BMJ Open

Pharmacological prevention of allergic-like reactions caused by contemporary iodinated contrast media: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033023
Article Type:	Protocol
Date Submitted by the Author:	17-Jul-2019
Complete List of Authors:	Umakoshi, Hiroyasu ; Toyohashi Municipal Hospital, Radiology Nihashi, Takashi ; Komaki Shimin Byoin, Department of Radiology Shimamoto, Hironori ; Toyohashi Municipal Hospital, Radiology Yamada, Takehiro ; Toyohashi Municipal Hospital, Radiology Ishiguchi, Hiroaki ; Komaki City Hospital, Radiology Takada, Akira ; Toyohashi Municipal Hospital, Radiology Hirasawa, Naoki; Komaki City Hospital, Radiology Ishihara, Shunichi ; Toyohashi Municipal Hospital, Radiology Takehara, Yasuo; Nagoya University Graduate School of Medicine Faculty of Medicine, Naganawa, Shinji; Nagoya University School of Medicine, Department of Radiology Davenport, Matthew ; Michigan Medicine, Radiology Terasawa, Teruhiko; Fujita Health University, Emergency and General Internal Medicine
Keywords:	Diagnostic radiology < RADIOLOGY & IMAGING, Premedication, Contrast media, Preventive effectiveness

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Pharmacological prevention of allergic-like reactions caused by contemporary iodinated contrast media: a systematic review protocol

Hiroyasu Umakoshi,[1,2] Takashi Nihashi,[2,3] Hironori Shimamoto,[1] Takehiro Yamada,[1] Hiroaki Ishiguchi,[3] Akira Takada,[1] Naoki Hirasawa,[3] Shunichi Ishihara,[1] Yasuo Takehara,[2] Shinji Naganawa,[2] Matthew S. Davenport,[4] Teruhiko Terasawa[5,6]

[1]Department of Radiology, Toyohashi Municipal Hospital, Toyohashi, Japan

[2]Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[3]Department of Radiology, Komaki City Hospital, Komaki, Japan

[4]Department of Radiology, Michigan Medicine, Ann Arbor, MI, USA

[5]Section of General Internal Medicine, Department of Emergency and General Internal Medicine, Fujita Health University, Toyoake, Japan

[6]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA

Word count

Abstract: 213 (<300)

Text: 2,478 (<4000)

References: 29

Corresponding author: Teruhiko Terasawa, MD, PhD

Section of General Internal Medicine, Department of Emergency and General Internal Medicine, Fujita Health University School of Medicine

1-98 Dengakugakubo, Kutsukakecho, Toyoake, Aichi 470-1192, Japan

Phone & Fax: +81-562-93-2497

E-mail: terasawa@fujita-hu.ac.jp

ABSTRACT

Introduction: Iodinated contrast media are commonly used in medical imaging and can cause allergic-like reactions, including rare but severe life-threatening reactions. Although several prophylactic approaches have been proposed for severe reactions, their effects remain unclear. Therefore, we aim to review systematically the preventive effects of commonly proposed regimens and predictors of severe reactions.

Methods and analysis: We will search the PubMed, EMBASE, and CENTRAL databases from January 1, 1990 through March 31, 2019 and will examine the bibliographies of eligible studies, pertinent review articles, and clinical practice guidelines. We will include prospective and retrospective studies of any design that evaluated the effects of pharmacological preventive strategies for allergic-like reactions prior to iodinated contrast media administration. Two assessors will independently extract the characteristics of the study and intervention and the quantitative results. Unique preventive strategies (e.g., dose, drug, and duration) will be analyzed separately. Average- and high-risk patients will be considered separately. The risk of bias will be assessed by two independent reviewers using standard design-specific validity assessment tools. A meta-analysis will be performed if appropriate.

Ethics and dissemination: Ethics approval is not applicable, as this will be a secondary analysis of publicly available data. The results of the analysis will be submitted for publication in a peer reviewed journal.

PROSPERO registration number: CRD42019134003.

Strengths and limitations of this study

-This will be the first systematic review and meta-analysis to assess and compare the preventive effectiveness of premedication strategies for allergic-like reactions caused by contemporary low-osmolar iodinated contrast materials.

-Comprehensive literature searches and up-to-date systematic review methodologies will be used to identify actionable evidence.

-If the number of studies is too small and/or clinical or statistical across-study heterogeneity is deemed too great, we may not be able to perform a quantitative synthesis.

INTRODUCTION

Iodinated contrast media are commonly used to augment computed tomography (CT) examinations for diagnosis and treatment monitoring. However, contemporary non-ionic iodinated contrast media cause physiologic (e.g., nausea) or allergic-like (e.g., urticaria) acute adverse reactions ranging from mild nausea or pruritus to hemodynamic shock and cardiopulmonary arrest in approximately 3% of patients.[1 2] Life-threatening reactions occur in approximately 4 in 10,000 cases.[1] As millions of doses of iodinated contrast media are administered annually, severe reactions are expected to occur commonly within a population.[3]

The mechanism underlying acute adverse reactions is not fully understood and is likely multifactorial.[2] These allergic-like reactions have clinical manifestations similar to those of typical allergic reactions involving the release of histamine and other inflammatory mediators, whereas the physiologic reactions involve a chemotoxic response to the administered contrast material without allergic-like symptoms. The distinction of allergic-like from physiologic reactions is important but is performed variably in clinical care and research settings. This distinction is important because prophylactic regimens (e.g., corticosteroids, antihistamines) are designed to prevent allergic-like reactions, but not physiologic reactions.

However, the best premedication strategy remains uncertain, and only weak evidence

supports prophylaxis for the prevention of severe reactions. The factors used to predict allergic-like reactions[2 4] do not specifically predict who will develop a severe reaction; rather, they generally predict who might have a reaction of any severity. Additionally, prophylaxis is not always effective (i.e., breakthrough reactions occur) and is associated with unintended side effects (e.g., increased costs and length of hospitalization); further, the comparative effectiveness of competing prophylactic regimens is unclear.[5 6 7 8 9 10] Although several standard regimens exist, including those proposed by American College of Radiology (ACR),[2] ad-hoc modifications of these regimens are common in clinical practice. Given this uncertainty, the 2019 European Society of Urogenital Radiology (ESUR) Guideline on Contrast Agents indicates that "premedication is not recommended because there is not good evidence of its effectiveness."[4]

Since the publication of two systematic reviews in 2006 that evaluated the effectiveness of premedication regimens,[11 12] several relevant studies and alternative strategies have been published (e.g., exchanging one contrast medium for an alternative) and used to influence the ACR and ESUR guidelines.[13 14] In addition, the two prior systematic reviews on this topic included prophylaxis in the context of now-outdated high-osmolality iodinated contrast media that are no longer used in clinical practice. Therefore, we planned a comprehensive quantitative synthesis of clinical data on the effects of premedication for the prevention of allergic-like reactions to contemporary iodinated contrast material.

METHODS AND ANALYSIS

This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement (PRISMA-P).[15] Based on the analytic framework shown in the **Figure**, we have formulated the following three key research questions:

Key Question 1. What is the preventive effect of standard-duration oral (12- or 13-hour), accelerated intravenous (≥5-hour), or emergent (<5-hour) premedication with or without a change of contrast media (CM) on acute (<1 hour) allergic-like reactions in patients receiving CM?

Key Question 2. What are the patient-level and intervention-level characteristics (i.e., predictors) associated with CM-induced acute allergic-like reactions?

Key Question 3. What are the complications and adverse events associated with premedication?

Literature search

We will search the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from January 1, 1990 through March 31, 2019 for both English- and non-English-language publications, using search terms such as "iodinated contrast media," "premedication," "allergic-like reaction," breakthrough reactions," and their synonyms. The complete search strategy and full list of databases are available as an online Supplementary file. We will include studies published after the 1990s, when

contemporary low-osmolar CMs were developed and disseminated widely. We will also examine the references of eligible studies, relevant review articles, and existing clinical practice guidelines developed by professional societies such as ACR and ESUR.[2 4]

Inclusion and exclusion criteria

We will include studies that assessed patients who received intravenous or intra-arterial non-ionic iodinated contrast material with or without premedication based on corticosteroids, anti-histamines, or both. The **Table** presents our detailed inclusion criteria, which follow the PICOD framework. We will exclude studies that tested other medications (e.g., ephedrine, diazepam, atropine) because these are not relevant to current clinical practice. We also will exclude studies that assessed patients who received high-osmolar contrast material. Both prospective and retrospective studies of any design that evaluated at least 10 patients will be included.

We will employ the current ACR categorization system to classify and grade acute adverse events, and physiologic reactions will be considered separately from allergic-like reactions.[2] Delayed reactions occurring more than 1 hour after contrast media administration will not be assessed. A breakthrough reaction will be defined as an acute allergic-like reaction of any severity that occurs despite premedication. We will classify any randomized controlled trials (RCTs) and any studies with a non-randomized design that compared two or more intervention groups (i.e., so-called

non-randomized studies of intervention [e.g., quasi-RCTs, cohort studies, case-control studies]) as "comparative studies." "Non-comparative studies" will include single-group studies and case series.

We will exclude editorials, comments, letters to the editor, and review articles. When multiple publications with potentially overlapping patient populations are reported, we will only include the publication with the largest sample size. We will contact the study authors by email if the publications do not report adequate information about the patient characteristics and reaction classifications. We will consider our request to be rejected if two email request reminders sent separately 14 days after the initial contact attempt are rejected.

The results of our electronic searches will be imported into reference management software and de-duplicated. Two paired investigators will screen non-overlapping sets of abstracts and will examine full-text articles for potentially eligible citations. A third investigator will adjudicate any discrepant results if consensus cannot be reached between the two reviewers.

Data extraction

We will extract the following descriptive data from eligible studies: first author, year of

publication, journal, study design (prospective *vs.* retrospective, comparative study *vs.* non-comparative study) as the study characteristics; age, sex, history and severity and type of any prior acute adverse reaction to iodinated contrast material, allergic diathesis including severe allergy(-ies) to other substances and asthma,[2] and other known risk factors for allergic-like reactions, as the participant characteristics; brand and/or generic names and doses of contrast media administered as contrast media characteristics; premedication strategies including drugs, doses, duration, and change in contrast agent as the intervention characteristics; details of and change in allergic-like reactions (kinds and severity), assessors of adverse reactions (number and experience), and categorization system to classify and grade acute adverse events, as the outcome characteristics. We will operationally define standard elective regimens as the 12- to 13-hour oral administration of corticosteroids, and standard accelerated regimens as a minimum 5-hour intravenous administration of corticosteroids with or without the use of an anti-histamine.[2] If a study adopted definitions or categorization systems other than those proposed by the ACR, we will specify these differences in sufficient detail. One primary investigator will extract the descriptive data, which will be verified by a second investigator.

Two reviewers will independently extract quantitative data. We will determine the relative risk of an allergic-like reaction between two (or more) groups in comparative studies. We will extract the number of patients in each group, as well as the number of patients who developed an allergic-like reaction. If relevant count data cannot be determined from the publication, we will instead extract the reported point estimates and their confidence intervals.

We will extract quantitative measures (e.g., risk ratios, odds ratios) of the association of the presence or absence of a predictor with the development of a breakthrough reaction. We will prefer adjusted values over unadjusted values if both are reported. *A priori* candidate predictors selected for extraction include specific index allergic-like reactions and their ACR grades, and any allergic diathesis and its severity.

Assessment of risk of bias

For RCTs, we will use the "revised tool to assess risk of bias in randomized trials" (RoB 2 tool)[16]. We will assess five specific domains of RCT study validity (i.e., randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, selective reporting) and then assign an overall risk of bias for each trial.

For non-randomized intervention studies, we will use the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for cohort studies,[17] and the Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) for case-control studies.[18] We will assess seven specific domains of study validity (i.e., confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selective reporting) and then assign an overall risk of bias for each study.

For single-group observational studies that assessed a predictor with the development of a breakthrough reaction, we will use a revised version of the Quality in Prognosis Studies tool (the QUIPS-2).[19] We will assess six specific domains of study validity (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis and reporting) and then assign an overall risk of bias for each study.

Two reviewers will independently assess each item and rate the domain-specific and overall risks of bias. Discrepant ratings will be resolved by consensus. A third independent investigator will adjudicate any unresolved discrepancies. The complete list of modified operational definitions used to rate each item will be available from the authors upon request.

Data synthesis

The primary outcome of interest will be the relative risk of an acute allergic-like reaction between competing premedication strategies. Secondary outcomes will include the breakthrough reaction rate of each specific regimen and the predictive performances of covariates for overall and severe breakthrough reactions. For all outcome measures, we will first construct an evidence map by performing qualitative syntheses based on graphs and tables to examine the diversity and volume of available evidence on this topic.[20 21] If feasible, we will then perform a quantitative synthesis.

