (Appendix file 6: Figure S1). However, the risk of bias was mostly unclear in the reference standard as well as in the flow and timing as the definition of the study populations itself was used as a reference standard in several studies.

Positive rates of skin tests

In patients with immediate HSR to ICM, the pooled positive rate of skin tests was 17% (95% CI, 11-26%; $I^2=45\%$) and was identical to that of IDT (11, 22, 24, 25, 27, 28, 31, 32)(Figure 2, Table 1). The pooled positive rate of SPTs was 3% (95% CI, 1-5%; $I^2=0\%$)(11, 24, 25, 27, 28, 31, 32). The pooled positive rates of IDT were shown to rise as the severity of reactions increased (mild HSR, 12% [95% CI, 6-23%], $I^2=38\%$ (22, 25-28, 31, 32); moderate

HSR, 16% [95% CI, 10-24%], $I^2=6\%$ (22, 25-29, 31, 32); severe HSR, 52% [95% CI, 31-74%], $I^2=42\%$ (11, 20, 22, 25, 27-32)). IDT-positivity in patients with immediate HSR was more frequently found when the culprit ICM was applied (applying culprit ICM, 23% [95% CI, 14-36%], $I^2=45\%$; not applying culprit ICM, 3% [95% CI, 1-6%], $I^2=20\%$ (11, 25, 26, 28, 31, 32)). IDTs performed between 1-6 months after the resolution of the reaction showed higher positive rates than those performed after 6 months in three (11, 26, 28) of four studies (11, 26-28), although the data were not pooled due to the limited number of studies (Table 1).

The pooled overall positive rate of skin tests in non-immediate HSR was 26% (95% CI, 15-41%; $I^2=45\%$)(11, 24, 26, 33, 36-39)(Figure 2, Table 2). The relationship between the positive rate of IDTs and reaction severity could not be evaluated due to insufficient data. The pooled positive rates of SPTs, IDTs, and PTs were 7% (95% CI, 1-30%; $I^2=45\%$)(24, 37), 22% (95% CI, 13-34%; $I^2=43\%$)(11, 24, 26, 33, 36-39), and 16% (95% CI, 9-26%; $I^2=41\%$)(11, 26, 33, 35, 37-39), respectively. When PT was performed in addition to IDT, it contributed to 7% of the overall positive rate of skin tests (95% CI, 3-15%; $I^2=29\%$)(11, 26, 33, 37-39). IDT-positivity in patients with non-immediate HSR was more frequently found when the culprit ICM was applied (applying culprit ICM, 20% [95% CI, 11-36%], $I^2=44\%$; not applying culprit ICM, 5% [95% CI, 2-11%], $I^2=29\%$ (11, 26, 33, 36-39)). IDTs performed between 1-6 months after the resolution of HSR showed higher positive rates than that performed after 6 months in two studies (11, 26)(Table 2).

False positivity of skin test was not found in three of four studies on immediate HSR (11, 21, 32) and only one study reported two false positives results among 11 controls in immediate reading (26). In six studies on non-immediate HSR, none reported any false positive skin test results (11, 21, 26, 36, 38, 39)(Appendix file 7: Table S6). There was only one case of immediate systemic reaction after the IDT presenting with urticaria, rhinoconjunctivitis, and glottis edema in a patient with a previous severe immediate HSR to

ICM (11).

Per-patient cross-reactivity rate

Pooled per-patient cross-reactivity rates were 39% (95% CI, 29-50%; $I^2=9\%$) in immediate HSR (11, 20-22, 25, 27-29, 31, 32) and 68% (95% CI, 48-83%; $I^2=36\%$) in non-immediate HSR (Figure 3, and Appendix file 8: Table S7)(11, 33, 34, 36-39). Pooled proportion of patients with cross-reactivity to more than half of the tested ICM were 9% (95% CI, 5-17%; $I^2=0\%$) in immediate HSR (11, 20-22, 25, 27-29, 31, 32) and 46% (95% CI, 26-68%; $I^2=30\%$) in non-immediate HSR (11, 33, 34, 36, 37). When four or more ICM were tested, skin test-negative ICM was detectable in 93% (95% CI, 85-97%; $I^2=0\%$) of skin test-positive patients with immediate HSR (11, 20, 25, 27-29, 31, 32) and 90% (95% CI 77-96%; $I^2=0\%$) of those with non-immediate HSR (11, 33, 34, 36, 37).

Per-test cross-reactivity rate

Pooled point estimates of per-test cross-reactivity rates between pairs of ICM ranged from 4% to 21% in immediate HSR and from 3% to 74% in non-immediate HSR (Table 3). When limited to non-ionic ICM, more frequent cross-reactivities across ICM were observed in non-immediate HSR (median, 38%; IQR, 22-51%) than in immediate HSR (median, 7%; IQR, 6-9%). Median cross-reactivity rates for each non-ionic ICM in non-immediate HSR were as follows: iopentol, 56% (IQR, 38-68%); iodixanol, 52% (IQR, 37-60%); ioversol, 50% (IQR, 36-62%); iohexol, 44% (IQR, 33-60%); iopromide, 41% (IQR, 30-49%); iopamidol, 40% (IQR, 30-50%); iomeprol, 35% (IQR, 30-41%); iotrolan, 22% (IQR, 18-24%); and iobitridol, 21% (IQR, 17-23%).

Tolerability to skin test-negative ICM

Pooled per-patient recurrence rates of HSR to skin test-negative ICM were 7% (95% CI, 4-14%; $I^2=0\%$) in immediate HSR (20, 22-24, 31, 32), and 35% (95% CI, 19-55%; $I^2=31\%$) in non-immediate HSR (Figure 4, and Appendix files 9-10: Table S8-9)(23, 24, 33, 36-39).

Sensitivity analysis and publication bias analysis

Pooled positive rates of skin tests based on the fixed-effects model were similar with those of random-effects model (Appendix file 11: Table S10). The pooled positive rates of skin tests were affected by the proportion of patients with mild HSR, use of culprit ICM, time interval between reaction and testing, and number of tested ICM. There was no evidence of publication bias on visual evaluation of funnel plots (Appendix files 12-14: Figures S2-4).

Discussion

HSR to ICM has traditionally been considered non-allergic, but there is growing evidence that IgE-mediated allergic reactions may be partly involved in immediate HSR and T cell-mediated reactions in non-immediate HSR (40). However, the role of allergy skin tests in patients with HSR to ICM has not been established currently. At present, the skin test is the most widely used diagnostic tool for drug allergy due to its easiness, and non-invasiveness (9). However, its routine use in ICM hypersensitivity is still a matter of debate (11, 14).

In this meta-analysis, we appraised the role of skin tests as a diagnostic tool to prove the causative agent in patients with HSR to ICM. Overall skin test-positivity has a limitation not only in immediate HSR but also in non-immediate HSR. Relatively low pooled positive rates of skin tests may support the traditional belief of the non-allergic mechanism of HSR to ICM. However, in patients with severe immediate HSR such as anaphylaxis, skin test was

assumed to be useful, given that the pooled proportion of skin test-positive cases increased up to 52%.

We found that IDTs were more suitable than SPTs because IDTs predominantly contributed to skin test-positivity whereas SPTs rarely found skin test-positive cases. Additional skin test-positive cases were found with PTs in patients with non-immediate HSR. Skin testing in patients with HSR to ICM was pretty safe with low rate of systemic reaction and false positivity was seldom found in the included studies (R1-4). Subgroup analysis revealed two factors affecting the positive rates of IDTs, which were use of culprit ICM and time interval between HSR and the skin test. Therefore, the exposure history to culprit ICM should be taken before performing skin test.

Prior to premedication, the key principles of management for drug hypersensitivity are to prohibit the use of culprit drug, to avoid cross-reactive agents, and to identify non-cross-reactive agents (14, 41). In contrast to the results from other drugs, pooled per-patient cross-reactivity rates among ICM in non-immediate HSR was much higher than those in immediate HSR. Such a high cross-reactivity in non-immediate HSR might be attributed to nonspecific stimulation or pharmacological interaction with immune receptors across ICM, although further validation is needed. Considering broad cross-reactivity but very high success rate detecting skin test-negative alternative ICM when performed with four or more ICM, skin tests seem to be useful tool to find non cross-reactive alternative ICM in patients experiencing HSR to ICM.

More frequent cross-reactivities were found over various ICM in non-immediate HSR. The underlying mechanisms of cross-reactivities among non-ionic ICM were demonstrated in previous studies by the presence of T-cell clones (42) along with specific recognition of the ICM in T cell receptors (43). Iobitridol and iotrolan showed the lowest per-test cross-reactivity rates among non-ionic ICM in non-immediate HSR. This *in vivo* result is

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in accord with the results of an *in vitro* test of T cell clones showing iobitridol and iotrolan to be the least stimulatory ICM among non-ionic ICM (42). More studies on iobitridol testing need to be performed to determine whether this agent is truly the least cross-reactive alternative ICM (24, 33, 38, 39, 44, 45). In immediate HSR to ICM, the exact mechanism of cross-reactivity remains unclear presently (46).

Skin test-negative ICM was more tolerable in immediate HSR than in non-immediate HSR. Our results shows that skin tests has limitation in predicting non-cross-reactive ICM in non-immediate HSR. The use of non-cross-reactive ICM determined by a skin test alone could not completely prevent the recurrence of HSR. However, it is worth mentioning that skin tests may be beneficial even in false negative cases because recurred HSR to skin test-negative ICM was shown to be milder than initial HSR (39) and the stimulation index on the basophil activation test with false skin test-negative ICM tended to be lower than that of skin test-positive ICM and higher than that of true skin test-negative ICM (32). Thus, skin tests may give physicians a chance to avoid severe reactions to ICM even in the cases where skin tests are false-negative possibly preventing recurrence of HSR even more effectively than when premedication is used alone (47).

The included studies evaluated a relatively small number of patients and its baseline characteristics were heterogeneous. These heterogeneities resulted in broadening of 95% CI and affected the pooled outcome in sensitivity analyses. This suggests that testing needs to be performed optimally to ensure reliable and comparable results of skin test positivity.

The confidence of suspicion on a previous HSR to ICM might have differed over the included studies. Also, different osmolarities and viscosities for each ICM used in testing may potentially affect the results, but has rarely been considered in the included studies. In our analysis, we did not evaluate the positive rates of IDT with undiluted ICM because the use of such a high concentration could increase false positivity by irritation (12). However,

testing with undiluted ICM may have an advantage in improving the sensitivity of PT in non-immediate HSR (38, 39).

Finally, the lack of reference standards, such as drug provocation test/graded challenge or full dose challenge, was another limitation in some of the included studies, as they can be a potential harm especially in patients with severe HSR to ICM (16).

In conclusion, our meta-analysis suggests that skin tests can be a potentially useful diagnostic tool to prove the reactive ICMs and may help determine non cross-reactive alternative ICM in patients with severe immediate HSR to ICM.

Conflicts of interests

JM Goo has received research grants from Guerbet SA and Toshiba Corporation not related to this study. The other authors have no potential conflict of interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Grading systems for classification of severity in HSR

Table S2. Baseline characteristics of included studies

Table S3. Reported outcomes of included studies.

Table S4. Protocols of skin tests of included studies evaluating immediate HSR to ICM.

Table S5. Protocols of skin tests of included studies evaluating non-immediate HSR to ICM.

Figure S1. Quality assessment of included studies on immediate and non-immediate hypersensitivity reactions to iodinated contrast media.

Table S6. Per-patient false positive rates of skin tests in control

Table S7. Per-patient cross-reactivity rates in skin test-positive patients with HSR to ICM

Table S8. Per-patient recurrence rate of HSR after challenge of skin test-negative ICM in patients with HSR to ICM

Table S9. Protocols of drug provocation test, graded challenge, and full dose challenge in included studies

Table S10. Summary of sensitivity analyses on positive rates of skin tests

Figure S2. Funnel plot of included studies evaluating positive rates of skin tests in immediate hypersensitivity reactions.

Figure S3. Funnel plot of included studies evaluating positive rates of skin tests in severe immediate hypersensitivity reactions.

Figure S4. Funnel plot of included studies evaluating positive rates of skin tests in non-immediate hypersensitivity reactions.

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Figure legends

Figure 1. Flow Diagram of the Literature Search

HSR, hypersensitivity reaction; ICM, iodinated contrast media.

Figure 2. Positive rates of skin tests in patients with HSR to ICM

HSR, hypersensitivity reaction; ICM, iodinated contrast media.

Figure 3. Per-patient cross-reactivity rates in skin test-positive patients with HSR to ICM

HSR, hypersensitivity reaction; ICM, iodinated contrast media.

Figure 4. Recurrence rates of HSR to skin-test negative ICM in patients with HSR to ICM

HSR, hypersensitivity reaction; ICM, iodinated contrast media.

Tables

Table 1. Per-patient positive rates of skin tests in patients with immediate HSR to ICM

Source	Positive rate of skin tests		Positive rate of IDT according to						
	SPT	IDT	Tested ICM		Severity of HSR			Time interval ^{‡‡‡}	
			culprit ICM [‡]	only alternative ICM ^{‡‡}	Mild	Mode rate	Severe	1-6 months	>6 months
Dewachter et al, 2001 (20)	50% (2/4)	100% (4/4)	100% (4/4)	0% (0/4)			100% (4/4)	4/4 (100%)	
Trcka et al, 2008 (22)	not done	4% (4/96)		NS	0% (0/40)	7% (3/44)	8% (1/12)		NS
Brockow et al, 2009	3% (4/122)	26% (32/121)	38% (24/63)	7% (8/121)	26% (24/92) ^{‡‡‡‡}		28% (8/29)	37% (17/46) [†]	19% (14/74) ^{††}

Caimmi et al, 2010 (24)	0% (0/101)	15% (15/101) †††	NS		†††		NS	
Dewachter et al, 2011 (25)	4% (1/24)	46% (12/26)	46% (12/26)	0% (0/26)	33% (3/9)	40% (4/10)	71% (5/7)	NS
Goksel et al, 2011 (26)	0% (0/14)	14% (2/14)	20% (2/10)	0% (0/4)	14% (1/7)	14% (1/7)	20% (2/10)	0% (0/4)
Pinnobhavan et al, 2011 (27)	0% (0/63)	24% (15/63)	24% (15/63)	0% (0/63)	23% (12/53)	0% (0/5)	60% (3/5)	24% (8/34) 24% (7/29)
Kim et al, 2013 (28)	3% (1/32)	26% (12/46)	22% (10/46)	4% (2/46)	13% (4/31)	25% (2/8)	57% (4/7)	37% (7/19)* 21% (3/14)
Kim et al, 2014 (29) ††††	2% (1/51)	65% (33/51)	48% (22/46)	22% (11/51)		18% (2/11)	78% (31/40)	NS
Renaudin et al, 2013 (30)	14% (1/7)	57% (4/7)	NS				57% (4/7)	NS
Prieto-Garcia et al, 2013 (31)	0% (0/106)	10% (11/106)	14% (11/78)	0% (0/106)	9% (6/66)	14% (4/29)	9% (1/11)	**
Salas et al, 2013 (32)	3% (3/90)	6% (5/90)	6% (4/65)	2% (1/90)	0% (0/69)	11% (2/18)	100% (3/3)	***

Abbreviations: HSR, hypersensitivity reaction; ICM, iodinated contrast media; SPT, skin prick test; IDT, intradermal test; NS, not specified. Numbers in parentheses indicate the number of patients. Skin tests only included SPT and IDT, of which readings were done within 20 minutes or less after testing (immediate reading). Positive rates of IDT were extracted based on IDT using 10^{-1} diluted ICM.

‡ Positive rate of IDT tested including culprit ICM.

‡‡ Positive rate of IDT tested not including culprit ICM.

‡‡‡ Time interval between immediate HSR and the skin test.

‡‡‡‡ Positive rates could not be separated according to the severity of HSR.

† Time interval ranged from 1 week to 1.5 months in this study.

†† A time interval between HSR and the skin test was unknown in one patient.

††† There were seventeen skin test-positive patients with immediate HSR to ICM. Among them, two patients were skin-test positive at delayed reading. Although the study described the severity of HSR in skin test-positive

patients, the positive rate of IDT could not be assessed as the severities of HSR in two skin test-positive patients at delayed reading were not identified in the text.

†††† The abstract presented for a conference without available full-text publication in 2013 was initially identified by a literature search and data could be obtained through contact with the corresponding author via e-mail. This study was officially published in 2014.

* Thirteen patients undergoing skin tests within one month after HSR was not included in this proportion.

Among them, only one patient was skin test-positive.

**82% (9/11) of skin test-positive patients underwent skin tests between 1-6 months after HSR.

***80% (4/5) of skin test-positive patients underwent skin tests between 1-6 months after HSR.

Table 2. Per-patient positive rates of skin tests in patients with non-immediate HSR to ICM

Source	Positive rate of skin tests‡					Positive rate of IDT according to						
	All tests	SP T	ID T	PT	Added value of PT to IDT	Tested ICM		Severity of HSR			Time	
						Culprit ICM‡	only alternative ICM‡‡	Mild	Moderate	Severe	1-6 months	> 6 months
Vernassiere et al, 2004 (33)	60% (9/15)	ND ‡‡‡	53% (8/15)	13% (2/15)	7% (1/15)	36% (5/14)	20% (3/15)		NS		53% (9/15) ††	NP
Jiménez et al, 2006 (35)	ND	ND	ND	25% (3/12)	ND	NS	NS		NS		NS	
Torres et al, 2008 (36)	29% (4/14)	ND	29% (4/14)	ND	ND	29% (4/14)	0% (0/14)		NS		29% (4/14) †††	NP
Brockow et al, 2009 (11)	39% (38/98)	ND	31% (31/98)	28% (22/79)	9% (7/79)	38% (28/74)	3% (3/98)		NS		48% (30/62) ††††	23% (8/35)
Seitz et al, 2009 (37)	19% (6/32)	3% (3/98)	19% (6/32)	16% (5/31)	0% (0/31)	19% (6/32)	0% (0/32)	14% (1/7)	15% (3/20)	40% (2/5)	NS	
Caimmi et al, 2010 (24)	18% (3/17)	16% (5/32)	18% (3/17)	ND	ND	NS	NS	19% (3/16)	0% (0/1)	ND	NS	
Goksel et al, 2011 (26)	20% (2/10)	ND	10% (1/10)	14% (1/7)	14% (1/7)	11% (1/9)	0% (0/1)	0% (0/3)	17% (1/6)	0% (0/1)	29% (2/7)	0% (0/3)

Hasdent eufel et al, 2011 (38)	32% (7/22)	ND	18% (4/22)	14% (3/22)	14% (3/22)	18% (4/22)	0% (0/22)	NS	NS
Torres et al, 2012 (39)	9% (14/161))†	ND	9% (14/161)	6% (10/161)	0% (0/161))†	7% (9/138)	3% (5/161)	NS	NS

HSR, hypersensitivity reaction; ICM, iodinated contrast media; SPT, skin prick test; IDT, intradermal test; PT, patch test; NS, not specified; ND, not done. Numbers in parentheses indicate the number of patients. Skin tests only includes SPT, IDT, and PT of which readings were done at least 1 day after testing (delayed reading).

Positive rates of IDT were extracted based on IDT with 10^{-1} diluted ICM(12).

‡ Positive rate of IDT tested including culprit ICM.

‡‡ Positive rate of IDT tested not including culprit ICM.

‡‡‡ Time interval between the resolution of symptoms related to non-immediate HSR and the skin test.

‡‡‡‡ Although SPT was performed, the positive rate of SPT was not extracted as it is uncertain whether delayed reading was done.

† The text described that PT did not additionally detect skin test-positive cases when compared with the results of IDT. However this description was based on the results of IDT using undiluted ICM. It was unclear whether PTs additionally found skin test-positive cases when IDT with 10^{-1} diluted ICM was applied.

†† All patients underwent skin tests 1.5 to 8 months after the resolution of HSR.

††† All patients underwent skin tests 2 months after the resolution of HSR. .

†††† Time interval ranged from 1week to 1.5 months in this study. Time interval between HSR and the skin test was unknown in one patient.