For summary relative measures (e.g., relative risk of an acute allergic-like reaction) based on count data, we will perform a random-effects meta-analysis using the binomial likelihood with logit link in a generalized linear modeling framework (i.e., random-effects logistic regression).[22] If already-estimated relative measures are the only extractable formats, we will utilize the log-transformed estimates and their variances as "plug-in" estimates. If appropriate, the meta-analytical model for a specific pairwise comparison will be extended to a network meta-analysis to synthesize data from both direct and indirect comparisons of all available studies in a single analysis.[22]

For summary estimates of the proportion measures in non-comparative studies, we will perform a random-effects meta-analysis of proportions using the binomial likelihood and logit link (i.e., so-called the binomial-normal model).[23]

Additional analyses

We will estimate the between-study standard deviation parameter, *tau*, and I^2 statistic and corresponding 95% credible intervals as measures of statistical heterogeneity. An I^2 >50% will indicate intermediate heterogeneity, while an I^2 >70% will indicate high heterogeneity.[24]

To explore statistical heterogeneity, we will perform subgroup analyses and, if feasible, a univariable random-effects meta-regression.[22] Preplanned candidate factors will include the use of standardized regimens (vs. non-standardized or *ad-hoc* regimens), alterations of the culprit contrast media (vs. not), use of the ACR categorization system for the classification and grading of reactions (vs. not), and severity and type of prior reactions to iodinated contrast media. We will consider conducting sensitivity analyses by reclassifying and/or re-grading the reported reactions based on the ACR classification system for studies not using this system, if pertinent individual-level data are presented.

We will assess funnel-plot asymmetry if at least 10 studies are included.[25] To address potential biases derived from missing outcome data, we will apply the approach proposed by Turner et al.[26] We will assess the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. [27]

Statistical software

We will conduct all analyses using Stata version 14/SE (Stata Corp., College Station, TX, USA) and OpenBUGS version 3.2.3 (members of OpenBUGS Project Management Group; see www.openbugs.net). All tests will be two-sided, and statistical significance will be defined as a P value <0.05.

Patient and Public Involvement

We did not involve patients or the public in the preparation of this systematic review protocol.

DISCUSSION

The revised ESUR guidelines on contrast agents (published March 2018) retracted the recommendations for the premedication of patients at an increased risk of contrast reaction, due to a lack of scientific evidence of efficacy.[4] This position is inconsistent with the latest guidelines of other professional societies, including the ACR (ACR Manual on Contrast Media v. 10.3),[2] the Canadian Association of Radiologists,[28] and the Japan Radiological Society.[29] Given the wide application of iodinated contrast media in medical imaging and interventional procedures, the uncertainty surrounding the optimization of prevention strategies, and the absence of recently published evidence reviews, we believe that it will be worthwhile to conduct a new systematic

review that critically examines the existing evidence. Using a comprehensive evidence map of the published literature on the effects of premedication and, if feasible, new meta-analytic results, we hope to clarify the actionable evidence regarding the use of premedication.

ETHICS AND DISSEMINATION

As this is a systematic review, we are not planning to obtain a formal ethical approval. The findings from the review will be disseminated through publications in peer-reviewed journals, and presentations at conferences.

Contributors

HU and TN originated the idea; HU, TN and TT drafted the initial version of the protocol; HU, TN and TT developed the search strategy; HS, TY, HI, AT, NH, SI, YT, SN, and MSD reviewed the protocol and suggested amendments. All authors read and approved the final version of the protocol. HU, TN, and TT are guarantors of the review.

Funding

TT was supported in part by the Ministry of Education, Culture, Sports, Science and Technology, Japan (JSPS KAKENHI Grant Numbers: 26460755 and 19K07877). The

funding source had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest

All authors declare no conflicts of interest associated with this publication.

For complete transparency outside the submitted work, Dr. Ishihara reports personal fees from Bayer Yakuhin, Ltd.; Dr. Takehara is an endowed chair sponsored by HIMEDIC Co. He does not receive any financial support from the corporation for conducting the research and writing this paper. He also reports personal fees from Daiichi Sankyo company, Ltd., Bayer Yakuhin, Ltd., GE Healthcare, Medi-Physics Co Ltd., Mitsubishi Tanabe Pharma Corporation, and National Cancer Center; Dr. Naganawa reports personal fees from Daiichi Sankyo company, Ltd., Kowa Company, Ltd., Bayer Yakuhin, Ltd., Fuji Pharma Co Ltd., Bracco-Eisai Co Ltd., FUJIFILM Toyama Chemical Co Ltd., Canon medical systems corporation, Siemens Healthineers Japan, Trust Clinic, Nagoya Jhohoku Radiology Clinic, Gakken Medical Shujunsha Co Ltd, and Neuryon AG; and Dr. Davenport reports the royalties from Wolters Kluwer and uptodate.com.

Disclosure

A preliminary work of this research project based on a brief literature search has been

presented in an educational session at the 77th annual meeting of the Japan Radiological Society 2018, Yokohama, Japan.

References

1. Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990;**175**(3):621-8.
2. ACR Committee on Drugs and Contrast Media. ACR Manual On Contrast Media Version 10.3 2018. Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf. Accessed on July 1, 2019.
3. Bettmann MA. Frequently asked questions: iodinated contrast agents. Radiographics 2004;**24 Suppl 1**:S3-10.
4. European Society of Urogenital Radiology. ESUR Guidelines on Contrast Media ver10.0 2018. Available from: http://www.esur.org/guidelines/en/index.php#a. Accessed on July 1, 2019.
5. Mervak BM, Davenport MS, Ellis JH, et al. Rates of Breakthrough Reactions in Inpatients at High Risk Receiving Premedication Before Contrast-Enhanced CT. Am J Roentgenol 2015;**205**(1):77-84.
6. Davenport MS, Cohan RH, Caoili EM, et al. Repeat contrast medium reactions in premedicated patients: frequency and severity. Radiology 2009;**253**(2):372-9.
7. Freed KS, Leder RA, Alexander C, et al. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. Am J Roentgenol 2001;**176**(6):1389-92.
8. Davenport MS, Cohan RH, Khalatbari S, et al. Hyperglycemia in hospitalized patients receiving corticosteroid premedication before the administration of radiologic contrast medium. Acad Radiol 2011;**18**(3):384-90.
9. Davenport MS, Mervak BM, Ellis JH, et al. Indirect Cost and Harm Attributable to Oral 13-Hour Inpatient Corticosteroid Prophylaxis before Contrast-enhanced CT. Radiology 2016;**279**(2):492-501.
10. Mesurolle B, Ariche M, Cohen D. Premedication before i.v. contrast-enhanced CT resulting in steroid-induced psychosis. Am J Roentgenol 2002;**178**(3):766-7.
11. Delaney A, Carter A, Fisher M. The prevention of anaphylactoid reactions to iodinated radiological contrast media: a systematic review. BMC Med Imaging 2006;**6**:2.
12. Tramer MR, von Elm E, Loubeyre P, et al. Pharmacological prevention of serious

anaphylactic reactions due to iodinated contrast media: systematic review. BMJ 2006;**333**(7570):675.

13. Abe S, Fukuda H, Tobe K, et al. Protective effect against repeat adverse reactions to iodinated contrast medium: Premedication vs. changing the contrast medium. Eur Radiol 2016;**26**(7):2148-54.
14. Park HJ, Park JW, Yang MS, et al. Re-exposure to low osmolar iodinated contrast media in patients with prior moderate-to-severe hypersensitivity reactions: A multicentre retrospective cohort study. Eur Radiol 2017;**27**(7):2886-93.
15. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;**350**:g7647.
16. Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, et al., eds. Cochrane Methods Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). Available from https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0. Accessed on July 1, 2019.
17. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;**355**:i4919.
18. Sterne JAC, Higgins JPT, Reeves BC, et al. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0. 2014 24 September 2014. Available from: http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-i/acrobat-nrsi/. Accessed on July 1, 2019.
19. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;**158**(4):280-6.
20. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018;**18**(1):143-43.
21. Miake-Lye IM, Hempel S, Shanman R, et al. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Syst Rev 2016;**5**:28-28.
22. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis

of randomized controlled trials. Med Decis Making 2013;**33**(5):607-17.

23. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med 2010;**29**(29):3046-67.
24. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;**327**(7414):557-60.
25. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;**343**:d4002.
26. Turner NL, Dias S, Ades AE, et al. A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Stat Med 2015;**34**(12):2062-80.
27. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;**336**(7650):924-6.
28. Morzycki A, Bhatia A, Murphy KJ. Adverse Reactions to Contrast Material: A Canadian Update. Can Assoc Radiol J 2017;**68**(2):187-93.
29. Japan Radiological Society. Revised recommendations on steroid premedication for reducing the risk of acute adverse effects of iodinated contrast agents and gadolinium contrast agents 2018. *Japanese.* Available from: http://www.radiology.jp/member_info/safty/20181115.html. Accessed on July 1, 2019.

Table. Inclusion criteria based on the PICOD framework

PICOD	Specific details
Population	Patients who received intravenous or intra-arterial non-ionic iodinated CM*
	-High-risk population
	-Low-risk population
	-No risk-stratified population
Interventions /Comparators and co-interventions	Premedication† 1. 12- or 13-hour corticosteroids with or without anti-histamine 2. 5-hour IV corticosteroids with or without anti-histamine 3. Any less than 5 hours, including steroids, anti-histamine, or both Co-interventions allowed:
	-Change of CM that caused past reactions
Outcomes	Rates of acute (<1 hour) allergic-like reactions‡
	-Acute reaction-related deaths within 30 days
	-Severe reactions only
	-Moderate and severe reactions only
	-Upgraded reactions compared to the index reactions
	-All allergic-like reactions
	Rates of adverse events induced by premedication
Predictors of acute allergic-like reactions	Patient-level characteristics

	-Prior allergic-like reactions
	-Prior physiologic reactions§
	-Allergic diathesis (e.g., asthma, food or drug allergy, etc.)
	Intervention-level characteristics
	-Type of premedication
	-Dosing of premedication
	-Change of CM (specific class/product and/or dosing)
Designs	Any study designs including at least 10 patients
	-Randomized controlled trials
	-Nonrandomized trials
	-Prospective and retrospective cohorts
	Comparative (two or more-group) design
	Single-group design

* Per-study defined risk criteria are allowed.

†Both standard and *ad-hoc* regimens are allowed, but will be analyzed separately. Standard oral regimens are defined as follows:[2] 13-hour regimen: prednisone 50 mg PO at 13, 7, and 1 hrs before CM injection +/- optional diphenhydramine 50 mg IV, IM, or PO at 1 hr before CM injection; 12-hour regimen: methylpredonisolone 32 mg PO at 12, and 2 hrs before CM injection +/- optional antihistamine. Standard urgent regimens are: methylprednisolone 40 mg or hydrocortisone 200 mg IV every 4 hrs until CM injection

(minimum cumulative duration 5 hours) +/- diphenhydramine 50 mg IV at 1 hr before CM injection. Any premedication that does not include corticosteroids or that is less than 5 hours in duration is non-standard.

‡Grades of allergic-like reactions are defined as follows[2]: mild reactions include limited urticaria/pruritis, cutaneous edema, limited "itchy"/"scratchy" throat, nasal congestion, sneezing, conjunctivitis, and rhinorrhea; moderate reactions include diffuse urticaria/pruritis, diffuse erythema with stable vital signs, facial edema without dyspnea, throat tightness or hoarseness without dyspnea, and wheezing/bronchospasm with mild or no hypoxia; and severe reactions include diffuse edema, facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing/bronchospasm with significant hypoxia, and anaphylactic shock (hypotension + tachycardia).

§Grades of physiologic reactions are defined as follows[2]: mild reactions include limited nausea/vomiting, transient flushing, warmth, chills, headache, dizziness, anxiety, altered taste, mild hypertension, and vasovagal reaction that resolves spontaneously; moderate reactions include protracted nausea/vomiting, hypertensive urgency, isolated chest pain, and vasovagal reaction that requires and is responsive to treatment; and severe reactions include vasovagal reaction resistant to treatment, arrhythmia, convulsions, seizures, and hypertensive emergency.

Abbreviations: CM = contrast medium; IM = intramuscularly; IV = intravenously; PO = orally

Figure legend

Figure. Analytic framework.

Abbreviations: CM = contrast media; KQ = key question

Key Question 1. What is the preventive effect of premedication with or without change of contrast media (CM) on acute (<1 hour) allergic-like reactions for patients receiving CM?
Key Question 2. What are the patient-level and intervention-level characteristics (i.e., predictors) associated with CM-induced acute allergic-like reactions?
Key Question 3. What are the complications and adverse events associated with premedication?