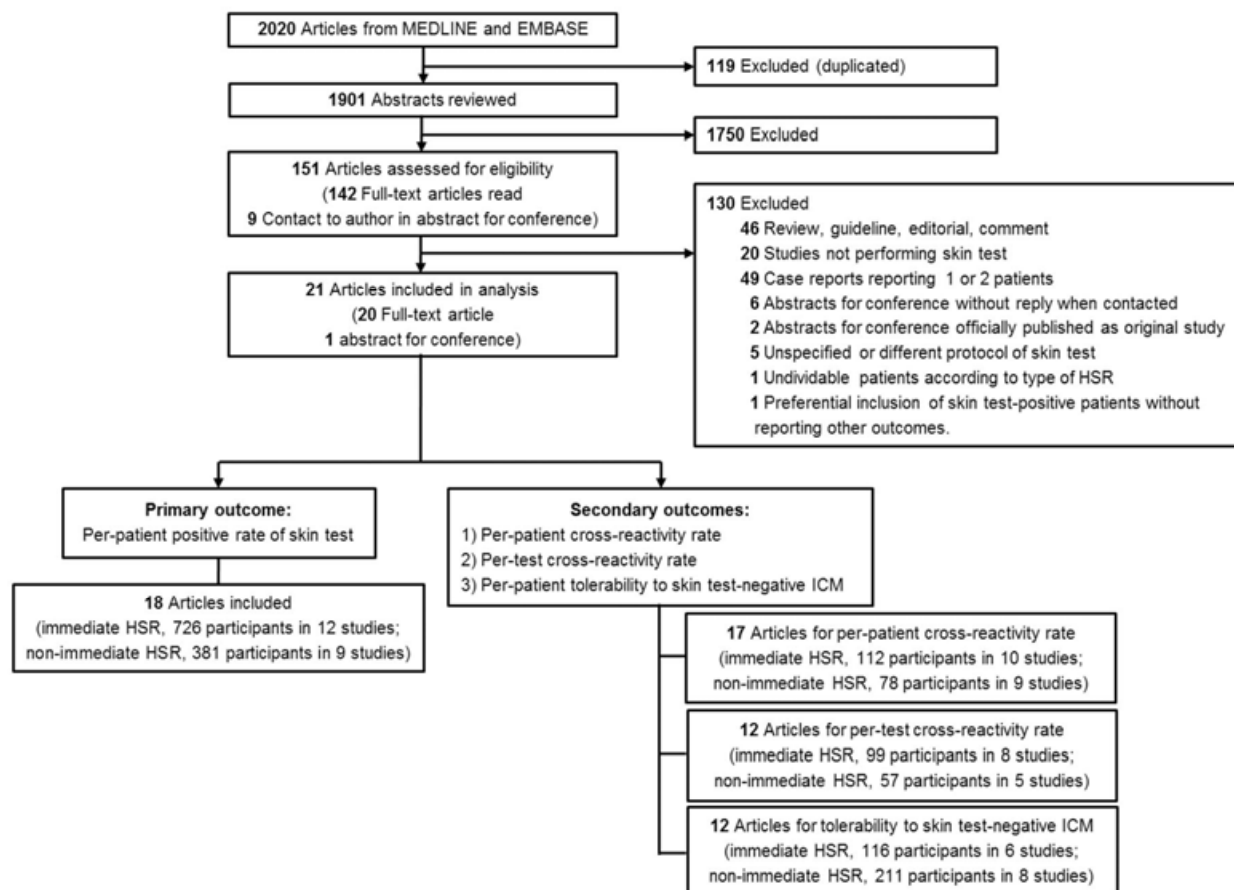
Table 3. Per-test cross-reactivity rates between pairs of ICM in skin test-positive patients with HSR to ICM

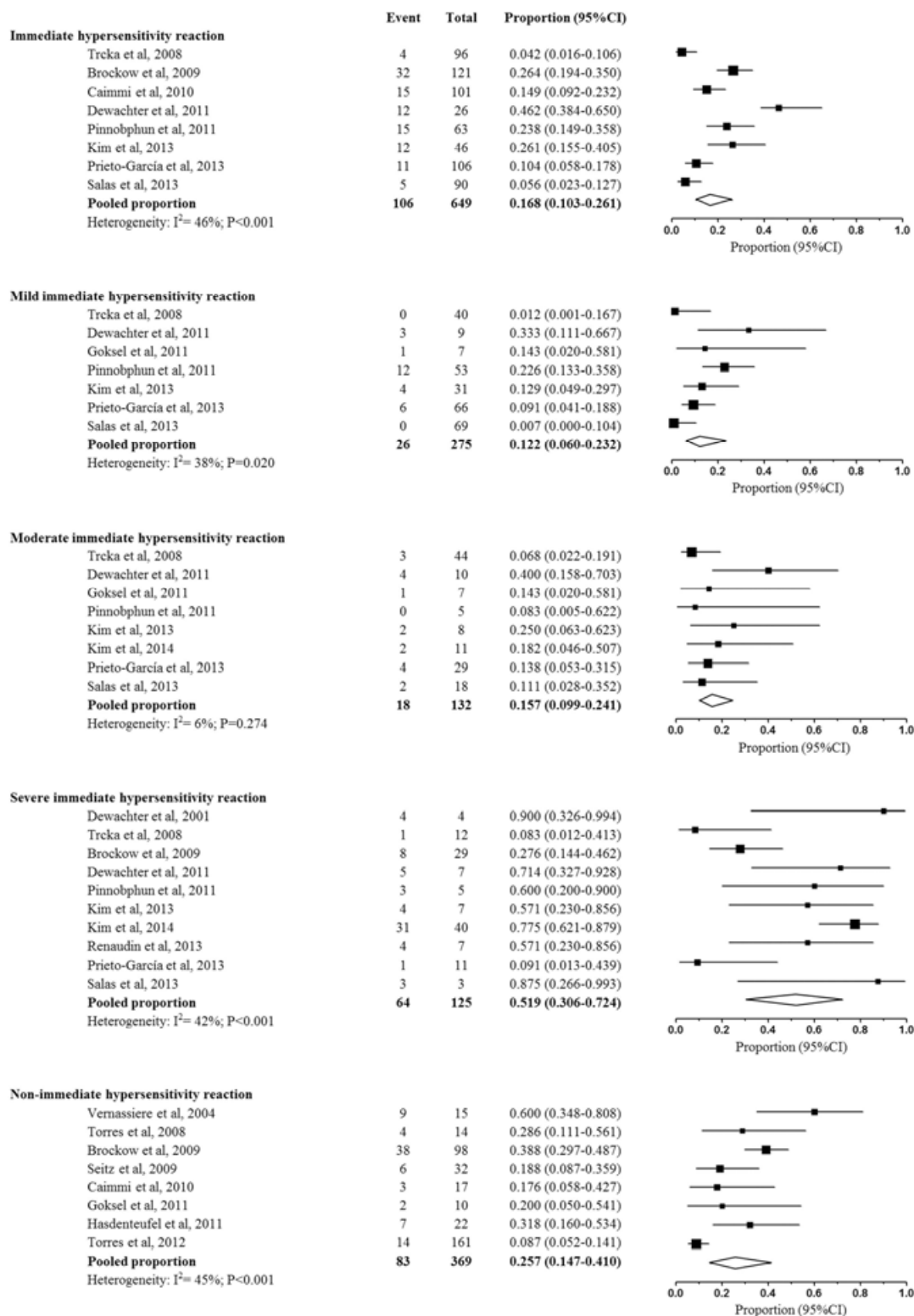
Immediate HSR		Ionic monomers		Ionic dimer	Nonionic monomers						Nonionic dimers		
		Amido - triozoate	Ioxita - laminate	Ioxaglate	Iobitridol	Iohexol	Iomepranol	Iopamidol	Iopentol	Iopromide	Ioversol	Iodixanol	Iotrolan
Ionic monomers	Amido-triozoate		12%‡ (3-44%)	10%‡‡ (3-32%)	11%‡‡ (3-35%)	8%‡‡ (2-30%)	11%‡‡ (3-34%)	10%‡‡ (3-32%)	9%‡ (1-44%)	6%‡ (1-34%)	8%‡‡ (2-30%)	8%‡‡ (2-32%)	8%‡ (0-62%)
	Ioxitalamate		7%‡‡ (2-23%)	8%‡‡ (2-24%)	8%‡‡ (2-24%)	7%‡‡ (2-23%)	10%‡‡ (2-33%)	5%‡ (1-30%)	8%‡‡ (2-27%)	4%‡‡ (1-18%)	4%‡‡ (1-18%)	6%‡ (0-54%)	
Ionic dimer	Ioxaglate				11%‡‡‡ (4-25%)	7%‡‡ (2-19%)	8%‡‡‡ (3-20%)	11%‡‡ (3-32%)	5%‡ (1-26%)	7%‡‡ (2-21%)	7%‡‡ (2-20%)	6%‡‡‡ (2-17%)	6%‡ (0-51%)
Nonionic monomers	Iobitridol					7%‡‡ (3-18%)	10%‡‡ (5-21%)	10%‡‡‡ (5-22%)	9%‡ (2-35%)	12%‡‡‡ (6-24%)	6%‡‡ (2-15%)	7%‡‡‡ (2-17%)	6%‡ (0-51%)
	Iohexol						11%‡‡ (5-22%)	8%‡‡‡ (4-17%)	5%‡ (1-28%)	9%‡‡‡ (4-18%)	7%‡‡ (3-17%)	10%‡‡ (5-23%)	6%‡ (0-54%)
	Iomepranol							6%‡‡‡ (2-15%)	13%‡‡ (2-50%)	21%‡‡‡ (11-36%)	8%‡‡ (3-20%)	11%‡‡‡ (5-24%)	6%‡ (0-51%)
	Iopamidol								7%‡‡ (1-29%)	12%‡‡‡ (6-22%)	5%‡‡ (2-14%)	5%‡‡‡ (2-14%)	6%‡ (0-51%)
	Iopentol									8%‡‡ (2-31%)	5%‡ (1-28%)	6%‡ (1-32%)	6%‡ (0-54%)
	Iopromide										4%‡‡ (1-14%)	9%‡‡‡ (4-18%)	6%‡ (0-51%)
	Ioversol											5%‡‡‡ (2-13%)	6%‡ (0-51%)
Nonionic dimers	Iodixanol												7%‡ (0-58%)

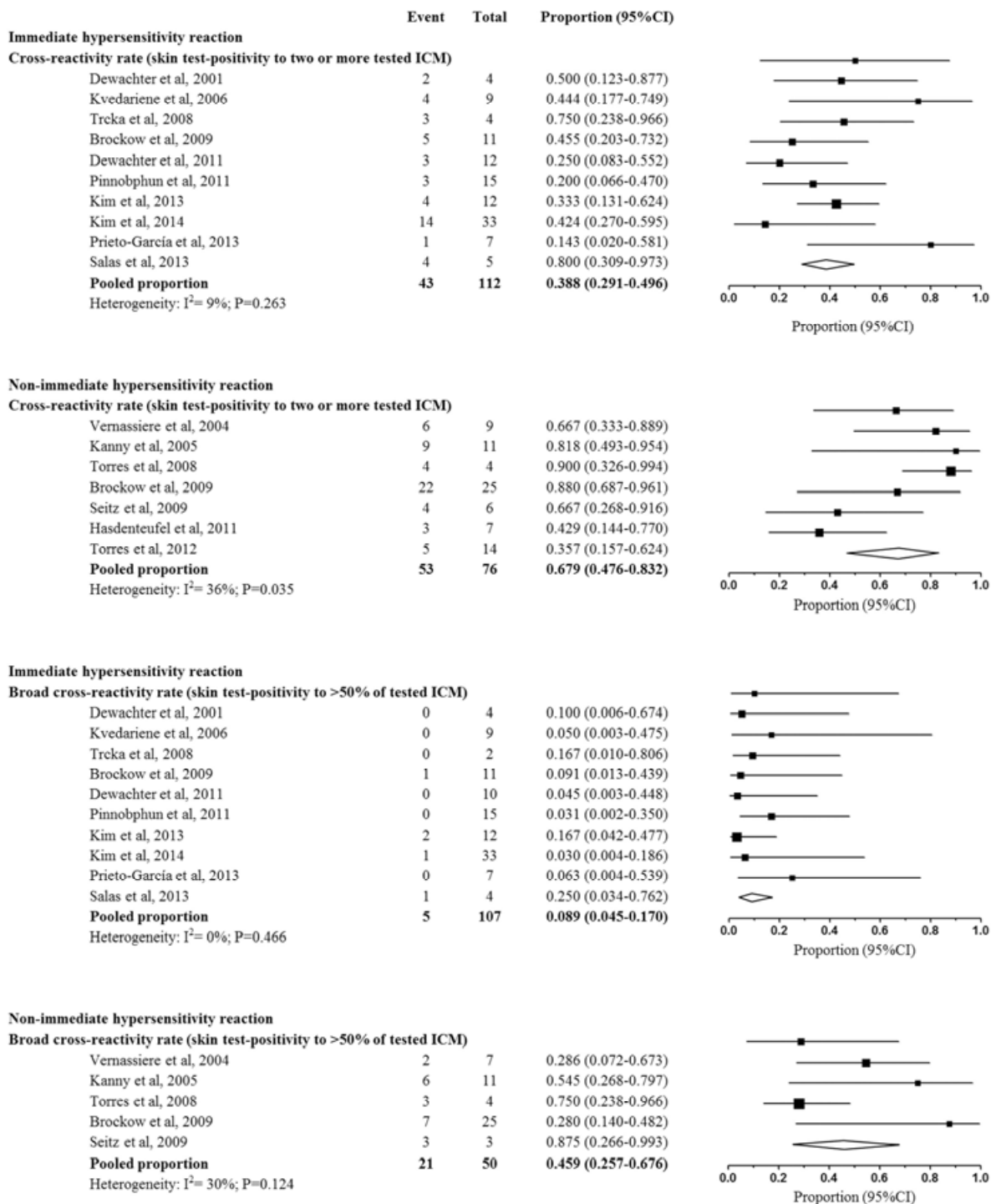
		Iotrolan											
Non-immediate HSR		Ionic monomers		Ionic dimer	Nonionic monomers						Nonionic dimers		
		Amido-triozoate	Ioxitalamate	Ioxaglate	Iobitridol	Iohecol	Iomepral	Iopamidol	Iopentol	Iopromide	Ioversol	Iodixanol	Iotrolan
Ionic monomers	Amido-triozoate		7%‡ (1-29%)	7%‡ (2-24%)	7%‡ (1-29%)	10%‡ (3-26%)	7%‡ (1-28%)	7%‡ (2-24%)	13%‡ (4-33%)	9%‡ (2-29%)	8%‡ (2-27%)	11%‡ (3-29%)	9%† (1-44%)
	Ioxitalamate			24%‡† (8-52%)	20%‡† (9-39%)	24%‡ † (8-52%)	21%‡† (9-42%)	28%‡† (12-53%)	34%‡ (5-84%)	30%‡ (7-71%)	32%‡ (6-77%)	31%‡† (11-61%)	3%† (0-35%)
Ionic dimer	Ioxaglate				16%‡† (7-32%)	26%‡ † (12-48%)	21%‡† (11-36%)	25%‡† (10-49%)	37%‡ (8-80%)	24%‡† (8-54%)	28%‡ † (8-65%)	28%‡† (12-51%)	7%† (1-35%)
Nonionic monomers	Iobitridol					25%‡ ‡ (10-48%)	13%‡† † (6-26%)	18%‡† (9-33%)	25%‡† (8-56%)	22%‡† (8-48%)	19%‡ ‡ (5-49%)	22% ‡† (12-37%)	9%‡ (2-35%)
	Iohecol						36%‡† (21-55%)	39%‡† (20-62%)		48%‡† (15-83%)			24%‡ (9-50%)
	Iomepral							33%‡† (16-55%)	42%‡† (17-72%)	33%‡† (17-54%)		41%‡† † (26-57%)	22%‡ (5-57%)
	Iopamidol									40%‡† (15-72%)	49%‡ † (12-87%)		21%‡ (5-59%)
	Iopentol												24%‡ (9-50%)
	Iopromide										42%‡ ‡ (17-71%)		19%‡ (2-74%)
	Ioversol												16%‡ (1-

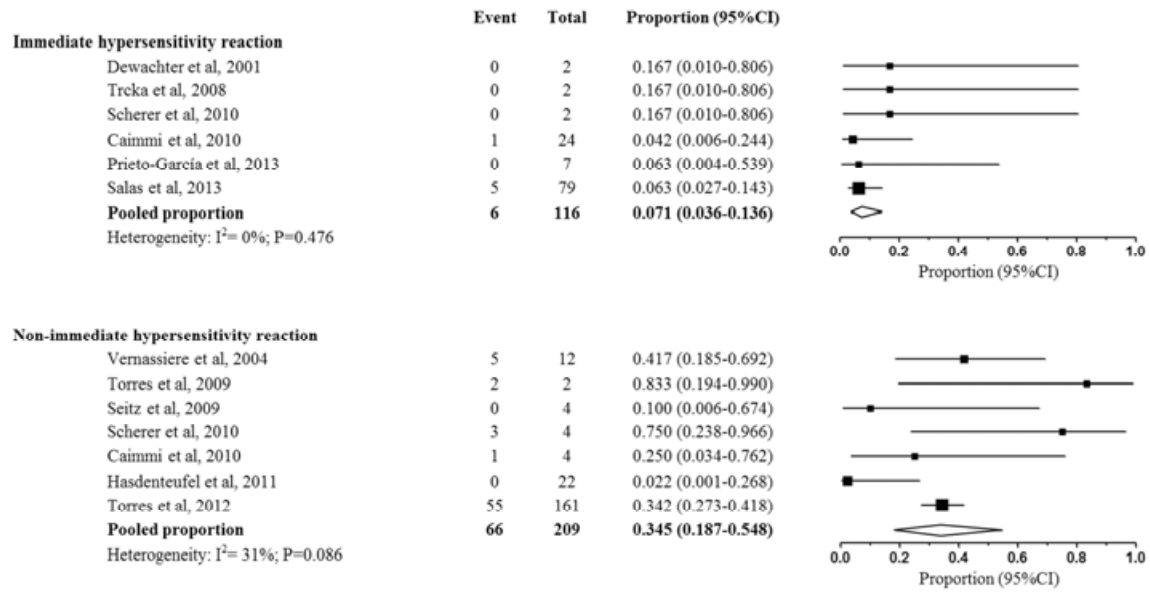
HSR, hypersensitivity reaction; ICM, iodinated contrast media; CI, confidence interval; I^2 , I^2 statistics for evaluating the heterogeneity across studies.

Cross-reactivity was extracted based on the results of intradermal test with 10^{-1} diluted ICM and patch test with undiluted ICM. If available, results of drug provocation test and graded challenge were also used. The number of † is the number of pooled studies. Pooled cross-reactivity rate is categorized and expressed in gray scale: white, pooled point estimate is $\leq 10\%$ and its upper limit of 95% CI is $\leq 30\%$; light gray, pooled point estimate is 11% and 15% or pooled point estimate is ≤ 10 with its upper limit of 95% CI is $>30\%$; gray, pooled point estimate ranged from 16% and 25%; dark gray, pooled point estimate ranged from 26% and 50%; black, pooled point estimate is $>50\%$.









Supporting information

Table S1. Grading systems for classification of severity in HSR

Table S2. Baseline characteristics of included studies

Table S3. Reported outcomes of included studies

Table S4. Protocols of skin tests of included studies evaluating immediate HSR to ICM

Table S5. Protocols of skin tests of included studies evaluating non-immediate HSR to ICM

Figure S1. Quality assessment of included studies on immediate and non-immediate hypersensitivity reactions to iodinated contrast media

Table S6. Per-patient false positive rates of skin tests in control

Table S7. Per-patient cross-reactivity rates in skin test-positive patients with HSR to ICM

Table S8. Per-patient recurrence rate of HSR after challenge of skin test-negative ICM in patients with HSR to ICM

Table S9. Protocols of drug provocation test, graded challenge, and full dose challenge in included studies

Table S10. Summary of sensitivity analyses on positive rates of skin tests

Figure S2. Funnel plot of included studies evaluating positive rates of skin tests in immediate hypersensitivity reactions

Figure S3. Funnel plot of included studies evaluating positive rates of skin tests in severe immediate hypersensitivity reactions

Figure S4. Funnel plot of included studies evaluating positive rates of skin tests in non-immediate hypersensitivity reactions

Supplemental Table 1. Grading systems for classification of severity in HSR

Source	Grading system in text	Adjusted grading
Immediate HSR		
Dewachter et al, 2001	Ring and Messmer	Brown
Kvedariene et al, 2006	Ring and Messmer	Brown
Tricka et al, 2008	Brown	Brown
Brockow et al, 2009	Ring and Messmer	Brown
Scherer et al,2010	NS	No
Caimmi et al,2010	Ring and Messmer	Brown
Dewachter et al, 2011	Ring and Messmer	Brown
Goksel et al,2011	Ring and Messmer	Brown
Pinnobphun et al, 2011	†	Brown
Kim et al,2013	Ring and Messmer	Brown
Kim et al,2014‡	†	Brown
Renaudin et al,2013	††	Brown
García et al, 2013	Brown	Brown
Salas et al,2013	Ring and Messmer	Brown
Non-immediate HSR		
Vernassiere et al, 2004	†††	Brockow

Kanny et al, 2005	NS	No
Kvedariene, et al, 2006	Brockow	Brockow
Jiménez et al,2006	NS	No
Torres et al, 2008	NS	No
Brockow et al,2009	Brockow	Brockow
Seitz et al,2009	Own criteria††††	Brockow
Scherer et al,2010	NS	No
Caimmi et al,2010	Brockow	Brockow
Goksel et al,2011	Brockow	Brockow
Hasdenteufel et al, 2011	NS	No
Torres et al,2012	Brockow	Brockow

Abbreviations: HSR, hypersensitivity reaction; NS, not specified. In immediate HSR, the grading system of Ring and Messmer is based on four grades and that of brown

SG is based on three grades. Scales between two grading systems were adjusted as follows: grade I in Ring and Messmer was categorized into mild grade in Brown SG; grade II in Ring and Messmer was categorized into moderate in Brown SG; grades III and IV in Ring and Messmer were categorized into severe grade in Brown SG. †

Data could be obtained through contact with the corresponding author via e-mail. †† The study included patients experiencing severe anaphylaxis. ††† Severity of HSR in

included patients could be assessed by our authors based on the description in the text according to the system of Brockow. †††† Grading systems of Brockow and Seitz are based on three grades. Scales between the two grading systems were adjusted as follows: grade I in Seitz was categorized into mild grade in Brockow; grade II in Seitz

was categorized into moderate in Brockow ; grade III in Seitz was categorized into severe grade in Brockow. ‡ The abstract presented for a conference without available

full-text publication in 2013 was initially identified by a literature search and data could be obtained through contact with the corresponding author via e-mail. This study was officially published in 2014.