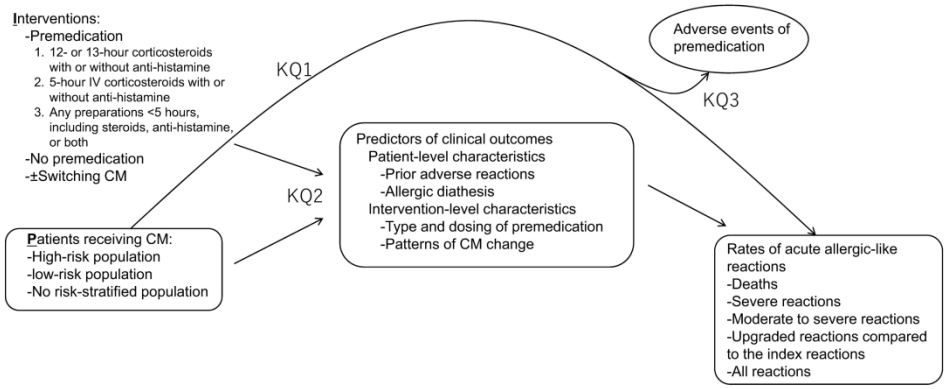


Figure. Analytic framework.
Abbreviations: CM = contrast media; KQ = key question

296x167mm (300 x 300 DPI)

SUPPLEMENTARY FILE

Search strategies

PubMed

1. "Contrast Media"[Pharmacological Action]
2. radiocontrast*
3. iodinated contrast*
4. contrast material*
5. iodine contrast*
6. iodixanol OR iohexol OR iopamidol OR ioversol OR ioxilan OR iopromide OR ioxaglate
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. "Adverse Effects"[Subheading]
9. Adverse
10. "side effect"
11. "side effects"
12. reaction*
13. harm*
14. complicat*
15. toxicit*
16. hypersensitiv*
17. breakthrough reaction*
18. anaphyla*
19. allerg*
20. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21. Premedication[Mesh]
22. premedicat*
23. prevent*
24. prophyla*
25. steroid*
26. corticosteroid*
27. antihistamine*
28. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
29. #7 AND #20 AND #28

Cochrane Central Register of Controlled Trials (Ovid)

1. contrast media.mp. or exp Contrast Media/
2. radiocontrast*.mp.
3. iodinated contrast*.mp.
4. contrast material*.mp.
5. Iodine/ or iodine contrast*.mp.
6. (iodixanol or iohexol or iopamidol or ioversol or ioxilan or iopromide or ioxaglate).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. 1 or 2 or 3 or 4 or 5 or 6
8. Adverse Effects.mp.
9. "Drug-Related Side Effects and Adverse Reactions"/ or adverse.mp.
10. side effect.mp.
11. side effects.mp.
12. reaction*.mp.
13. Patient Harm/ or harm*.mp.
14. complicat*.mp.
15. toxicit*.mp.
16. Hypersensitivity/ or hypersensitiv*.mp.
17. breakthrough reaction*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
18. Anaphylaxis/ or anaphyla*.mp.
19. allerg*.mp.
20. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. premedication.mp. or Premedication/
22. premedicat*.mp.
23. prevent*.mp.
24. prophyla*.mp.
25. steroid*.mp.
26. Glucocorticoids/ or corticosteroid*.mp.
27. antihistamine*.mp. or Histamine H1 Antagonists/
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 7 and 20 and 28

Embase

1. 'contrast medium'/exp OR 'contrast medium'
2. radiocontrast*
3. 'iodinated contrast medium'/exp OR 'iodinated contrast medium'
4. iodinated AND contrast*
5. ('contrast'/exp OR contrast) AND material*
6. ('iodine'/exp OR iodine) AND contrast*
7. 'iodixanol'/exp OR iodixanol OR 'iohexol'/exp OR iohexol OR 'iopamidol'/exp OR iopamidol OR 'ioversol'/exp OR ioversol OR 'ioxilan'/exp OR ioxilan OR 'iopromide'/exp OR iopromide OR 'ioxaglate'/exp OR ioxaglate
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. 'adverse event'/exp OR 'adverse event'
10. Adverse
11. 'side effect'/exp OR 'side effect'
12. 'side effects'
13. reaction*
14. harm*
15. 'complication'/exp OR 'complication'
16. complicat*
17. 'toxicity'/exp OR 'toxicity'
18. toxicit*
19. 'hypersensitivity'/exp OR 'hypersensitivity'
20. hypersensitiv*
21. breakthrough AND reaction*
22. 'anaphylaxis'/exp OR 'anaphylaxis'
23. anaphyla*
24. allerg*
25. 'immediate type hypersensitivity'/exp OR 'immediate type hypersensitivity'
26. 'allergy'/exp OR 'allergy'
27. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28. 'premedication'/exp OR 'premedication'
29. premedicat*
30. 'prevention'/exp OR 'prevention'
31. prevent*
32. 'prophylaxis'/exp OR 'prophylaxis'

33. prophyla*
34. 'steroid'/exp OR 'steroid'
35. steroid*
36. 'corticosteroid'/exp OR 'corticosteroid'
37. corticosteroid*
38. 'antihistaminic agent'/exp OR 'antihistaminic agent'
39. 'histamine h1 receptor antagonist'/exp OR 'histamine h1 receptor antagonist'
40. antihistamine*
41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
42. #8 AND #27 AND #41
43. #42 AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'short survey'/it)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reporting Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	5
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7 and supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9-10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Pharmacologic and non-pharmacologic interventions to prevent hypersensitivity reactions of non-ionic iodinated contrast media: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033023.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Jan-2020
Complete List of Authors:	Umakoshi, Hiroyasu ; Toyohashi Municipal Hospital, Radiology Nihashi, Takashi ; Komaki Shimin Byoin, Department of Radiology Shimamoto, Hironori ; Toyohashi Municipal Hospital, Radiology Yamada, Takehiro ; Toyohashi Municipal Hospital, Radiology Ishiguchi, Hiroaki ; Komaki City Hospital, Radiology Takada, Akira ; Toyohashi Municipal Hospital, Radiology Hirasawa, Naoki; Komaki City Hospital, Radiology Ishihara, Shunichi ; Toyohashi Municipal Hospital, Radiology Takehara, Yasuo; Nagoya University Graduate School of Medicine Faculty of Medicine, Naganawa, Shinji; Nagoya University, Department of Radiology Davenport, Matthew ; University of Michigan, Department of Radiology and Urology, Michigan Radiology Quality Collaborative, University of Michigan Health System Terasawa, Teruhiko; Fujita Health University, Emergency and General Internal Medicine
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Diagnostics, Evidence based practice, Radiology and imaging
Keywords:	Diagnostic radiology < RADIOLOGY & IMAGING, Premedication, Contrast media, Preventive effectiveness

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Pharmacologic and non-pharmacologic interventions to prevent hypersensitivity reactions of non-ionic iodinated contrast media: a systematic review protocol

Hiroyasu Umakoshi,[1,2] Takashi Nihashi,[2,3] Hironori Shimamoto,[1] Takehiro Yamada,[1] Hiroaki Ishiguchi,[3] Akira Takada,[1] Naoki Hirasawa,[3] Shunichi Ishihara,[1] Yasuo Takehara,[2] Shinji Naganawa,[2] Matthew S. Davenport,[4] Teruhiko Terasawa[5,6]

[1]Department of Radiology, Toyohashi Municipal Hospital, Toyohashi, Japan

[2]Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[3]Department of Radiology, Komaki City Hospital, Komaki, Japan

[4]Departments of Radiology and Urology, Michigan Medicine, Ann Arbor, MI, USA

[5]Section of General Internal Medicine, Department of Emergency and General Internal Medicine, Fujita Health University, Toyoake, Japan

[6]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA

Word count

Abstract: 249 (<300)

Text: 2628 (<4000)

References: 35

Corresponding author: Teruhiko Terasawa, MD, PhD

Section of General Internal Medicine, Department of Emergency and General Internal Medicine, Fujita Health University School of Medicine

1-98 Dengakugakubo, Kutsukakecho, Toyoake, Aichi 470-1192, Japan

Phone & Fax: +81-562-93-2497

E-mail: terasawa@fujita-hu.ac.jp

ABSTRACT

Introduction: Iodinated contrast media are commonly used in medical imaging and can cause hypersensitivity reactions, including rare but severe life-threatening reactions. Although several prophylactic approaches have been proposed for severe reactions, their effects remain unclear. Therefore, we aim to review systematically the preventive effects of pharmacologic and non-pharmacologic interventions and predictors of acute, hypersensitivity reactions.

Methods and analysis: We will search the PubMed, EMBASE, and CENTRAL databases from January 1, 1990 through December 31, 2019 and will examine the bibliographies of eligible studies, pertinent review articles, and clinical practice guidelines. We will include prospective and retrospective studies of any design that evaluated the effects of pharmacological and non-pharmacological preventive interventions for adverse reactions of non-ionic iodinated contrast media. Two assessors will independently extract the characteristics of the study and intervention and the quantitative results. Two independent reviewers will assess the risk of bias using standard design-specific validity assessment tools. The primary outcome will be reduction in acute contrast media-induced hypersensitivity reactions. The secondary outcomes will include characteristics associated with the development of contrast media-induced acute hypersensitivity reactions, and adverse events associated with specific preventive interventions. Unique premedication regimens (e.g., dose, drug, and duration) and non-pharmacological strategies will be analyzed separately. Average- and high-risk patients will be considered separately. A meta-analysis will be performed if

appropriate.

Ethics and dissemination: Ethics approval is not applicable, as this will be a secondary analysis of publicly available data. The results of the analysis will be submitted for publication in a peer reviewed journal.

PROSPERO registration number: CRD42019134003.

Strengths and limitations of this study

-This will be the first systematic review and meta-analysis to assess and compare the preventive effectiveness of pharmacologic and non-pharmacologic interventions for preventing acute hypersensitivity reactions caused by non-ionic iodinated contrast media.

-Comprehensive literature searches and up-to-date systematic review methodologies will be used to identify actionable evidence.

-If the number of studies is too small, or clinical or statistical across-study heterogeneity is deemed too great, a quantitative synthesis may not be feasible.

INTRODUCTION

Iodinated contrast media are commonly used to enhance computed tomography (CT) examinations for diagnosis and treatment monitoring. However, non-ionic iodinated contrast media cause adverse reactions ranging from mild nausea or pruritus to hemodynamic shock and cardiopulmonary arrest in approximately 3% of patients.[1 2] Life-threatening reactions occur in approximately 4 in 10,000 cases.[1] As millions of doses of iodinated contrast media are administered annually, severe reactions are expected to occur commonly within a population.[3]

The mechanism underlying adverse reactions induced by contrast media is not fully understood and is likely multifactorial.[2] However, based on a general framework for the classification of adverse drug reactions, the reactions induced by contrast media can be divided into two types—commonly referred to as type A and type B reactions.[4 5] Type A reactions are physiologic and often dose-dependent reactions that are expected from the pharmacologic properties of the administered contrast media. Type B reactions are hypersensitivity reactions that are neither physiologic nor dose-dependent, and are usually unpredictable. Distinction between type A and type B reactions can facilitate designing prophylactic strategies for preventing contrast media-induced adverse reactions; nevertheless, the distinction is not straightforward, and some professional societies have discordant classification systems.[4]

No perfect strategy has been established to mitigate the risk of acute severe contrast media-induced hypersensitivity reactions. Only weak evidence supports pharmacological interventions including corticosteroids and/or antihistamines.[2] For example, premedication often fails[6] and can induce adverse effects such as corticosteroid-induced hyperglycemia and indirectly contributed to prolonged hospitalization.[7 8] Purported risk factors for contrast media-induced reactions predict reactions of any severity; they do not specifically predict acute life-threatening reactions.[2 9] Further, the comparative effectiveness of alternative preventive strategies involving pharmacological and non-pharmacological interventions has not been systematically evaluated.[6 7 8 10 11 12] Although professional societies including the American College of Radiology (ACR) propose several premedication regimens,[2] only one has been tested in a randomized design, and that study had methodological challenges.[13] Premedication practice varies,[14 15] which precludes a standardized comparative assessment among alternative pharmacologic and non-pharmacological interventions. Given this uncertainty, the 2019 European Society of Urogenital Radiology (ESUR) Guideline on Contrast Agents indicates that "premedication is not recommended because there is not good evidence of its effectiveness (page 7, A1.1)."[9]

Since the publication of two systematic reviews in 2006 that evaluated the effectiveness of premedication regimens,[16 17] several relevant studies of pharmacological and alternative, non-pharmacological strategies (e.g., exchanging one contrast medium for an alternative) have been published and have influenced the ACR and ESUR

guidelines.[18 19] In addition, the two prior systematic reviews on this topic included pharmacological prophylaxis only in the context of now-outdated high-osmolality iodinated contrast media that are no longer used in clinical practice. Therefore, we planned a comprehensive quantitative synthesis of clinical data on the effects of pharmacological and non-pharmacological prophylactic strategies for the prevention of acute adverse reactions to non-ionic iodinated contrast material.

METHODS AND ANALYSIS

This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement (PRISMA-P).[20] Based on the analytic framework shown in the **Figure 1**, we have formulated the following three key research questions and related sub-questions:

Key Question 1. What is the effect of interventions to reduce acute (<1 hour) hypersensitivity (Type B) reactions in patients receiving contrast media?

Key Question 1a: What is the preventive effect of guideline-recommended oral (12- or 13-hour), guideline-recommended accelerated intravenous (5- to 11-hour), or non-guideline emergent intravenous (<5-hour) premedication on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key Question 1b: What is the preventive effect of a change of contrast media alone on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key Question 1c: What is the preventive effect of combination of standard oral (12- or 13-hour) premedication and a change of contrast media on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key Question 1d: What is the preventive effect of other interventions (other than the above listed) on acute (<1 hour) hypersensitivity reactions?