Supplemental Table2. Baseline characteristics of included studies

Source	Study population							Culprit ICM		Skin tests			
	Total No.	Age (year)	Female	Prior ICM exposure before HSR	Severity of HSR†			Percentage identified	Nonionic ICM among identified	Skin test ††	Maximum ICM conc. for IDT †††	No. of ICM for skin test	Time interval between HSR and skin test
					Mild	Moderate	Severe						
Immediate HSR													
Dewachter et al,2001, France	4	mean, 70 ±9 (61-80)	0% (0/4)	100% (4/4)	0% (0/4)	0% (0/4)	100% (4/4)	100% (4/4)	50% (2/4)	SPT, IDT	10 ⁻¹	5	1.5 months
Kvedariene et al, 2006, France‡	32	median, 56	66% (29/44)	49% (20/41)	34% (11/32)	41% (13/32)	25% (8/32)	39% (17/41)	71% (12/17)	SPT, IDT	10 ⁻¹	11	median, 48 months
Trcka et al, 2008, Germany	96	mean, 59 (23-83)	72% (69/96)	NS	41% (40/96)	46% (44/96)	13% (12/96)	NS	NS	IDT	10 ⁻¹	4	<1yr, 74% >1yr, 26%
Brockow et al, 2009, Europe‡	122	median, 54 (12–83)	66% (80/122)	49% (53/108)	31% (38/122)	45% (55/122)	24% (29/122)	52% (63/122)	86% (54/63)	SPT, IDT	10 ⁻¹	13	<1yr, 43% >1yr, 57%
Scherer et al, 2010, Switzerland ‡	9	mean, 62*	63%* (12/19)	NS		NS		66% (6/9)	83% (5/6)	SPT, IDT	10 ⁻¹	12	NS
Caimmi et al, 2010, France‡	101	median, 56* (45–65)	59%* (71/120)	NS	42% (42/101)	33% (34/101)	25% (25/101)	NS	NS	SPT, IDT	10 ⁻¹	10	NS
Dewachter et al, 2011, France	26	mean, 50±18 (18-73)	65% (17/26)	72% (18/25)	35% (9/26)	38% (10/26)	27% (7/26)	100% (26/26)	85% (22/26)	SPT, IDT	undiluted	11	mainly <1yr, suggested*
Goksel et al, 2011, Turkey‡	14	mean, 52±14 (25-69)	64% (9/14)	43% (6/14)	50% (7/14)	50% (7/14)	0% (0/14)	71% (10/14)	100% (10/10)	SPT, IDT	10 ⁻¹	1	median, 2.5 months (2 months-37 yrs)
Pinnobphun et al, 2011, Thailand	63	mean, 52 (23-79)	67% (42/63)	NS	84%‡‡ (53/63)	8%‡‡ (5/63)	8%‡‡ (5/63)	100% (63/63)	NS	SPT, IDT	10 ⁻¹	9	mean, 4 months (1week-3.5 yrs)

Kim et al, 2013, Korea	46	mean, 51±12	57% (27/46)	62% (28/45)	68% (31/46)	17% (8/46)	15% (7/46)	100% (46/46)	100% (46/46)	SPT, IDT	10 ⁻¹	4	mean, 0.8 ± 1.7 yrs
Kim et al, 2014, Korea††	51	mean, 53±11 (26-74)	67% (34/51)	65% (33/51)	0% (0/51)	22% (11/51)	78% (40/51)	90% (46/51)	100% (46/46)	SPT, IDT	10 ⁻¹	6	<1yr, 41% >1yr, 59%
Renaudin et al, 2013, France	7	NS	NS	NS			100% (7/7)	NS	NS	SPT, IDT	10 ⁻¹	NS	NS
Prieto-Garcia et al, 2013, Spain	106	mean, 57±17	60% (64/106)	NS	63% (66/106)	27% (29/106)	10% (11/106)	74% (78/106)	99% (77/78)	SPT, IDT	undiluted	8	median, 2 months (1-22.5)
Salas et al, 2013, Spain	90	median, 54±27	60% (63/90)	NS	77% (69/90)	20% (18/90)	3% (3/90)	72% (65/90)	100% (65/65)	SPT, IDT	10 ⁻¹	7	mean, 2.0 ± 18.3 yrs
Non-immediate HSR													
Vernassiere, et al, 2004, France	15	mean, 55 (37-78)	73% (11/15)	NS	60% (9/15)	40% (6/15)	0% (0/15)	93% (14/15)	100% (14/14)	IDT, PT	undiluted	7	1.5 to 8 Months
Kanny et al, 2005, France†††	11	median, 59 (19-83)	73% (8/11)	45% (5/11)		NS		100% (11/11)	82% (9/11)	IDT, PT	undiluted	11	NS
Kvedariene, et al, 2006, France†	11	median, 56	66% (29/44)	49% (20/41)	34% (11/32)	41% (13/32)	25% (8/32)	39% (17/41)	71% (12/17)	SPT, IDT	10 ⁻¹	11	median, 48 months
Jiménez et al, 2006, Spain	12	mean, 56 (39-76)	42% (5/12)	50% (6/12)		NS		100% (12/12)	100% (12/12)	PT	NS	1	NS
Torres et al 2008, Spain	14	mean, 62 ± 7 (51-71)*	50% (3/6)*	NS		NS		100% (14/14)	NS	IDT	10 ⁻¹	6	2 months
Brockow et al, 2009, Europe†	98	median, 58 (12–80)	58% (57/98)	53% (48/91)	95% (93/98)	5% (5/98)	0% (0/98)	75% (74/98)	93% (69/74)	SPT, IDT, PT	10 ⁻¹	13	<1yr, 73% >1yr, 27%
Seitz et al, 2009, Germany	32	mean, 48 (24–71)	53% (17/32)	NS	22% (7/32)	62% (20/32)	16% (5/32)	100% (32/32)	100% (32/32)	SPT, IDT, PT	10 ⁻¹	3	NS

Scherer et al, 2010, Switzerland ‡	10	mean, 62	63% (12/19)	NS		NS		80% (8/10)	100% (8/8)	SPT, IDT, PT	10 ⁻¹	12	NS
Caimmi et al, 2010, France‡	17	median, 56 (45–65)	59%** (71/120)	NS	94% (16/17)	6% (1/17)	0% (1/17)	NS	NS	IDT	10 ⁻¹	10	NS
Goksel et al, 2011, Turkey‡	10	median, 53 (18–75)	90% (9/10)	60% (6/10)	30% (3/10)	60% (6/10)	10% (1/10)	90% (9/10)	100% (9/9)	IDT, PT	10 ⁻¹	2	median, 2 months (2–12)
Hasdenteufel, et al, 2011, France	22	mean, 56 ± 14 (8–78)	32% (7/22)	NS		NS		100% (22/22)	100% (22/22)	IDT, PT	undiluted	7	NS
Torres et al, 2012, Spain	161	median, 59	49% (79/161)	NS	10% (16/161)	89% (143/161)	1% (2/161)	86% (138/161)	99% (136/138)	IDT, PT	undiluted	7	median, 3.7 months (1.4–19.5)

HSR, hypersensitivity reaction; ICM, iodinated contrast media; No., numbers; Conc., concentration; SPT, skin prick test; IDT, intradermal test; PT, patch test; NS, not specified. Numbers in parentheses indicate the number of patients.

† The severity scale of HSR were inhomogenous across studies. Severities of HSR were readjusted according to the grading scale of Brown for immediate HSR, and that of Brockow for non-immediate HSR.

†† Skin tests only included SPT and IDT of which readings were performed within 20 minutes or less after testing (immediate reading) for immediate HSR. For non-immediate HSR, skin tests included SPT, IDT, and PT of which readings were done at least 1 day after testing (delayed reading).

††† Positive rates of IDT were extracted based on IDT using 10⁻¹ diluted ICM even in studies using ICM up to an undiluted concentration.

‡ These studies evaluated skin tests in both patients with immediate HSR and patients with non-immediate HSR.

‡‡ The abstract presented for a conference without available full-text publication in 2013 was initially identified by a literature search and data could be obtained through contact with the corresponding author via e-mail. This study was officially published in 2014.

‡‡‡ This study reported one skin test-positive patient with immediate HSR to ICM and was excluded in the analysis in immediate HSR. * Demographics of included patients could not be separated according to the type of HSR.

Supplemental Table 3. Reported outcomes of included studies

Source	Primary outcome		Secondary outcome					
	Per-patient positive rate of skin tests		Per-patient cross-reactivity rate		Per-test cross-reactivity rate		Per-patient tolerability to skin test-negative ICM	
	Extractability in text	Extracted	Extractability in text	Extracted	Extractability in text	Extracted	Extractability in text	Extracted
Immediate HSR								
Dewachter et al, 2001	Yes†	Yes	Yes	Yes	No		Yes	Yes
Kvedariene et al, 2006	Yes	No††	Yes	Yes††	No		No	
Trcka et al, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brockow et al, 2009	Yes	Yes†††	Yes	Yes†††	Yes	Yes†††	No	
Scherer et al, 2010	Yes	No†††	Yes	No†††	No		Yes†††	Yes†††
Caimmi et al, 2010	Yes	Yes††	No		No		Yes	Yes
Dewachter et al, 2011	Yes	Yes	Yes	Yes	Yes	Yes	No	
Goksel et al, 2011	Yes	Yes	Yes	Yes	No		No	
Pinnobphun et al, 2011	Yes	Yes	No	Yes‡	No	Yes‡	No	
Kim et al, 2013	Yes	Yes	No	Yes‡	No	Yes‡	No	
Kim et al, 2014*	Yes	Yes	No	Yes‡	No	Yes‡	No	
Renaudin et al, 2013	Yes	Yes	No		No		No	
Prieto-Garcia et al, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Salas et al, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Non-immediate HSR								
Vernassiere et al, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kanny et al, 2005	No††††		Yes	Yes	Yes	Yes	No	
Kvedariene, et al, 2006	Yes	No††	Yes	Yes††			No	
Jiménez et al, 2006	Yes	Yes	No		No		Yes	Yes
Torres et al, 2008	Yes	Yes	Yes	Yes	Yes‡‡	Yes	Yes	Yes
Brockow et al, 2009	Yes	Yes†††	Yes	Yes†††	Yes	Yes†††	No	
Seitz et al, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Scherer et al, 2010	Yes	No†††	Yes	No†††	No		Yes	Yes†††
Caimmi et al, 2010	Yes	No††	Yes	No	No		Yes	Yes
Goksel et al, 2011	Yes	Yes	No		No		No	
Hasdenteufel et al, 2011	Yes	Yes	Yes	Yes	No		No	
Torres et al, 2012	Yes	Yes	Yes	Yes	No		Yes	Yes

HSR, hypersensitivity reaction; ICM, iodinated contrast media. † The primary aim of the study was to report five patients with severe immediate HSR to ICM rather than to report skin test-positive patients. The study included four patients undergoing skin tests and one expired patient not undergoing skin tests. The positive rate of IDT was judged to be extractable. †† The study population of Kvedariene et al. in 2006 was completely contained in that of Caimmi et al. in 2010 who reported the positive rate of skin tests. Thus, the positive rate of skin tests was not extracted from the study of Kvedariene et al. Instead, per-patient cross-reactivity rates not reported in the study of Caimmi et al. were extracted from the study of Kvedariene et al. ††† Some of included patients in the study of Scherer et al. in 2010 were included in the study of Brockow et al. in 2009. As the number of included patients was larger in the study of Brockow et al., per-patient positive rates of skin tests, per-patient, and per-test cross-

reactivity rates were extracted from the study of Brockow et al. Per-patient tolerability to skin test-negative ICM not reported in that of Brockow et al. was extracted from the study of Scherer et al. †††† Kanny et al. included only skin test-positive patients. Thus, the positive rate of skin tests could not be assessed. However, per-patient and per-test cross-reactivity rates were extractable in skin test-positive patients and were extracted from the study of Kanny et al. ‡ Full-text articles did not describe complete data on the results of skin tests to tested ICM nor provide a list of the tested ICM. It was extracted from raw data through contact with the corresponding author via e-mail. ‡‡ The study described that skin tests were performed with a complete battery of ICM. * The abstract presented for a conference without available full-text publication in 2013 was initially identified by a literature search and data could be obtained through contact with the corresponding author via e-mail. This study was officially published in 2014.

Supplemental Table 4. Protocols of skin tests of included studies evaluating immediate HSR to ICM

Source	Skin test	SPT				IDT				
		Test site	Conc.	Reading time	Diameter of wheal for positivity	Test site	Maximum Conc.	Procedure	Reading time	Diameter of wheal for positivity
Dewachter et al, 2001	SPT, IDT	forearm	undiluted	15 min	≥half the positive control	back	10 ⁻¹	ICM (0.15ml) raising a bleb (about 3mm)	15 min	≥2 of bleb size
Kvedariene et al, 2006	SPT, IDT	NS	undiluted	15 min	≥3 mm	NS	10 ⁻¹	NS	15-20 min	≥3 mm
Trcka et al, 2008	IDT			not done		forearm	10 ⁻¹	NS	20 min	≥3 mm
Brockow et al, 2009	SPT, IDT	forearm	undiluted	20 min	≥3 mm	forearm, or back	10 ⁻¹	ICM (0.03–0.05ml) raising a bleb (4–5 mm)	20 min	≥3 mm
Scherer et al, 2010	SPT, IDT						††			
Caimmi et al, 2010	SPT, IDT	NS	undiluted	15 min	≥3 mm	NS	10 ⁻¹	NS	15–20 min	≥3 mm
Dewachter et al, 2011	SPT, IDT	forearm	undiluted	15 min	≥half the positive control	back	undiluted	ICM(0.02–0.03ml) raising a bleb (about 3mm)	15-20 min	≥2 of bleb size
Goksel et al, 2011	SPT, IDT	forearm	undiluted	15 min	≥3 mm	forearm, or upper arm	10 ⁻¹	ICM(0.03–0.05ml) raising a bleb (3–5 mm)	15 min	≥3 mm
Pinnobphun et al, 2011	SPT, IDT	NS	undiluted	NS	≥3 mm	NS	10 ⁻¹	ICM (0.02ml) raising a bleb	NS	≥3 mm

Kim et al, 2013	SPT, IDT	NS	NS	NS	NS	forearm	10 ⁻¹	ICM (0.03-0.05ml) raising a bleb (2-4 mm)	15-20 min	≥3 mm
Kim et al, 2014‡	SPT, IDT	forearm	undiluted	15 min	≥3 mm	forearm	10 ⁻¹	NS	15 min	≥3 mm
Renaudin et al, 2013	SPT, IDT						†††			
Prieto-Garcia et al, 2013	SPT, IDT	NS	undiluted	15 min	≥3 mm	NS	10 ⁻¹ or undiluted ††††	NS	15 min	≥3 mm
Salas et al, 2013	SPT, IDT	NS	undiluted	NS	NS	forearm	10 ⁻¹	NS	NS	NS

HSR, hypersensitivity reaction; ICM, iodinated contrast media; Conc., concentration; SPT, skin prick test; IDT, intradermal test; NS, not specified. Numbers in parentheses indicate the number of patients. Skin test only included SPT and IDT of which readings were performed within 20 minutes or less after testing (immediate reading) for immediate HSR. Positive rates of IDT were extracted based on IDT using 10⁻¹ diluted ICM even in studies using ICM up to an undiluted concentration. †, ††, ††† Studies described that skin test were performed according to† the recommendation of the European Academy of Allergy and Clinical Immunology (EAACI) in 1989. †† the protocol of Brockow et al in 2009, and ††† the recommendation of EAACI in 2005. †††† Among the eight ICM used for skin test, iopamidol, ioversol, and iobitridol were tested undiluted. Results of IDT did not differ when using 10⁻¹ diluted and undiluted ICM. ‡The abstract presented for a conference without available full-text publication in 2013 was initially identified by a literature search and data could be obtained through contact with the corresponding author via e-mail. This study was officially published in 2014.

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Supplemental Table 5. Protocols of skin tests of included studies evaluating non-immediate HSR to ICM

Source	Skin test	SPT			IDT				PT			Criteria for positive skin test	
		Test site	Conc.	Reading time	Test site	Maximum conc.	Procedure	Reading time	Test site	Maximum conc.	Procedure		Reading time
Vernassiere et al, 2004	IDT, PT			unclear reading time	arm	undiluted‡	ICM (0.4ml) raising a bleb	1-7 days	upper back	undiluted	ICM in Finn chamber on Scanpor tape or Hayes Chamber†	NS†	NS†
Kanny et al, 2005	IDT, PT			immediate reading	back	undiluted	ICM (0.02–0.04 ml) raising a bleb (3–4 mm)	1-2 days	*	undiluted	NS	1,2 days	erythematous induration at test site
Kvedariene, et al, 2006	SPT, IDT	NS	undiluted	††	NS	10 ⁻¹	NS	††			not done		††
Jiménez et al, 2006	PT			not done			not done		upper back	undiluted	ICM in Finn chamber on Scanpor tape for 2 days	2,4 days	†
Torres et al, 2008	IDT			not done	forearm	10 ⁻¹	ICM (0.1ml) raising a bleb	8hr, 1-2 days			not done		††
Brockow et al, 2009	SPT, IDT, PT	fore-arm	undiluted	2/3 days	forearm or back	10 ⁻¹	ICM (0.03–0.05ml) raising a bleb (4–5 mm)	1-3 days	back	undiluted	ICM in Finn chamber on adhesive tape for 2 days.	1 day ‡‡	erythematous induration at test site
Seitz et al, 2009	SPT, IDT, PT	fore-arm	undiluted	2-4 days	forearm	10 ⁻¹	††	2-4 days	upper back	undiluted	††	2-4 days	erythematous infiltration at test site

Scherer et al, 2010	SPT, IDT						+++					
Caimmi et al, 2010	IDT	immediate reading	NS	10 ⁻¹	NS	NS			not done		++	
Goksel et al, 2011	IDT, PT	immediate reading	forearm, upper arm	10 ⁻¹	ICM (0.03–0.05 ml) raising a bleb (3–5 mm)	1-3 days	back	10 ⁻¹	ICM in plastic chamber on adhesive tape for 3 days	1-3 days	erythematous induration at test site	
Hasdenteufel et al, 2011	IDT, PT	immediate reading	back	undiluted	ICM (0.02 ml) raising a bleb (3–4 mm)	1-3 days	†	undiluted	†	1-4 days	erythematous induration at test site	
Torres et al, 2012	IDT, PT	not done	forearm	undiluted	††	1-3 days	++++	undiluted	++++	2,3 days	erythematous induration at test site	

HSR, hypersensitivity reaction; ICM, iodinated contrast media; Conc., concentration; SPT, skin prick test; IDT, intradermal test; PT, patch test; NS, not specified.

Numbers in parentheses indicate the number of patients. Skin tests only included SPT, IDT, and PT of which readings were performed 1 day or more after testing (non-immediate reading) for non-immediate HSR. Positive rates of IDT were extracted based on IDT using 10⁻¹ diluted ICM even in studies using ICM up to an undiluted

concentration. †, ††, †††, †††† Studies described that skin tests were performed according to † the internationally accepted method used in patch testing, †† the

recommendation of EAACI in 2002, and in 2005. ††† the protocol of Brockow et al. in 2009, and †††† recommendations of the European Society of Contact Dermatitis. ‡

In the case of ioxaglate and iodixanol, IDT was performed using 10⁻¹ diluted ICM. ‡‡ Positive reactions were also reported to the physician at other time points.