Key Question 1e: What is the preventive effect of any interventions for acute (<1 hour) adverse reactions of any type (i.e, both type A and B reactions)?

Key Question 2. What are the patient-level and intervention-level characteristics (i.e., predictors) associated with contrast media-induced acute hypersensitivity (Type B) reactions?

Key Question 3. What are the complications and adverse events associated with specific interventions to reduce contrast media-induced adverse reactions?

Literature search

We will search the PubMed, EMBASE, and Cochrane Central Register of Controlled

Trials (CENTRAL) databases from January 1, 1990 through December 31, 2019 for both English- and non-English-language publications, using search terms such as "iodinated contrast media," "premedication," "adverse reaction," "breakthrough reactions," and their synonyms. The complete search strategy and full list of databases are available as an online Supplementary file. We will include studies published after 1990, when non-ionic contrast media were developed and disseminated widely. We also will examine the references of eligible studies, relevant review articles, and existing clinical practice guidelines developed by professional societies such as the ACR and ESUR.[2 9] All potentially eligible non-English publications will be translated into English before full-text assessment.

Inclusion and exclusion criteria

We will include studies that assessed patients who received intravenous or intra-arterial non-ionic iodinated contrast material and any interventions to reduce contrast media-induced adverse reactions. The **Table 1** presents our detailed inclusion criteria, which follow a generally accepted framework to formulate a systematic review question comprising 5 key components: populations, interventions, comparator interventions, outcomes, and study designs.[21] Regarding pharmacological prophylactic interventions, we will focus on premedication based on corticosteroids, anti-histamines, or both, and exclude studies that tested other medications (e.g., ephedrine, diazepam, atropine) because these are not relevant to current clinical practice. We also will exclude studies that assessed patients who received high-osmolality contrast media because they are no

longer used in clinical practice. Both prospective and retrospective studies of any design that evaluated at least 10 patients will be included.

Several frameworks for categorizing clinical symptoms and severity induced by pharmacological agents including contrast media exist. We will employ an accepted general two-group framework (type A and type B) to classify acute contrast media-induced adverse reactions reported in primary studies in the main analysis.[5] We then will reclassify the reported acute adverse reactions using the current ACR categorization system[2] in a sensitivity analysis to assess the applicability and difference between the two frameworks. Delayed reactions occurring more than 1 hour after contrast media administration will not be assessed. A breakthrough reaction will be defined as an acute type B reaction of any severity that occurs despite premedication. We will operationally classify any randomized controlled trials (RCTs) and any studies with a non-randomized design that compared two or more intervention groups (i.e., so-called non-randomized studies of intervention [e.g., quasi-RCTs, cohort studies, case-control studies]) as "comparative studies." "Non-comparative studies" will include single-group studies and case series.

We will exclude editorials, comments, letters to the editor, and review articles. Multiple publications with potentially overlapping patient populations can overestimate the volume of evidence. Therefore, for overlapping study populations, we will only include the publication with the largest sample size. We will contact the study authors by email

if the publications do not report adequate information about the patient characteristics and reaction classifications. We will consider our request to be rejected if two email request reminders sent separately 14 days after the initial contact attempt are not returned.

The results of our electronic searches will be imported into reference management software and duplicate results will be removed. Multiple paired investigators will independently double-screen non-overlapping sets of abstracts (e.g., the first half of the abstracts will be assigned to team A [2 investigators] and the second half of the abstracts will be assigned to team B [2 investigators] in the case of two paired teams) and examine full-text articles for potentially eligible citations. We will use Abstrackr (Center for Evidence Synthesis in Health, Brown University, Providence, RI, available at abstrackr.cebm.brown.edu), a free, open-source, citation screening program for abstract screening. A third investigator will adjudicate any discrepant results if consensus cannot be reached between the two reviewers.

Data extraction

We will extract the following descriptive data from eligible studies. Study characteristics will include first author, year of publication, journal, and study design (prospective *vs.* retrospective, comparative study *vs.* non-comparative study).

Participant characteristics will include age, sex, history and severity and type of any prior acute adverse reaction to iodinated contrast material, allergic diathesis including severe allergy(-ies) to other substances and asthma,[2] and other known risk factors for adverse reactions. Contrast media characteristics will include brand and generic names and doses of contrast media administered. Intervention characteristics will include premedication strategies including drugs, doses, duration, and change in contrast agent. Outcome characteristics will include details of and change in adverse reactions (kinds and severity), assessors of adverse reactions (number and experience), and categorization system to classify and grade acute adverse events. We will operationally define guideline-recommended regimens as the 12- to 13-hour oral administration of corticosteroids with or without use of an anti-histamine, and standard accelerated regimen as a 5- to 11-hour intravenous administration of corticosteroids with or without the use of an anti-histamine.[2] If a study adopted ad-hoc definitions or categorization systems other than the two-group classification framework or those proposed by the ACR, we will specify these differences in sufficient detail. One primary investigator will extract the descriptive data, which will be verified by a second investigator.

Two reviewers will independently double-extract quantitative data from each publication. We will determine the relative risk of a hypersensitivity reaction between two (or more) groups in comparative studies. We will extract the number of patients in each group, as well as the number of patients who developed a hypersensitivity reaction. If relevant count data cannot be determined from the publication, we will instead extract the reported point estimates and their confidence intervals.

We will extract quantitative measures (e.g., risk ratios, odds ratios) of the association of the presence or absence of a predictor with the development of a breakthrough reaction. We will prefer adjusted values over unadjusted values if both are reported. *A priori* candidate predictors selected for extraction include specific index type B reactions and their grades, and any allergic diathesis and its severity.

Assessment of risk of bias

For RCTs, we will use the revised tool to assess risk of bias in randomized trials (RoB 2 tool).[22] We will assess five domains of RCT study validity (i.e., randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, selective reporting) and then assign an overall risk of bias for each trial.

For non-randomized intervention studies, we will use the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for cohort studies,[23] and the

Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) for case-control studies.[24] We will assess seven domains of study validity (i.e., confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selective reporting) and then assign an overall risk of bias for each study.

For single-group observational studies that assessed a predictor in a specific clinical context (e.g., development of a breakthrough reaction under a premedication regimen), we will use a revised version of the Quality in Prognosis Studies tool (the QUIPS-2).[25] We will assess six domains of study validity (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis and reporting) and then assign an overall risk of bias for each study.

Two reviewers will independently assess each item and rate the domain-specific and overall risks of bias. Discrepant ratings will be resolved by consensus. A third independent investigator will adjudicate any unresolved discrepancies. The complete list of modified operational definitions used to rate each item will be available from the authors upon request.

Data synthesis

The primary outcome of interest will be the relative risk of an acute type B (hypersensitivity) reaction between specific prevention strategies. Secondary outcomes will include the breakthrough reaction rate of each specific strategy and the predictive performances of covariates for overall and severe breakthrough reactions. For all outcome measures, we will first construct an evidence map by performing qualitative syntheses based on graphs and tables to examine the diversity and volume of available evidence on this topic.[26 27] If feasible, we will then perform a quantitative synthesis.

For summary relative measures (e.g., relative risk of an acute type B reaction) based on count data, we will perform a random-effects meta-analysis using the binomial likelihood with logit link in a generalized linear modeling framework (i.e., random-effects logistic regression).[28] If already-estimated relative measures are the only extractable formats, we will utilize the log-transformed estimates and their variances as "plug-in" estimates. If appropriate, the meta-analytical model for a specific pairwise comparison will be extended to a network meta-analysis to synthesize data from both direct and indirect comparisons of all available studies in a single analysis.[28]

For summary estimates of the proportion measures in non-comparative studies, we will perform a random-effects meta-analysis of proportions using the binomial likelihood and logit link (i.e., so-called the binomial-normal model).[29]

Additional analyses

We will estimate the between-study standard deviation parameter, *tau*, and I^2 statistic and corresponding 95% credible intervals as measures of statistical heterogeneity. An I^2 >50% will indicate intermediate heterogeneity, while an I^2 >70% will indicate high heterogeneity.[30]

To explore statistical heterogeneity, we will perform subgroup analyses and, if feasible, a univariable random-effects meta-regression.[28] Preplanned candidate factors will include the use of guideline-recommended premedication regimens (vs. non-guideline-recommended or *ad-hoc* regimens), alterations of the culprit contrast media (vs. not), use of the general two-group classification framework vs. the ACR categorization systems for the classification and grading of reactions (vs. others), and severity and type of prior reactions to iodinated contrast media. We will consider conducting sensitivity analyses by reclassifying and/or re-grading the reported reactions based on the two-group classification system and the ACR classification system for studies not using these classification frameworks, if pertinent individual-level data are presented.

We will assess funnel-plot asymmetry if at least 10 studies are included.[31] To address potential biases derived from missing outcome data, we will apply the approach proposed by Turner et al.[32] We will assess the certainty of evidence using the Grading

of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[33]

Statistical software

We will conduct all analyses using Stata version 14/SE (Stata Corp., College Station, TX, USA) and OpenBUGS version 3.2.3 (members of OpenBUGS Project Management Group; see www.openbugs.net). All tests will be two-sided, and statistical significance will be defined as a P value <0.05.

Patient and Public Involvement

We did not involve patients or the public in the preparation of this systematic review protocol.

DISCUSSION

The revised 2019 ESUR guidelines on Contrast Agents retracted recommendations for the premedication of patients at an increased risk of contrast reaction due to a lack of scientific evidence of efficacy.[9] This position is inconsistent with the latest guidelines of other professional societies, including the ACR (ACR Manual on Contrast Media v. 10.3),[2] the Canadian Association of Radiologists,[34] and the Japan Radiological Society.[35] Also, concerns have been raised on the relevance and impact of the

classification systems and nomenclature of contrast media-induced adverse reactions, and their recommended management proposed in guidelines.[4] Given the wide application of iodinated contrast media in medical imaging and interventional procedures, the uncertainty surrounding the optimization of prevention strategies based on the proposed framework, and the absence of recently published evidence reviews, we believe that it will be worthwhile to conduct a new systematic review that critically examines the existing evidence on interventions to reduce acute contrast media-induced adverse reactions. Using a comprehensive evidence map of the published literature on the effects of pharmacologic and non-pharmacologic interventions and, if feasible, new meta-analytic results, we hope to clarify the actionable evidence regarding the use of preventive interventions.

ETHICS AND DISSEMINATION

As this is a systematic review, we are not planning to obtain a formal ethical approval. The findings from the review will be disseminated through publications in peer-reviewed journals, and presentations at conferences.

Contributors

HU and TN originated the idea; HU, TN and TT drafted the initial version of the protocol; HU, TN and TT developed the search strategy; HS, TY, HI, AT, NH, SI, YT, SN, and MSD reviewed the protocol and suggested amendments. All authors read and

approved the final version of the protocol. HU, TN, and TT are guarantors of the review.

Funding

TT was supported in part by the Ministry of Education, Culture, Sports, Science and Technology, Japan (JSPS KAKENHI Grant Numbers: 26460755 and 19K07877). The funding source had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest

All authors declare no conflicts of interest associated with this publication.

For complete transparency outside the submitted work, Dr. Ishihara reports personal fees from Bayer Yakuhin, Ltd.; Dr. Takehara is an endowed chair sponsored by HIMEDIC Co. He does not receive any financial support from the corporation for conducting the research and writing this paper. He also reports personal fees from Daiichi Sankyo company, Ltd., Bayer Yakuhin, Ltd., GE Healthcare, Medi-Physics Co Ltd., Mitsubishi Tanabe Pharma Corporation, National Cancer Center; Dr. Naganawa reports personal fees from Daiichi Sankyo company, Ltd., Kowa Company, Ltd., Bayer Yakuhin, Ltd., Fuji Pharma Co Ltd., Bracco-Eisai Co Ltd., FUJIFILM Toyama Chemical Co Ltd., Canon medical systems corporation, Siemens Healthineers Japan,

Trust Clinic, Nagoya Jhohoku Radiology Clinic, Gakken Medical Shujunsha Co Ltd, Neuryon AG; and Dr. Davenport reports royalties from Wolters Kluwer and uptodate.com.

Disclosure

A preliminary work of this research project based on a brief literature search has been presented in an educational session at the 77th annual meeting of the Japan Radiological Society 2018, Yokohama, Japan.