Supplemental Table 6. Per-patient false positive rates of skin tests in control

Source	Definition of control†	False positive rate of skin tests
Immediate HSR		
Dewachter et al, 2001	not specified††	0%?†† (0/10)?
Kvedariene et al, 2006	tolerated ICM exposure	0% (0/10)
Brockow et al, 2009	tolerated ICM exposure	0% (0/11)
Goksel et al, 2011	tolerated ICM exposure	11% (2/18)
Salas et al, 2013	tolerated ICM exposure	0% (0/20)
Non-immediate HSR		
Vernassiere et al, 2004	suspect of immediate HSR to ICM††	0%†† (0/13)
Jiménez et al, 2006	not specified	0%††† (0/35)
Kvedariene et al, 2006	tolerated ICM exposure	0% (0/10)
Torres et al, 2008	tolerated ICM exposure	0% (0/10)
Brockow et al, 2009	tolerated ICM exposure	0% (0/11)
Goksel et al, 2011	tolerated ICM exposure	0% (0/18)
Hasdenteufel et al, 2011	tolerated ICM exposure	0%†††† (0/20)
Torres et al, 2012	tolerated ICM exposure	0%†††† (0/25)

HSR, hypersensitivity reaction; ICM, iodinated contrast media. †Ideally, control should be subjects who were exposed to a ICM within the last six months without any evidence of HSR to ICM (6). ††This data was not pooled in the meta-analysis of false positive rates of skin tests in control. ††† Only patch test was performed. This data was not pooled in meta-analysis of false positive rates of skin tests in control. †††† Skin tests were performed partly or completely using undiluted ICM in intradermal test in control

Supplemental Table 7. Per-patient cross-reactivity rates in skin test-positive patients with HSR to ICM

Source	Total number of patients	Median number of tested ICM	Per-patient cross-reactivity rate			Availability of skin test negative ICM*
			Positive skin test to at least two tested ICM	Positive skin test to >50% of tested ICM†	Median number of cross-reactive ICM	
Immediate HSR						
Dewachter et al, 2001	4	5	50% (2/4)	0% (0/4)	2	100% (4/4)
Kvedariene et al, 2006	9	up to 11	44% (4/9)	0% (0/9)	2.5 (range, 2-5)	NS
Trcka et al, 2008	4	3.5 (range, 3-4)	75% (3/4)	0% (0/2)	2	NS
Brockow et al, 2009	11††	11 (range, 8-12)	45% (5/11)	9% (1/11)	5 (range, 2-6)	100% (27/27)
Dewachter et al, 2011	12	6 (range, 2-11)	25% (3/12)	0% (0/10)	3 (range, 2-3)	100% (10/10)
Pinnobphun et al, 2011	15	9	20% (3/15)	0% (0/15)	3	100% (15/15)
Kim et al, 2013	12	4	33% (4/12)	17% (2/12)	3 (range, 2-4)	83% (10/12)
Kim et al, 2014‡	33	7	42% (14/33)	3% (1/33)	3 (range, 2-4)	100% (33/33)
Prieto-Garcia et al, 2013	7	8 (range, 4-8)	14%††† (1/7)	0% (0/7)	3	100% (7/7)
Salas et al, 2013	5	7 (range, 3-8)	80%††† (4/5)	25% (1/4)	3 (range, 2-4)	100% (4/4)
Non-immediate HSR						
Vernassiere et al, 2004	9	7 (range, 3-7)	67%††† (6/9)	29% (2/7)	3 (range, 2-7)	86% (6/7)
Kanny et al, 2005	11	9 (range, 5-11)	82% (9/11)	67% (6/11)	8 (range, 3-10)	91% (10/11)

Kvedariene, et al, 2006	1	upto 12	100% (1/1)	100% (1/1)	9	NS
Torres et al, 2008	4	6	100% (4/4)	75% (3/4)	4 (range, 3-5)	100% (4/4)
Brockow et al, 2009	25††	11 (range, 8-13)	88% (22/25)	28% (7/25)	3 (range, 2-11)	97% (32/33)
Seitz et al, 2009	6	3.5 (range, 3-10)	67% (4/6)	100% (3/3)	6 (range, 3-8)	67% (2/3)
Goksel et al, 2011	1	2	100% (1/1)		2	NS
Hasdenteufel et al, 2011	7	upto 11	43% (3/7)	††††	3 (range, 2-3)	††††
Torres et al, 2012	14	upto 7	36%†† (5/14)	††††	2 (range, 2-3)	††††

HSR, hypersensitivity reaction; ICM, iodinated contrast media; NS, not specified. Cross-reactivity was extracted based on the results of intradermal tests with 10⁻¹ diluted ICM and patch tests with undiluted ICM. If drug provocation test was performed, results of drug provocation test were also used to assess cross-reactivity. Cross-reactivity was considered present when allergological tests including skin test or drug provocation test were positive to at least two ICM in skin test-positive patients.

†when four or more ICM were tested.

†† The text only described the result of cross-reactive testing with 8 or more ICM in patients with positive skin test.

††† The cross-reactivity rate was extracted based on not only skin tests but also drug provocation tests.

†††† Results of skin tests for evaluating cross-reactivity were described mainly focusing on positive cross-reactive ICM rather than whole results in the text.

‡ The abstract presented for a conference without available full-text publication in 2013 was initially identified by a literature search and data could be obtained through contact with the corresponding author via e-mail. This study was officially published in 2014.

Supplemental Table 8. Per-patient recurrence rate of HSR after challenge of skin test-negative ICM in patients with HSR to ICM

Source	Method of challenge	Recurrence rate of HSR	According to culprit or alternative ICM	
		to skin test-negative ICM	confined to skin test-negative culprit ICM	confined to skin test-negative alternative ICM
Immediate HSR				
Dewachter et al, 2001	full dose challenge	0% (0/2)	ND	0% (0/2)
Trcka et al, 2008	graded challenge with/without following full dose challenge	0% (0/2)	ND	0% (0/2)
Scherer et al, 2010	full dose challenge	0% (0/2)	ND	0% (0/2)
Caimmi et al, 2010	full dose challenge	4% (1/24)	100% (1/1)	0% (0/23)
Salas et al, 2013	drug provocation test	6% (5/79)	3~4% (2/50~61†)	≤17% (3/≥18††)
Prieto-Garcia et al, 2013	graded challenge with/without following full dose challenge	0% (0/7)	ND	0% (0/7)
Non-immediate HSR				
Vernassiere et al, 2004	graded challenge	42% (5/12)	100% (3/3)	18% (2/11)
Jiménez et al, 2006 †	full dose challenge	100% (2/2)	100% (2/2)	ND
Torres et al, 2008	drug provocation test	100% (2/2)	100% (2/2)	ND
Seitz et al, 2009	graded challenge with/without following full dose challenge	0% (0/4)	ND	0% (0/4)
Scherer et al, 2010	full dose challenge or graded challenge	75% (3/4)	ND	75% (3/4)

Caimmi et al, 2010	full dose challenge	25% (1/4)	ND	25% (1/4)
Hasdenteufel et al, 2011	full dose challenge	0% (0/22)	ND	0% (0/22)
Torres et al, 2012	drug provocation test	34% (55/161)	22% (25/115)	≥30% (36/≤119†††)

HSR, hypersensitivity reaction; ICM, iodinated contrast media; ND, not done.

†Only patch test was performed. This data was not pooled in meta-analysis as IDT was not performed.

†† In this study, skin test-negative culprit ICM was challenged when culprit ICM was known. There were eleven skin test-negative patients who refused to undergo drug provocation test. As the number of identified culprit ICM was not unknown in patients who refused drug provocation test, the exact number of patients could not be assessed.

††† The exact number of patients could not be identified as the exact number of patients undergoing drug provocation test using skin-test negative alternative ICM was unknown.

Supplemental Table 9. Protocols of drug provocation test, graded challenge, and full dose challenge in included studies

Source	Method of challenge	Initial dose (mL)	Step	Time interval between steps
Immediate HSR				
Dewachter et al, 2001	full dose challenge		Re-administration of full dose ICM	
Trcka et al, 2008	graded challenge with/without following full dose challenge	0.05	7 (day1,0.05-0.5-1-5-7.5-10-25 mL)	30 min
Scherer et al, 2010	full dose challenge		Re-administration of full dose ICM	
Caimmi et al, 2010	full dose challenge		Re-administration of full dose ICM	
Prieto-Garcia et al, 2013	graded challenge with/without following full dose challenge	5	4 (day1, 5-25-30 mL; day2, 60 mL)	30 min
Salas et al, 2013	drug provocation test	5	4 (day 1, 5-15-30-50 mL)	45 min
Non-immediate HSR				
Vernassiere et al, 2004	graded challenge	1/100 of the dose required for radiological examination	3 (1/100-1/10-full dose)	2-24 hr
Jiménez et al, 2006	full dose challenge		Re-administration of full dose ICM	
Torres et al, 2008	drug provocation test	1/10 of the dose required for radiological examination	3 (day1, 1/10-1/10?;day7, full dose)	8hr, 8hr,1 week
Seitz et al, 2009	graded challenge with/without following full dose challenge	1	5 (day1, 1-5-7.5-10-30 mL)	1 hour
Scherer et al, 2010	full dose challenge or graded challenge		Re-administration of full dose ICM, not specified in regard to graded challenge	
Caimmi et al, 2010	full dose challenge		Re-administration of full dose ICM	

Hasdenteufel et al, 2011	full dose challenge		Re-administration of full dose ICM	
Torres et al, 2012	drug provocation test	5	6 (day1, 5-10-15 mL; day7, 20-30-50 mL)	1hour

HSR, hypersensitivity reaction; ICM, iodinated contrast media.

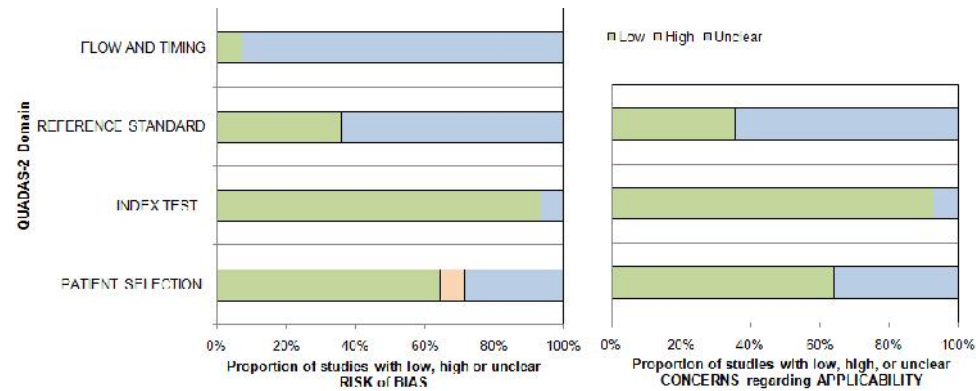
Supplemental Table 10. Summary of sensitivity analyses on positive rates of skin tests