References

1. Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990;**175**(3):621-8.
2. ACR Committee on Drugs and Contrast Media. ACR Manual On Contrast Media Version 10.3 2018. Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf. Accessed on July 1, 2019.
3. Bettmann MA. Frequently asked questions: iodinated contrast agents. Radiographics 2004;**24 Suppl 1**:S3-10.
4. Bohm I, Morelli J, Nairz K, et al. Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review. Postgrad Med 2017;**129**(2):259-66.
5. Pichler WJ. Drug hypersensitivity: Classification and clinical features. UpToDate. Available from: https://www.uptodate.com/contents/drug-hypersensitivity-classification-and-clinical-features. Accessed on Jan 1, 2020.
6. Davenport MS, Cohan RH, Caoili EM, et al. Repeat contrast medium reactions in premedicated patients: frequency and severity. Radiology 2009;**253**(2):372-9.
7. Davenport MS, Cohan RH, Khalatbari S, et al. Hyperglycemia in hospitalized patients receiving corticosteroid premedication before the administration of radiologic contrast medium. Acad Radiol 2011;**18**(3):384-90.
8. Davenport MS, Mervak BM, Ellis JH, et al. Indirect Cost and Harm Attributable to Oral 13-Hour Inpatient Corticosteroid Prophylaxis before Contrast-enhanced CT. Radiology 2016;**279**(2):492-501.
9. European Society of Urogenital Radiology. ESUR Guidelines on Contrast Media ver10.0 2018, Updated January 28, 2019. Available from: http://www.esur.org/guidelines/en/index.php#a. Accessed on July 1, 2019.
10. Mervak BM, Davenport MS, Ellis JH, et al. Rates of Breakthrough Reactions in Inpatients at High Risk Receiving Premedication Before Contrast-Enhanced CT. AJR Am J Roentgenol 2015;**205**(1):77-84.
11. Freed KS, Leder RA, Alexander C, et al. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. AJR Am J Roentgenol

2001;**176**(6):1389-92.
12. Mesurolle B, Ariche M, Cohen D. Premedication before i.v. contrast-enhanced CT resulting in steroid-induced psychosis. AJR Am J Roentgenol 2002;**178**(3):766-7.
13. Lasser EC, Berry CC, Mishkin MM, et al. Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. AJR Am J Roentgenol 1994;**162**(3):523-6.
14. O'Malley RB, Cohan RH, Ellis JH, et al. A survey on the use of premedication prior to iodinated and gadolinium-based contrast material administration. J Am Coll Radiol 2011;**8**(5):345-54.
15. The Japan Radiological Society. A nationwide survey on the use of premidication prior to Iodinated contrast material administration 2015, Updated 2015/7/21. Available from: http://www.radiology.jp/content/files/20150721-2.pdf. Accessed on Jan 1, 2020.
16. Delaney A, Carter A, Fisher M. The prevention of anaphylactoid reactions to iodinated radiological contrast media: a systematic review. BMC Med Imaging 2006;**6**:2.
17. Tramer MR, von Elm E, Loubeyre P, et al. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. BMJ 2006;**333**(7570):675.
18. Abe S, Fukuda H, Tobe K, et al. Protective effect against repeat adverse reactions to iodinated contrast medium: Premedication vs. changing the contrast medium. Eur Radiol 2016;**26**(7):2148-54.
19. Park HJ, Park JW, Yang MS, et al. Re-exposure to low osmolar iodinated contrast media in patients with prior moderate-to-severe hypersensitivity reactions: A multicentre retrospective cohort study. Eur Radiol 2017;**27**(7):2886-93.
20. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;**350**:g7647.
21. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 1997;**127**(5):380-7.
22. Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, et al., eds. Cochrane Methods Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1).

Available from https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0. Accessed on July 1, 2019.

23. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;**355**:i4919.
24. Sterne JAC, Higgins JPT, Reeves BC, et al. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0. 2014, Updated on 24 September 2014. http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-i/acrobat-nrsi/. Accessed on July 1, 2019.
25. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;**158**(4):280-6.
26. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC medical research methodology 2018;**18**(1):143-43.
27. Miake-Lye IM, Hempel S, Shanman R, et al. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Systematic reviews 2016;**5**:28-28.
28. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;**33**(5):607-17.
29. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med 2010;**29**(29):3046-67.
30. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;**327**(7414):557-60.
31. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;**343**:d4002.
32. Turner NL, Dias S, Ades AE, et al. A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Stat Med 2015;**34**(12):2062-80.
33. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ

2008;**336**(7650):924-6.
34. Morzycki A, Bhatia A, Murphy KJ. Adverse Reactions to Contrast Material: A Canadian Update. Can Assoc Radiol J 2017;**68**(2):187-93.
35. The Japan Radiological Society. Revised recommendations on steroid premedication for reducing the risk of acute adverse effects of iodinated contrast agents and gadolinium contrast agents 2018. Available from: http://www.radiology.jp/member_info/safty/20181115.html. Accessed on July 1, 2019.

Table 1. Inclusion criteria based on the PICOD framework

PICOD	Specific details
Population	Patients who received intravenous or intra-arterial non-ionic iodinated CM* -High-risk population -Low-risk population -No risk-stratified population
Interventions /Comparators and co-interventions	Pharmacological interventions† 1. 12- or 13-hour oral corticosteroids with or without anti-histamine 2. 5- to 11-hour IV corticosteroids with or without anti-histamine 3. Any premedication less than 5 hours using corticosteroids, anti-histamine, or both Non-pharmacological interventions -Change of CM that caused prior Type B hypersensitivity reaction
Outcomes	Rates of acute (<1 hour) Type B hypersensitivity reactions‡ -Acute reaction-related deaths within 30 days -Severe reactions only -Moderate and severe reactions only -Upgraded reactions compared to the index reactions -All hypersensitivity reactions Rates of adverse events induced by preventive interventions
Predictors of acute	Patient-level characteristics

adverse reactions	-Prior Type B hypersensitivity reactions
	-Prior Type A physiologic reactions§
	-Allergic diathesis (e.g., asthma, food or drug allergy, etc.)
	Intervention-level characteristics
	-Types and regimens of interventions
	-Dosing of specific premedication drugs
	-Change of CM (specific class/product and/or dosing)
Designs	Any study designs including at least 10 patients
	-Randomized controlled trials
	-Nonrandomized trials
	-Prospective and retrospective cohorts
	Comparative (two or more-group) design
	Single-group design

* Per-study defined risk criteria are allowed.

†Both guideline-recommended and *ad-hoc* regimens are allowed, but will be analyzed separately. guideline-recommended oral regimens are defined as follows:[2] 13-hour regimen: prednisone 50 mg PO at 13, 7, and 1 hrs before CM injection +/- optional diphenhydramine 50 mg IV, IM, or PO at 1 hr before CM injection; 12-hour regimen: methylpredonisolone 32 mg PO at 12, and 2 hrs before CM injection +/- optional antihistamine. Guideline-recommended urgent regimens are: methylprednisolone 40 mg or

hydrocortisone 200 mg IV every 4 hrs until CM injection (minimum cumulative duration 5 hours) +/- diphenhydramine 50 mg IV at 1 hr before CM injection. Any premedication that does not include corticosteroids or that is less than 5 hours in duration is non-standard.

‡Grades of Type B hypersensitivity reactions are defined as follows[2]: mild reactions include limited urticaria/pruritis, cutaneous edema, limited "itchy"/"scratchy" throat, nasal congestion, sneezing, conjunctivitis, and rhinorrhea; moderate reactions include diffuse urticaria/pruritis, diffuse erythema with stable vital signs, facial edema without dyspnea, throat tightness or hoarseness without dyspnea, and wheezing/bronchospasm with mild or no hypoxia; and severe reactions include diffuse edema, facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing/bronchospasm with significant hypoxia, and anaphylactic shock (hypotension + tachycardia).

§Grades of Type A physiologic reactions are defined as follows[2]: mild reactions include limited nausea/vomiting, transient flushing, warmth, chills, headache, dizziness, anxiety, altered taste, mild hypertension, and vasovagal reaction that resolves spontaneously; moderate reactions include protracted nausea/vomiting, hypertensive urgency, isolated chest pain, and vasovagal reaction that requires and is responsive to treatment; and severe reactions include vasovagal reaction resistant to treatment, arrhythmia, convulsions, seizures, and hypertensive emergency.

Abbreviations: CM = contrast medium; IM = intramuscularly; IV = intravenously; PICOD = populations, interventions, comparator interventions, outcomes, and study designs; PO = orally

Figure legend

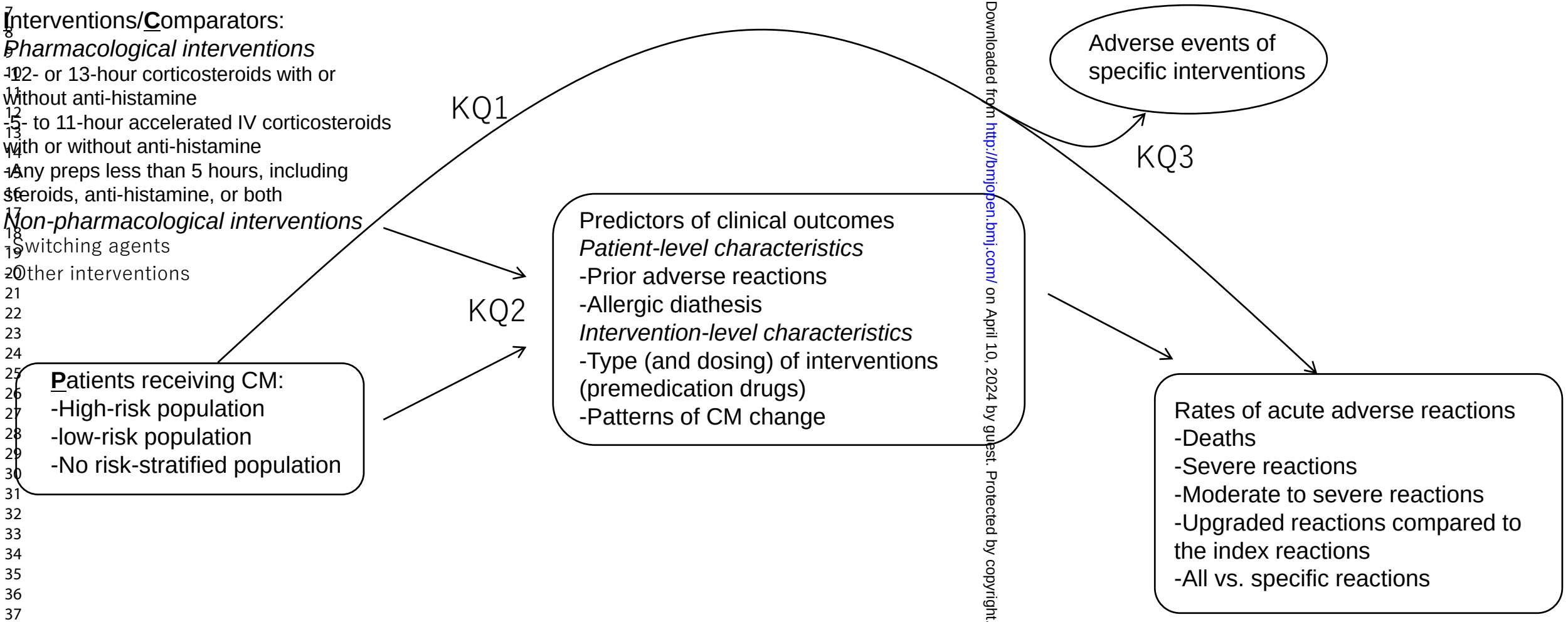
Figure 1. Analytic framework.

Abbreviations: CM = contrast media; KQ = key question

Key Question 1. What is the effect of interventions to reduce acute (<1 hour) hypersensitivity (Type B) reactions in patients receiving CM?

Key Question 2. What are the patient-level and intervention-level characteristics (i.e., predictors) associated with CM-induced acute hypersensitivity (Type B) reactions?

Key Question 3. What are the complications and adverse events associated with specific interventions to reduce CM-induced adverse reactions?



SUPPLEMENTARY FILE

Search strategies

PubMed

1. "Contrast Media"[Pharmacological Action]
2. radiocontrast*
3. iodinated contrast*
4. contrast material*
5. iodine contrast*
6. iodixanol OR iohexol OR iopamidol OR ioversol OR ioxilan OR iopromide OR iobitridol OR iomeprol
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. "Adverse Effects"[Subheading]
9. Adverse
10. "side effect"
11. "side effects"
12. reaction*
13. harm*
14. complicat*
15. toxicit*
16. hypersensitiv*
17. breakthrough reaction*
18. anaphyla*
19. allerg*
20. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21. Premedication[Mesh]
22. premedicat*
23. prevent*
24. prophyla*
25. steroid*
26. corticosteroid*
27. antihistamine*
28. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
29. #7 AND #20 AND #28

Cochrane Central Register of Controlled Trials (Ovid)

1. contrast media.mp. or exp Contrast Media/
2. radiocontrast*.mp.
3. iodinated contrast*.mp.
4. contrast material*.mp.
5. Iodine/ or iodine contrast*.mp.
6. (iodixanol or iohexol or iopamidol or ioversol or ioxilan or iopromide or iobitridol or iomeprol).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. 1 or 2 or 3 or 4 or 5 or 6
8. Adverse Effects.mp.
9. "Drug-Related Side Effects and Adverse Reactions"/ or adverse.mp.
10. side effect.mp.
11. side effects.mp.
12. reaction*.mp.
13. Patient Harm/ or harm*.mp.
14. complicat*.mp.
15. toxicit*.mp.
16. Hypersensitivity/ or hypersensitiv*.mp.
17. breakthrough reaction*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
18. Anaphylaxis/ or anaphyla*.mp.
19. allerg*.mp.
20. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. premedication.mp. or Premedication/
22. premedicat*.mp.
23. prevent*.mp.
24. prophyla*.mp.
25. steroid*.mp.
26. Glucocorticoids/ or corticosteroid*.mp.
27. antihistamine*.mp. or Histamine H1 Antagonists/
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 7 and 20 and 28

Embase

1. 'contrast medium'/exp OR 'contrast medium'
2. radiocontrast*
3. 'iodinated contrast medium'/exp OR 'iodinated contrast medium'
4. iodinated AND contrast*
5. ('contrast'/exp OR contrast) AND material*
6. ('iodine'/exp OR iodine) AND contrast*
7. 'iodixanol'/exp OR iodixanol OR 'iohexol'/exp OR iohexol OR 'iopamidol'/exp OR iopamidol OR 'ioversol'/exp OR ioversol OR 'ioxilan'/exp OR ioxilan OR 'iopromide'/exp OR iopromide OR 'iobitridol'/exp OR iobitridol OR 'iomeprol'/exp OR iomeprol
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. 'adverse event'/exp OR 'adverse event'
10. Adverse
11. 'side effect'/exp OR 'side effect'
12. 'side effects'
13. reaction*
14. harm*
15. 'complication'/exp OR 'complication'
16. complicat*
17. 'toxicity'/exp OR 'toxicity'
18. toxicit*
19. 'hypersensitivity'/exp OR 'hypersensitivity'
20. hypersensitiv*
21. breakthrough AND reaction*
22. 'anaphylaxis'/exp OR 'anaphylaxis'
23. anaphyla*
24. allerg*
25. 'immediate type hypersensitivity'/exp OR 'immediate type hypersensitivity'
26. 'allergy'/exp OR 'allergy'
27. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28. 'premedication'/exp OR 'premedication'
29. premedicat*
30. 'prevention'/exp OR 'prevention'
31. prevent*

32. 'prophylaxis'/exp OR 'prophylaxis'
33. prophyla*
34. 'steroid'/exp OR 'steroid'
35. steroid*
36. 'corticosteroid'/exp OR 'corticosteroid'
37. corticosteroid*
38. 'antihistaminic agent'/exp OR 'antihistaminic agent'
39. 'histamine h1 receptor antagonist'/exp OR 'histamine h1 receptor antagonist'
40. antihistamine*
41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
42. #8 AND #27 AND #41
43. #42 AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'short survey'/it)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reporting Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6-7
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18-19
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8-9 and supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12-13
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	15
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13-14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	15
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Pharmacologic and non-pharmacologic interventions to prevent hypersensitivity reactions of non-ionic iodinated contrast media: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033023.R2
Article Type:	Protocol
Date Submitted by the Author:	11-Feb-2020
Complete List of Authors:	Umakoshi, Hiroyasu ; Toyohashi Municipal Hospital, Radiology Nihashi, Takashi ; Komaki Shimin Byoin, Department of Radiology Shimamoto, Hironori ; Toyohashi Municipal Hospital, Radiology Yamada, Takehiro ; Toyohashi Municipal Hospital, Radiology Ishiguchi, Hiroaki ; Komaki City Hospital, Radiology Takada, Akira ; Toyohashi Municipal Hospital, Radiology Hirasawa, Naoki; Komaki City Hospital, Radiology Ishihara, Shunichi ; Toyohashi Municipal Hospital, Radiology Takehara, Yasuo; Nagoya University Graduate School of Medicine Faculty of Medicine, Naganawa, Shinji; Nagoya University, Department of Radiology Davenport, Matthew ; University of Michigan, Department of Radiology and Urology, Michigan Radiology Quality Collaborative, University of Michigan Health System Terasawa, Teruhiko; Fujita Health University, Emergency and General Internal Medicine
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Diagnostics, Evidence based practice, Radiology and imaging
Keywords:	Diagnostic radiology < RADIOLOGY & IMAGING, Premedication, Contrast media, Preventive effectiveness

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Pharmacologic and non-pharmacologic interventions to prevent hypersensitivity reactions of non-ionic iodinated contrast media: a systematic review protocol

Hiroyasu Umakoshi,[1,2] Takashi Nihashi,[2,3] Hironori Shimamoto,[1] Takehiro Yamada,[1] Hiroaki Ishiguchi,[3] Akira Takada,[1] Naoki Hirasawa,[3] Shunichi Ishihara,[1] Yasuo Takehara,[2] Shinji Naganawa,[2] Matthew S. Davenport,[4] Teruhiko Terasawa[5,6]

[1]Department of Radiology, Toyohashi Municipal Hospital, Toyohashi, Japan

[2]Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[3]Department of Radiology, Komaki City Hospital, Komaki, Japan

[4]Departments of Radiology and Urology, Michigan Medicine, Ann Arbor, MI, USA

[5]Section of General Internal Medicine, Department of Emergency and General Internal Medicine, Fujita Health University, Toyoake, Japan

[6]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA

Word count

Abstract: 249 (<300)

Text: 2628 (<4000)

References: 35

Corresponding author: Teruhiko Terasawa, MD, PhD

Section of General Internal Medicine, Department of Emergency and General Internal Medicine, Fujita Health University School of Medicine

1-98 Dengakugakubo, Kutsukakecho, Toyoake, Aichi 470-1192, Japan

Phone & Fax: +81-562-93-2497

E-mail: terasawa@fujita-hu.ac.jp

ABSTRACT

Introduction: Iodinated contrast media are commonly used in medical imaging and can cause hypersensitivity reactions, including rare but severe life-threatening reactions. Although several prophylactic approaches have been proposed for severe reactions, their effects remain unclear. Therefore, we aim to review systematically the preventive effects of pharmacologic and non-pharmacologic interventions and predictors of acute, hypersensitivity reactions.

Methods and analysis: We will search the PubMed, EMBASE, and CENTRAL databases from January 1, 1990 through December 31, 2019 and will examine the bibliographies of eligible studies, pertinent review articles, and clinical practice guidelines. We will include prospective and retrospective studies of any design that evaluated the effects of pharmacological and non-pharmacological preventive interventions for adverse reactions of non-ionic iodinated contrast media. Two assessors will independently extract the characteristics of the study and intervention and the quantitative results. Two independent reviewers will assess the risk of bias using standard design-specific validity assessment tools. The primary outcome will be reduction in acute contrast media-induced hypersensitivity reactions. The secondary outcomes will include characteristics associated with the development of contrast media-induced acute hypersensitivity reactions, and adverse events associated with specific preventive interventions. Unique premedication regimens (e.g., dose, drug, and duration) and non-pharmacological strategies will be analyzed separately. Average- and

high-risk patients will be considered separately. A meta-analysis will be performed if appropriate.

Ethics and dissemination: Ethics approval is not applicable, as this will be a secondary analysis of publicly available data. The results of the analysis will be submitted for publication in a peer reviewed journal.

PROSPERO registration number: CRD42019134003.

Strengths and limitations of this study

-This will be the first systematic review and meta-analysis to assess and compare the preventive effectiveness of pharmacologic and non-pharmacologic interventions for preventing acute hypersensitivity reactions caused by non-ionic iodinated contrast media.

-Comprehensive literature searches and up-to-date systematic review methodologies will be used to identify actionable evidence.

-If the number of studies is too small, or clinical or statistical across-study heterogeneity is deemed too great, a quantitative synthesis may not be feasible.

INTRODUCTION

Iodinated contrast media are commonly used to enhance computed tomography (CT) examinations for diagnosis and treatment monitoring. However, non-ionic iodinated contrast media cause adverse reactions ranging from mild nausea or pruritus to hemodynamic shock and cardiopulmonary arrest in approximately 3% of patients.[1 2] Life-threatening reactions occur in approximately 4 in 10,000 cases.[1] As millions of doses of iodinated contrast media are administered annually, severe reactions are expected to occur commonly within a population.[3]

The mechanism underlying adverse reactions induced by contrast media is not fully understood and is likely multifactorial.[2] However, based on a general framework for the classification of adverse drug reactions, the reactions induced by contrast media can be divided into two types—commonly referred to as type A and type B reactions.[4 5] Type A reactions are physiologic and often dose-dependent reactions that are expected from the pharmacologic properties of the administered contrast media. Type B reactions are hypersensitivity reactions that are neither physiologic nor dose-dependent, and are usually unpredictable. Distinction between type A and type B reactions can facilitate designing prophylactic strategies for preventing contrast media-induced adverse reactions; nevertheless, the distinction is not straightforward, and some professional societies have discordant classification systems.[4]

No perfect strategy has been established to mitigate the risk of acute severe contrast media-induced hypersensitivity reactions. Only weak evidence supports pharmacological interventions including corticosteroids and/or antihistamines.[2] For example, premedication often fails[6] and can induce adverse effects such as corticosteroid-induced hyperglycemia and indirectly contributed to prolonged hospitalization.[7 8] Purported risk factors for contrast media-induced reactions predict reactions of any severity; they do not specifically predict acute life-threatening reactions.[2 9] Further, the comparative effectiveness of alternative preventive strategies involving pharmacological and non-pharmacological interventions has not been systematically evaluated.[6 7 8 10 11 12] Although professional societies including the American College of Radiology (ACR) propose several premedication regimens,[2] only one has been tested in a randomized design, and that study had methodological challenges.[13] Premedication practice varies,[14 15] which precludes a standardized comparative assessment among alternative pharmacologic and non-pharmacological interventions. Given this uncertainty, the 2019 European Society of Urogenital Radiology (ESUR) Guideline on Contrast Agents indicates that "premedication is not recommended because there is not good evidence of its effectiveness (page 7, A1.1)."[9]

Since the publication of two systematic reviews in 2006 that evaluated the effectiveness of premedication regimens,[16 17] several relevant studies of pharmacological and

alternative, non-pharmacological strategies (e.g., exchanging one contrast medium for an alternative) have been published and have influenced the ACR and ESUR guidelines.[18 19] In addition, the two prior systematic reviews on this topic included pharmacological prophylaxis only in the context of now-outdated high-osmolality iodinated contrast media that are no longer used in clinical practice. Therefore, we planned a comprehensive quantitative synthesis of clinical data on the effects of pharmacological and non-pharmacological prophylactic strategies for the prevention of acute adverse reactions to non-ionic iodinated contrast media.

METHODS AND ANALYSIS

This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement (PRISMA-P).[20] Based on the analytic framework shown in the **Figure 1**, we have formulated the following three key research questions and related sub-questions:

Key Question 1. What is the effect of interventions to reduce acute (<1 hour) hypersensitivity (Type B) reactions in patients receiving contrast media?

Key Question 1a: What is the preventive effect of guideline-recommended oral (12- or 13-hour), guideline-recommended accelerated intravenous (5- to 11-hour), or non-guideline emergent intravenous (<5-hour)

premedication on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key Question 1b: What is the preventive effect of a change of contrast media alone on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key Question 1c: What is the preventive effect of combining standard oral (12- or 13-hour) premedication and a change of contrast media on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key Question 1d: What is the preventive effect of other interventions (other than the above listed) on acute (<1 hour) hypersensitivity reactions?

Key Question 1e: What is the preventive effect of any interventions for acute (<1 hour) adverse reactions of any type (i.e., both type A and B reactions)?

Key Question 2. What are the patient-level and intervention-level characteristics (i.e., predictors) associated with contrast media-induced acute hypersensitivity (Type B) reactions?

Key Question 3. What are the complications and adverse events associated with specific interventions to reduce contrast media-induced adverse reactions?

Literature search

We will search the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from January 1, 1990 through December 31, 2019 for both English- and non-English-language publications, using search terms such as "iodinated contrast media," "premedication," "adverse reaction," "breakthrough reactions," and their synonyms. The complete search strategy and full list of databases are available as an online Supplementary file. We will include studies published after 1990, when non-ionic contrast media were developed and disseminated widely. We also will examine the references of eligible studies, relevant review articles, and existing clinical practice guidelines developed by professional societies such as the ACR and ESUR.[2 9] All potentially eligible non-English publications will be translated into English before full-text assessment.

Inclusion and exclusion criteria

We will include studies that assessed patients who received intravenous or intra-arterial non-ionic iodinated contrast media and any interventions to reduce contrast media-induced adverse reactions. The **Table 1** presents our detailed inclusion criteria, which follow a generally accepted framework to formulate a systematic review question comprising 5 key components: populations, interventions, comparator interventions, outcomes, and study designs.[21] Regarding pharmacological prophylactic interventions, we will focus on premedication based on corticosteroids, anti-histamines, or both, and

exclude studies that tested other medications (e.g., ephedrine, diazepam, atropine) because these are not relevant to current clinical practice. We also will exclude studies that assessed patients who received high-osmolality contrast media because they are no longer used in clinical practice. Both prospective and retrospective studies of any design that evaluated at least 10 patients will be included.

Several frameworks for categorizing clinical symptoms and severity induced by pharmacological agents including contrast media exist. We will employ an accepted general two-group framework (type A and type B) to classify acute contrast media-induced adverse reactions reported in primary studies in the main analysis.[5] We then will reclassify the reported acute adverse reactions using the current ACR categorization system[2] in a sensitivity analysis to assess the applicability and difference between the two frameworks. Delayed reactions occurring more than 1 hour after contrast media administration will not be assessed. A breakthrough reaction will be defined as an acute type B reaction of any severity that occurs despite premedication. We will operationally classify any randomized controlled trials (RCTs) and any studies with a non-randomized design that compared two or more intervention groups (i.e., so-called non-randomized studies of intervention [e.g., quasi-RCTs, cohort studies, case-control studies]) as "comparative studies." "Non-comparative studies" will include single-group studies and case series.