Stratified Analysis	No. of studies	No. of patients	Pooled proportion (95% Confidence interval)	I ² statistics	P value
Immediate HSR					
Fixed-effects model	8	649	0.193 (0.161-0.229)		
Patients with mild HSR					
<40%	3	210	0.298 (0.204-0.413)	37%	0.087
≥40%	5	439	0.108 (0.058-0.191)	44%	0.002
Known culprit ICM					
≥75%	3	135	0.304 (0.196-0.438)	36%	0.093
<75% or NS	5	514	0.109 (0.055-0.205)	46%	<0.001
Number of ICM for skin tests					
≥9	4	311	0.256 (0.167-0.372)	42%	0.01
<9 or NS	4	401	0.096 (0.041-0.209)	45%	0.001
Time interval between HSR and the skin test (mean or median)					
≤1year	5	337	0.183 (0.088-0.343)	46%	<0.001
>1year or NS	3	312	0.143 (0.063-0.293)	46%	0.001
Severe immediate HSR					
Fixed-effects model	10	125	0.539 (0.434-0.641)		
Known culprit ICM					
≥75%	6	70	0.715 (0.595-0.811)	44%	0.405
<75% or NS	4	55	0.237 (0.072-0.555)	36%	0.067
Number of ICM for skin tests					
≥9	3	41	0.484 (0.208-0.770)	38%	0.073

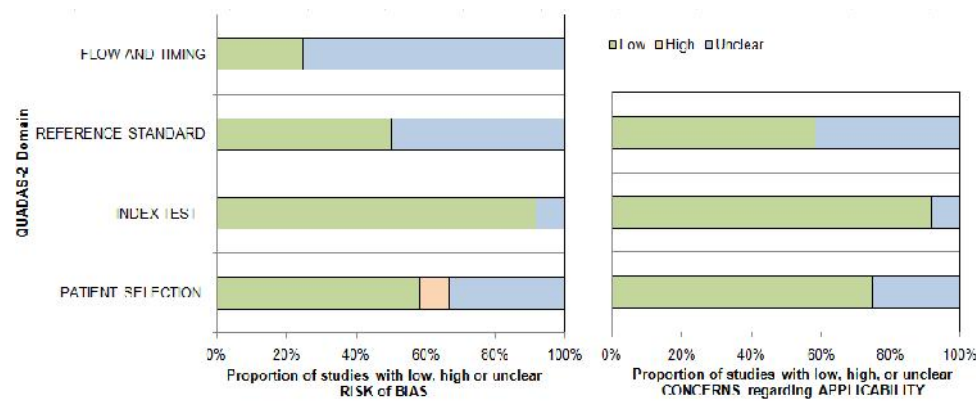
<9 or NS	7	84	0.527 (0.250-0.789)	42%	0.002
Time interval between HSR and the skin test (mean or median)					
≤1yr	6	46	0.593 (0.312-0.824)	33%	0.069
>1yr or NS	4	79	0.427 (0.145-0.765)	46%	<0.001
Non-immediate HSR					
Fixed-effects model	8	369	0.261 (0.213-0.314)		
Proportion of patients with mild HSR					
<40%	5	239	0.190 (0.103-0.325)	40%	0.019
≥40%	3	130	0.385 (0.213-0.591)	39%	0.058
Known culprit ICM					
≥75%	7	352	0.269 (0.146-0.441)	46%	0.001
<75% or NS	1	17	0.176 (0.058-0.427)		
Number of ICM for skin tests					
≥9	2	115	0.303 (0.137-0.545)	38%	0.095
<9 or NS	6	254	0.247 (0.121-0.440)	45%	<0.001
Time interval between HSR and the skin test (mean or median)					
≤1year	5	298	0.279 (0.118-0.528)	47%	<0.001
>1year or NS	3	71	0.231 (0.146-0.345)	0%	0.316

HSR, hypersensitivity reaction; ICM, iodinated contrast media; NS; not specified.

Supplemental Figure 1. Quality assessment of included studies on immediate and non-immediate hypersensitivity reactions to iodinated contrast media

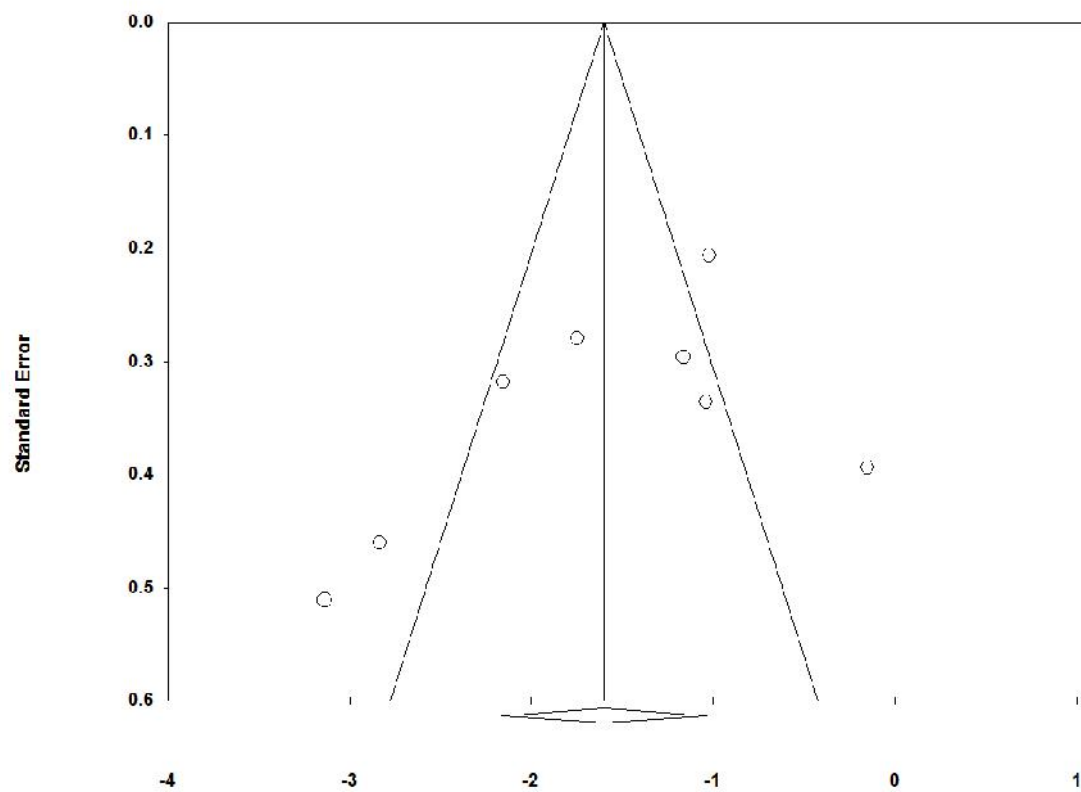


Immediate hypersensitivity reactions to iodinated contrast media

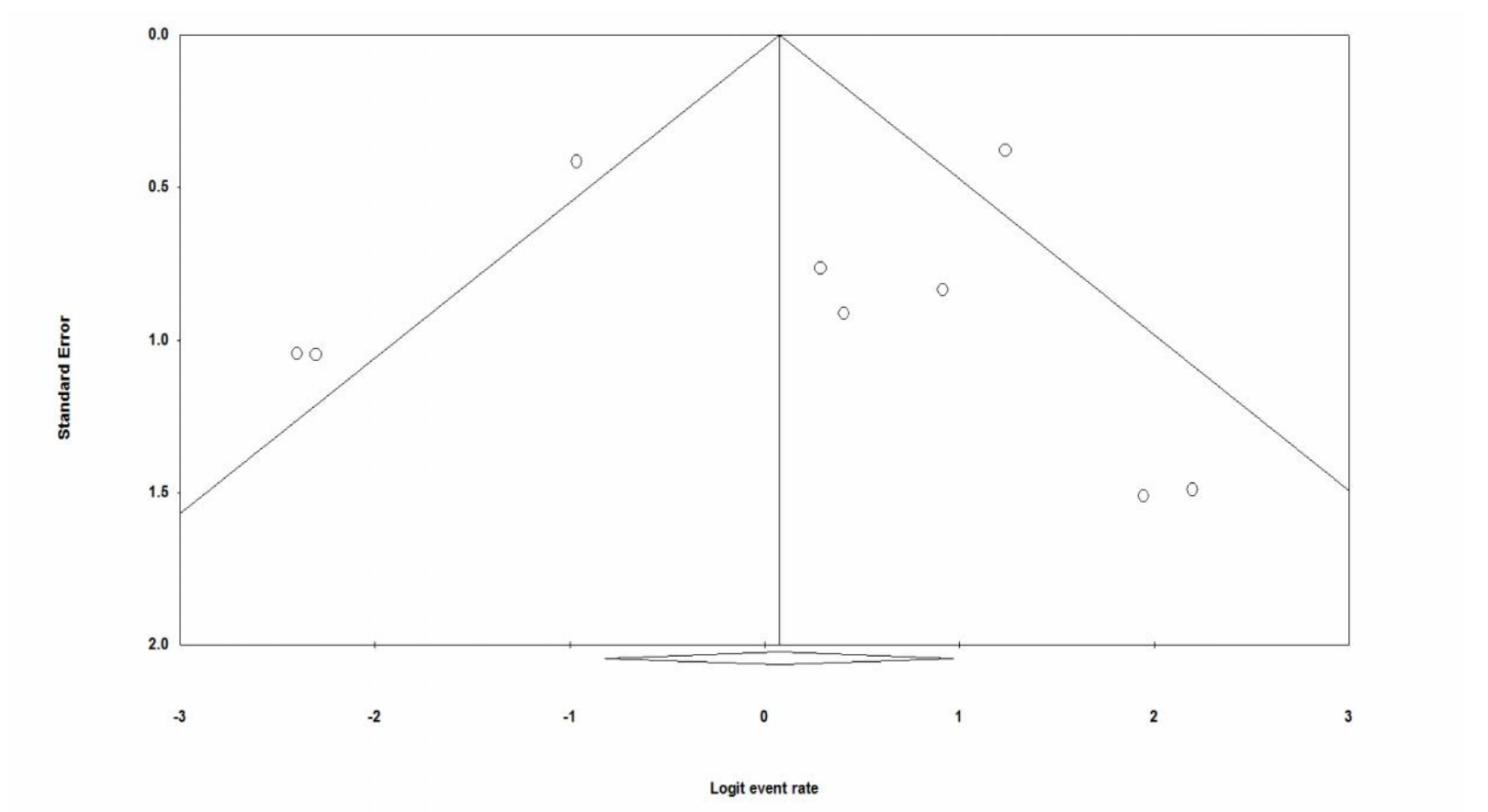


Non-immediate hypersensitivity reactions to iodinated contrast media

Supplemental Figure 2. Funnel plot of included studies evaluating positive rates of skin tests in immediate hypersensitivity reactions



Supplemental Figure 3. Funnel plot of included studies evaluating positive rates of skin tests in severe immediate hypersensitivity reactions



Supplemental Figure 4. Funnel plot of included studies evaluating positive rates of skin tests in non-immediate hypersensitivity reactions