We will exclude editorials, comments, letters to the editor, and review articles. Multiple publications with potentially overlapping patient populations can overestimate the volume of evidence. Therefore, for overlapping study populations, we will only include the publication with the largest sample size. We will contact the study authors by email if the publications do not report adequate information about the patient characteristics and reaction classifications. We will consider our request to be rejected if two email request reminders sent separately 14 days after the initial contact attempt are not returned.

The results of our electronic searches will be imported into reference management software and duplicate results will be removed. Multiple paired investigators will independently double-screen non-overlapping sets of abstracts (e.g., the first half of the abstracts will be assigned to team A [2 investigators] and the second half of the abstracts will be assigned to team B [2 investigators] in the case of two paired teams) and examine full-text articles for potentially eligible citations. We will use Abstrackr (Center for Evidence Synthesis in Health, Brown University, Providence, RI, available at abstrackr.cebm.brown.edu), a free, open-source, citation screening program for abstract screening. A third investigator will adjudicate any discrepant results if consensus cannot be reached between the two reviewers.

Data extraction

We will extract the following descriptive data from eligible studies. Study characteristics will include first author, year of publication, journal, and study design (prospective *vs.* retrospective, comparative study *vs.* non-comparative study). Participant characteristics will include age, sex, history and severity and type of any prior acute adverse reaction to iodinated contrast media, allergic diathesis including severe allergy(-ies) to other substances and asthma,[2] and other known risk factors for adverse reactions. Contrast media characteristics will include brand and generic names and doses of contrast media administered. Intervention characteristics will include premedication strategies including drugs, doses, duration, and change in contrast media. Outcome characteristics will include details of and change in adverse reactions (kinds and severity), assessors of adverse reactions (number and experience), and categorization system to classify and grade acute adverse events. We will operationally define guideline-recommended regimens as the 12- to 13-hour oral administration of corticosteroids with or without use of an anti-histamine, and standard accelerated regimen as a 5- to 11-hour intravenous administration of corticosteroids with or without the use of an anti-histamine.[2] If a study adopted ad-hoc definitions or categorization

systems other than the two-group classification framework or those proposed by the ACR, we will specify these differences in sufficient detail. One primary investigator will extract the descriptive data, which will be verified by a second investigator.

Two reviewers will independently double-extract quantitative data from each publication. We will determine the relative risk of a hypersensitivity reaction between two (or more) groups in comparative studies. We will extract the number of patients in each group, as well as the number of patients who developed a hypersensitivity reaction. If relevant count data cannot be determined from the publication, we will instead extract the reported point estimates and their confidence intervals.

We will extract quantitative measures (e.g., risk ratios, odds ratios) of the association of the presence or absence of a predictor with the development of a breakthrough reaction. We will prefer adjusted values over unadjusted values if both are reported. *A priori* candidate predictors selected for extraction include specific index type B reactions and their grades, and any allergic diathesis and its severity.

Assessment of risk of bias

For RCTs, we will use the revised tool to assess risk of bias in randomized trials (RoB 2

tool).[22] We will assess five domains of RCT study validity (i.e., randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, selective reporting) and then assign an overall risk of bias for each trial.

For non-randomized intervention studies, we will use the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for cohort studies,[23] and the Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) for case-control studies.[24] We will assess seven domains of study validity (i.e., confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selective reporting) and then assign an overall risk of bias for each study.

For single-group observational studies that assessed a predictor in a specific clinical context (e.g., development of a breakthrough reaction under a premedication regimen), we will use a revised version of the Quality in Prognosis Studies tool (the QUIPS-2).[25] We will assess six domains of study validity (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis and reporting) and then assign an overall risk of bias for each study.

Two reviewers will independently assess each item and rate the domain-specific and overall risks of bias. Discrepant ratings will be resolved by consensus. A third independent investigator will adjudicate any unresolved discrepancies. The complete list of modified operational definitions used to rate each item will be available from the authors upon request.

Data synthesis

The primary outcome of interest will be the relative risk of an acute type B (hypersensitivity) reaction between specific prevention strategies. Secondary outcomes will include the breakthrough reaction rate of each specific strategy and the predictive performances of covariates for overall and severe breakthrough reactions. For all outcome measures, we will first construct an evidence map by performing qualitative syntheses based on graphs and tables to examine the diversity and volume of available evidence on this topic.[26 27] If feasible, we will then perform a quantitative synthesis.

For summary relative measures (e.g., relative risk of an acute type B reaction) based on count data, we will perform a random-effects meta-analysis using the binomial likelihood with logit link in a generalized linear modeling framework (i.e., random-effects logistic regression).[28] If already-estimated relative measures are the only extractable formats, we will utilize the log-transformed estimates and their variances as

"plug-in" estimates. If appropriate, the meta-analytical model for a specific pairwise comparison will be extended to a network meta-analysis to synthesize data from both direct and indirect comparisons of all available studies in a single analysis.[28]

For summary estimates of the proportion measures in non-comparative studies, we will perform a random-effects meta-analysis of proportions using the binomial likelihood and logit link (i.e., so-called the binomial-normal model).[29]

Additional analyses

We will estimate the between-study standard deviation parameter, *tau*, and I^2 statistic and corresponding 95% credible intervals as measures of statistical heterogeneity. An I^2 >50% will indicate intermediate heterogeneity, while an I^2 >70% will indicate high heterogeneity.[30]

To explore statistical heterogeneity, we will perform subgroup analyses and, if feasible, a univariable random-effects meta-regression.[28] Preplanned candidate factors will include the use of guideline-recommended premedication regimens (vs. non-guideline-recommended or *ad-hoc* regimens), alterations of the culprit contrast media (vs. not), use of the general two-group classification framework vs. the ACR categorization systems for the classification and grading of reactions (vs. others), and severity and type

of prior reactions to iodinated contrast media. We will consider conducting sensitivity analyses by reclassifying and/or re-grading the reported reactions based on the two-group classification system and the ACR classification system for studies not using these classification frameworks, if pertinent individual-level data are presented.

We will assess funnel-plot asymmetry if at least 10 studies are included.[31] To address potential biases derived from missing outcome data, we will apply the approach proposed by Turner et al.[32] We will assess the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. [33]

Statistical software

We will conduct all analyses using Stata version 14/SE (Stata Corp., College Station, TX, USA) and OpenBUGS version 3.2.3 (members of OpenBUGS Project Management Group; see www.openbugs.net). All tests will be two-sided, and statistical significance will be defined as a P value <0.05.

Patient and Public Involvement

We did not involve patients or the public in the preparation of this systematic review protocol.

DISCUSSION

The revised 2019 ESUR guidelines on Contrast Agents retracted recommendations for the premedication of patients at an increased risk of contrast reaction due to a lack of scientific evidence of efficacy.[9] This position is inconsistent with the latest guidelines of other professional societies, including the ACR (ACR Manual on Contrast Media v. 10.3),[2] the Canadian Association of Radiologists,[34] and the Japan Radiological Society.[35] Also, concerns have been raised on the relevance and impact of the classification systems and nomenclature of contrast media-induced adverse reactions, and their recommended management proposed in guidelines.[4] Given the wide application of iodinated contrast media in medical imaging and interventional procedures, the uncertainty surrounding the optimization of prevention strategies based on the proposed framework, and the absence of recently published evidence reviews, we believe that it will be worthwhile to conduct a new systematic review that critically examines the existing evidence on interventions to reduce acute contrast media-induced adverse reactions. Using a comprehensive evidence map of the published literature on the effects of pharmacologic and non-pharmacologic interventions and, if feasible, new meta-analytic results, we hope to clarify the actionable evidence regarding the use of preventive interventions.

ETHICS AND DISSEMINATION

As this is a systematic review, we are not planning to obtain a formal ethical approval. The findings from the review will be disseminated through publications in peer-reviewed journals, and presentations at conferences.

Contributors

HU and TN originated the idea; HU, TN and TT drafted the initial version of the protocol; HU, TN and TT developed the search strategy; HS, TY, HI, AT, NH, SI, YT, SN, and MSD reviewed the protocol and suggested amendments. All authors read and approved the final version of the protocol. HU, TN, and TT are guarantors of the review.

Funding

TT was supported in part by the Ministry of Education, Culture, Sports, Science and Technology, Japan (JSPS KAKENHI Grant Numbers: 26460755 and 19K07877). The funding source had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest

All authors declare no conflicts of interest associated with this publication.

For complete transparency outside the submitted work, Dr. Ishihara reports personal fees from Bayer Yakuhin, Ltd.; Dr. Takehara is an endowed chair sponsored by HIMEDIC Co. He does not receive any financial support from the corporation for conducting the research and writing this paper. He also reports personal fees from Daiichi Sankyo company, Ltd., Bayer Yakuhin, Ltd., GE Healthcare, Medi-Physics Co Ltd., Mitsubishi Tanabe Pharma Corporation, National Cancer Center; Dr. Naganawa reports personal fees from Daiichi Sankyo company, Ltd., Kowa Company, Ltd., Bayer Yakuhin, Ltd., Fuji Pharma Co Ltd., Bracco-Eisai Co Ltd., FUJIFILM Toyama Chemical Co Ltd., Canon medical systems corporation, Siemens Healthineers Japan, Trust Clinic, Nagoya Jhohoku Radiology Clinic, Gakken Medical Shujunsha Co Ltd, Neuryon AG; and Dr. Davenport reports royalties from Wolters Kluwer and uptodate.com.

Disclosure

A preliminary work of this research project based on a brief literature search has been presented in an educational session at the 77th annual meeting of the Japan Radiological Society 2018, Yokohama, Japan.

References

1. Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990;**175**(3):621-8.
2. ACR Committee on Drugs and Contrast Media. ACR Manual On Contrast Media Version 10.3 2018. Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf. Accessed on July 1, 2019.
3. Bettmann MA. Frequently asked questions: iodinated contrast agents. Radiographics 2004;**24 Suppl 1**:S3-10.
4. Bohm I, Morelli J, Nairz K, et al. Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review. Postgrad Med 2017;**129**(2):259-66.
5. Pichler WJ. Drug hypersensitivity: Classification and clinical features. UpToDate. Available from: https://www.uptodate.com/contents/drug-hypersensitivity-classification-and-clinical-features. Accessed on Jan 1, 2020.
6. Davenport MS, Cohan RH, Caoili EM, et al. Repeat contrast medium reactions in premedicated patients: frequency and severity. Radiology 2009;**253**(2):372-9.
7. Davenport MS, Cohan RH, Khalatbari S, et al. Hyperglycemia in hospitalized patients receiving corticosteroid premedication before the administration of radiologic contrast medium. Acad Radiol 2011;**18**(3):384-90.
8. Davenport MS, Mervak BM, Ellis JH, et al. Indirect Cost and Harm Attributable to Oral 13-Hour Inpatient Corticosteroid Prophylaxis before Contrast-enhanced CT. Radiology 2016;**279**(2):492-501.
9. European Society of Urogenital Radiology. ESUR Guidelines on Contrast Media ver10.0 2018, Updated January 28, 2019. Available from: http://www.esur.org/guidelines/en/index.php#a. Accessed on July 1, 2019.
10. Mervak BM, Davenport MS, Ellis JH, et al. Rates of Breakthrough Reactions in Inpatients at High Risk Receiving Premedication Before Contrast-Enhanced CT. AJR Am J Roentgenol 2015;**205**(1):77-84.
11. Freed KS, Leder RA, Alexander C, et al. Breakthrough adverse reactions to low-

osmolar contrast media after steroid premedication. AJR Am J Roentgenol 2001;**176**(6):1389-92.

12. Mesurolle B, Ariche M, Cohen D. Premedication before i.v. contrast-enhanced CT resulting in steroid-induced psychosis. AJR Am J Roentgenol 2002;**178**(3):766-7.
13. Lasser EC, Berry CC, Mishkin MM, et al. Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. AJR Am J Roentgenol 1994;**162**(3):523-6.
14. O'Malley RB, Cohan RH, Ellis JH, et al. A survey on the use of premedication prior to iodinated and gadolinium-based contrast material administration. J Am Coll Radiol 2011;**8**(5):345-54.
15. The Japan Radiological Society. A nationwide survey on the use of premidication prior to Iodinated contrast material administration 2015, Updated 2015/7/21. Available from: http://www.radiology.jp/content/files/20150721-2.pdf. Accessed on Jan 1, 2020.
16. Delaney A, Carter A, Fisher M. The prevention of anaphylactoid reactions to iodinated radiological contrast media: a systematic review. BMC Med Imaging 2006;**6**:2.
17. Tramer MR, von Elm E, Loubeyre P, et al. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. BMJ 2006;**333**(7570):675.
18. Abe S, Fukuda H, Tobe K, et al. Protective effect against repeat adverse reactions to iodinated contrast medium: Premedication vs. changing the contrast medium. Eur Radiol 2016;**26**(7):2148-54.
19. Park HJ, Park JW, Yang MS, et al. Re-exposure to low osmolar iodinated contrast media in patients with prior moderate-to-severe hypersensitivity reactions: A multicentre retrospective cohort study. Eur Radiol 2017;**27**(7):2886-93.
20. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;**350**:g7647.
21. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 1997;**127**(5):380-7.
22. Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in

randomized trials. In: Chandler J, McKenzie J, Boutron I, et al., eds. Cochrane Methods Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). Available from https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0. Accessed on July 1, 2019.

23. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;**355**:i4919.
24. Sterne JAC, Higgins JPT, Reeves BC, et al. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0. 2014, Updated on 24 September 2014. http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-i/acrobat-nrsi/. Accessed on July 1, 2019.
25. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;**158**(4):280-6.
26. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC medical research methodology 2018;**18**(1):143-43.
27. Miake-Lye IM, Hempel S, Shanman R, et al. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Systematic reviews 2016;**5**:28-28.
28. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;**33**(5):607-17.
29. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med 2010;**29**(29):3046-67.
30. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;**327**(7414):557-60.
31. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;**343**:d4002.
32. Turner NL, Dias S, Ades AE, et al. A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Stat

Med 2015;**34**(12):2062-80.
33. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;**336**(7650):924-6.
34. Morzycki A, Bhatia A, Murphy KJ. Adverse Reactions to Contrast Material: A Canadian Update. Can Assoc Radiol J 2017;**68**(2):187-93.
35. The Japan Radiological Society. Revised recommendations on steroid premedication for reducing the risk of acute adverse effects of iodinated contrast agents and gadolinium contrast agents 2018. Available from: http://www.radiology.jp/member_info/safty/20181115.html. Accessed on July 1, 2019.

Table 1. Inclusion criteria based on the PICOD framework

PICOD	Specific details
Population	Patients who received intravenous or intra-arterial non-ionic iodinated CM* -High-risk population -Low-risk population -No risk-stratified population
Interventions /Comparators and co-interventions	Pharmacological interventions† 1. 12- or 13-hour oral corticosteroids with or without anti-histamine 2. 5- to 11-hour IV corticosteroids with or without anti-histamine 3. Any premedication less than 5 hours using corticosteroids, anti-histamine, or both Non-pharmacological interventions -Change of CM that caused prior Type B hypersensitivity reaction
Outcomes	Rates of acute (<1 hour) Type B hypersensitivity reactions‡ -Acute reaction-related deaths within 30 days -Severe reactions only -Moderate and severe reactions only -Upgraded reactions compared to the index reactions -All hypersensitivity reactions Rates of adverse events induced by preventive interventions

Predictors of acute adverse reactions	Patient-level characteristics
	-Prior Type B hypersensitivity reactions
	-Prior Type A physiologic reactions§
	-Allergic diathesis (e.g., asthma, food or drug allergy, etc.)
	Intervention-level characteristics
	-Types and regimens of interventions
	-Dosing of specific premedication drugs
	-Change of CM (specific class/product and/or dosing)
Designs	Any study designs including at least 10 patients
	-Randomized controlled trials
	-Nonrandomized trials
	-Prospective and retrospective cohorts
	Comparative (two or more-group) design
	Single-group design

* Per-study defined risk criteria are allowed.

†Both guideline-recommended and *ad-hoc* regimens are allowed, but will be analyzed separately. guideline-recommended oral regimens are defined as follows:[2] 13-hour regimen: prednisone 50 mg PO at 13, 7, and 1 hrs before CM injection +/- optional diphenhydramine 50 mg IV, IM, or PO at 1 hr before CM injection; 12-

hour regimen: methylpredonisolone 32 mg PO at 12, and 2 hrs before CM injection +/- optional antihistamine. Guideline-recommended urgent regimens are: methylprednisolone 40 mg or hydrocortisone 200 mg IV every 4 hrs until CM injection (minimum cumulative duration 5 hours) +/- diphenhydramine 50 mg IV at 1 hr before CM injection. Any premedication that does not include corticosteroids or that is less than 5 hours in duration is non-standard.

‡Grades of Type B hypersensitivity reactions are defined as follows[2]: mild reactions include limited urticaria/pruritis, cutaneous edema, limited "itchy"/"scratchy" throat, nasal congestion, sneezing, conjunctivitis, and rhinorrhea; moderate reactions include diffuse urticaria/pruritis, diffuse erythema with stable vital signs, facial edema without dyspnea, throat tightness or hoarseness without dyspnea, and wheezing/bronchospasm with mild or no hypoxia; and severe reactions include diffuse edema, facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing/bronchospasm with significant hypoxia, and anaphylactic shock (hypotension + tachycardia).

§Grades of Type A physiologic reactions are defined as follows[2]: mild reactions include limited nausea/vomiting, transient flushing, warmth, chills, headache, dizziness, anxiety, altered taste, mild hypertension, and vasovagal reaction that resolves spontaneously; moderate reactions include protracted nausea/vomiting, hypertensive urgency, isolated chest pain, and vasovagal reaction that requires and is responsive to treatment; and severe reactions include vasovagal reaction resistant to treatment, arrhythmia, convulsions, seizures, and hypertensive emergency.

Abbreviations: CM = contrast medium; IM = intramuscularly; IV = intravenously; PICOD = populations, interventions, comparator interventions, outcomes, and study designs; PO = orally

Figure legend

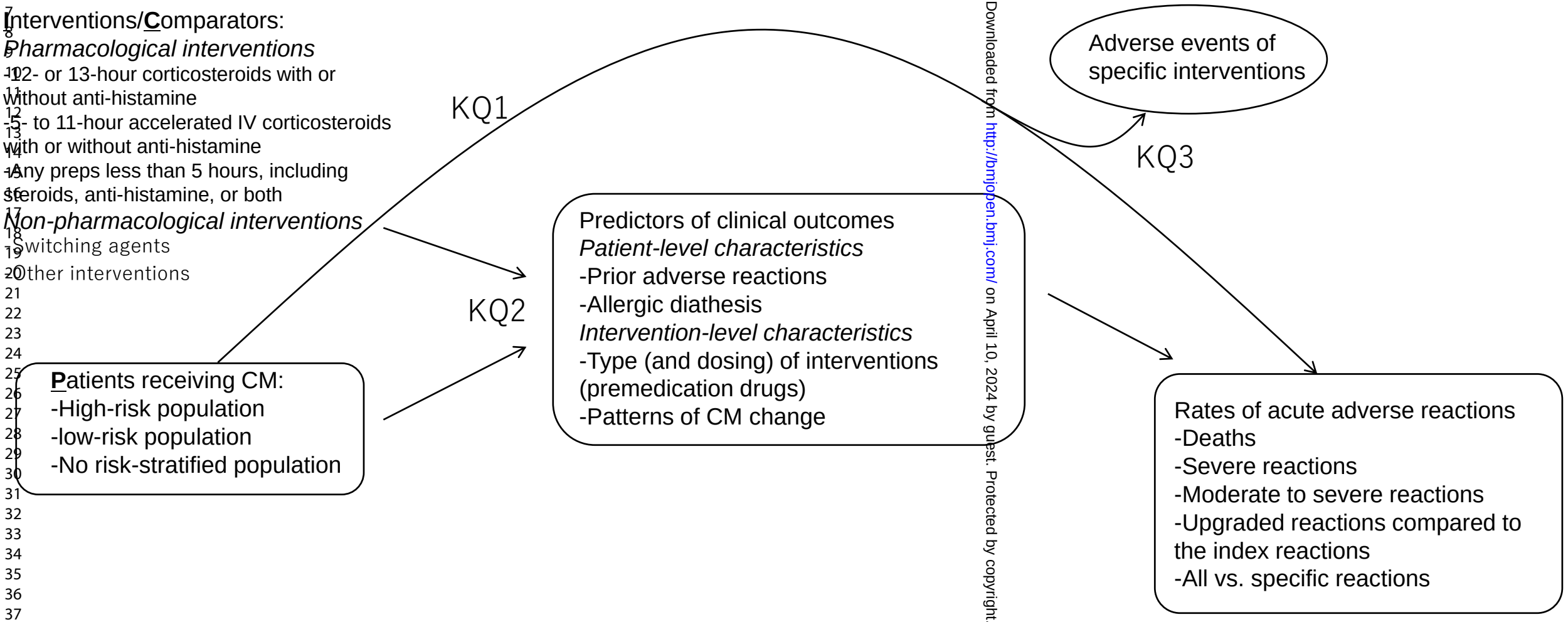
Figure 1. Analytic framework.

Abbreviations: CM = contrast media; KQ = key question

Key Question 1. What is the effect of interventions to reduce acute (<1 hour) hypersensitivity (Type B) reactions in patients receiving CM?

Key Question 2. What are the patient-level and intervention-level characteristics (i.e., predictors) associated with CM-induced acute hypersensitivity (Type B) reactions?

Key Question 3. What are the complications and adverse events associated with specific interventions to reduce CM-induced adverse reactions?



SUPPLEMENTARY FILE

Search strategies

PubMed

1. "Contrast Media"[Pharmacological Action]
2. radiocontrast*
3. iodinated contrast*
4. contrast material*
5. iodine contrast*
6. iodixanol OR iohexol OR iopamidol OR ioversol OR ioxilan OR iopromide OR iobitridol OR iomeprol
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. "Adverse Effects"[Subheading]
9. Adverse
10. "side effect"
11. "side effects"
12. reaction*
13. harm*
14. complicat*
15. toxicit*
16. hypersensitiv*
17. breakthrough reaction*
18. anaphyla*
19. allerg*
20. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21. Premedication[Mesh]
22. premedicat*
23. prevent*
24. prophyla*
25. steroid*
26. corticosteroid*
27. antihistamine*
28. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
29. #7 AND #20 AND #28

Cochrane Central Register of Controlled Trials (Ovid)

1. contrast media.mp. or exp Contrast Media/
2. radiocontrast*.mp.
3. iodinated contrast*.mp.
4. contrast material*.mp.
5. Iodine/ or iodine contrast*.mp.
6. (iodixanol or iohexol or iopamidol or ioversol or ioxilan or iopromide or iobitridol or iomeprol).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. 1 or 2 or 3 or 4 or 5 or 6
8. Adverse Effects.mp.
9. "Drug-Related Side Effects and Adverse Reactions"/ or adverse.mp.
10. side effect.mp.
11. side effects.mp.
12. reaction*.mp.
13. Patient Harm/ or harm*.mp.
14. complicat*.mp.
15. toxicit*.mp.
16. Hypersensitivity/ or hypersensitiv*.mp.
17. breakthrough reaction*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
18. Anaphylaxis/ or anaphyla*.mp.
19. allerg*.mp.
20. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. premedication.mp. or Premedication/
22. premedicat*.mp.
23. prevent*.mp.
24. prophyla*.mp.
25. steroid*.mp.
26. Glucocorticoids/ or corticosteroid*.mp.
27. antihistamine*.mp. or Histamine H1 Antagonists/
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 7 and 20 and 28

Embase

1. 'contrast medium'/exp OR 'contrast medium'
2. radiocontrast*
3. 'iodinated contrast medium'/exp OR 'iodinated contrast medium'
4. iodinated AND contrast*
5. ('contrast'/exp OR contrast) AND material*
6. ('iodine'/exp OR iodine) AND contrast*
7. 'iodixanol'/exp OR iodixanol OR 'iohexol'/exp OR iohexol OR 'iopamidol'/exp OR iopamidol OR 'ioversol'/exp OR ioversol OR 'ioxilan'/exp OR ioxilan OR 'iopromide'/exp OR iopromide OR 'iobitridol'/exp OR iobitridol OR 'iomeprol'/exp OR iomeprol
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. 'adverse event'/exp OR 'adverse event'
10. Adverse
11. 'side effect'/exp OR 'side effect'
12. 'side effects'
13. reaction*
14. harm*
15. 'complication'/exp OR 'complication'
16. complicat*
17. 'toxicity'/exp OR 'toxicity'
18. toxicit*
19. 'hypersensitivity'/exp OR 'hypersensitivity'
20. hypersensitiv*
21. breakthrough AND reaction*
22. 'anaphylaxis'/exp OR 'anaphylaxis'
23. anaphyla*
24. allerg*
25. 'immediate type hypersensitivity'/exp OR 'immediate type hypersensitivity'
26. 'allergy'/exp OR 'allergy'
27. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28. 'premedication'/exp OR 'premedication'
29. premedicat*
30. 'prevention'/exp OR 'prevention'
31. prevent*

32. 'prophylaxis'/exp OR 'prophylaxis'
33. prophyla*
34. 'steroid'/exp OR 'steroid'
35. steroid*
36. 'corticosteroid'/exp OR 'corticosteroid'
37. corticosteroid*
38. 'antihistaminic agent'/exp OR 'antihistaminic agent'
39. 'histamine h1 receptor antagonist'/exp OR 'histamine h1 receptor antagonist'
40. antihistamine*
41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
42. #8 AND #27 AND #41
43. #42 AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'short survey'/it)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reporting Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6-7
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18-19
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8-9 and supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12-13
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	15
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13-14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	15
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	16

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.