

Stent implantation in patients with metal allergy: a systemic review and meta-analysis

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Objectives The aim of this study was to assess whether outcomes of patients with metal allergy after coronary stent implantation differ from those of patients without metal allergy.

Methods A meta-analysis was carried out to compare the outcome in patients who are allergic to the metal material of a stent with those who are nonallergic. A computer-based online retrieval of databases and manual searches were performed to identify articles that addressed the association between in-stent restenosis (ISR) and contact allergy to stent materials, without language restrictions. The meta-analysis was carried out with a fixed-effect model using STATA 11. Odds ratio (OR) was used as an effect size.

Result Nine relevant articles, encompassing 1223 patients, were identified. Being allergic to stent material obviously increased the risk of ISR. With the fixed model, ORs for allergic patients and nonallergic patients were 2.65 (confidence interval 1.82–3.82). A subgroup analysis of race was carried out. OR in the Asian group was higher than that in the European group (3.71 vs. 2.25), which might

suggest that Asians who are allergic to stent material have a higher risk of ISR than Europeans.

Conclusion Allergy to stent material worsens the prognosis of patients with coronary stent implantation. New well-designed prospective clinical trials are required to confirm this relationship and to establish the indispensability of a skin patch test before coronary stent implantation. *Coron Artery Dis* 24:684–689 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Stent implantation, one of the first-choice therapies for coronary heart disease, has been performed in patients worldwide since it was proven to be more effective than balloon angioplasty [1,2]. However, in-stent restenosis (ISR) is one of the major complications of stent implantation that markedly affects the outcomes of patients who have undergone stent implantation. In a previous study, it has been made clear that a drug-eluting stent may improve the outcomes of patients and reduce ISR [3], but it remains unclear whether or not contact allergy to stent material is a risk factor of ISR.

Nowadays, stents are mainly made of stainless steel, which is mainly composed of iron, nickel, molybdenum, or chromium. Among these elements, nickel is the most common cause of contact allergy. Contact allergy to nickel, reported widely worldwide, is classified as a type IV hypersensitivity, mediated by T cells [4]. However, whether such hypersensitivity that takes place in the coronary artery will worsen outcomes in patients has been studied less frequently. Many studies suggested that the risk of ISR would increase in patients with metal allergy, such as a study by Iijima *et al.* [5] in 2005. However, a study carried out by Thyssen *et al.* [6] in 2011 suggested that there was no evidence supporting such a relationship.

No meta-analyses have been carried out to date on the relationship between allergy to stent material and ISR. To determine whether such an association exists, we carried out a meta-analysis of case-control studies that examined this.

Methods

Search strategy

Searches were performed in the electronic databases MEDLINE, EMBASE, and Cochrane library in December 2012 to identify articles that reported a relationship between contact allergy to stent material and ISR. Manual searches of key journals and abstracts from major annual meetings were performed in the fields of cardiac interventional therapy and cardiovascular disease in an effort to discover relevant unpublished data. Additional unpublished studies were also sought from web sites. The search strategy included the following: text word stent and text word allergy or the text word hypersensitivity. No language restrictions were used in the search.

Inclusion criteria

A study was included if it fulfilled the following criteria: (a) it reports a difference in allergic state between patients with ISR and patients without ISR. (b) Contact

Table 1 Characteristics of studies on allergy to stent material and in-stent restenosis

References	Country	Race	Sample size	Exclusion criteria	Confirmation of contact allergy
Koster <i>et al.</i> [10]	Germany	European	131	Immunosuppressive therapy or immune disorders Dermatitis Irritation at the site for the epicutaneous patch test	Skin patch test
Hillen <i>et al.</i> [11]	Germany	European	34	Follow-up reangiography less than 3 months	Skin patch test
Iijima <i>et al.</i> [5]	Japan	Asian	109	Patients with initial stent implantation had other stents previously placed in other locations in the coronaries or other intravascular site Patients who were not able to provide an informed consent	Skin patch test
Norgaz <i>et al.</i> [12]	Turkey	European	43	Patients who had undergone previous coronary interventions Patients with acute coronary syndromes Patients without immune-suppressive diseases Patients taking immune-suppressive drugs	Skin patch test
Saito <i>et al.</i> [13]	Japan	Asian	128	Bypass surgery or any surgery with metal material implant known allergic disease Stent implantation in branch arteries with N>2.5 mm other than standard exclusion criteria for PCI	Skin patch test
Svedman <i>et al.</i> [14]	Sweden	European	338	None	Skin patch test
El-Mawardy <i>et al.</i> [15]	Egypt	Unknown	50	Patients presenting with acute coronary syndrome Patients who had received drug-eluting stents or stents of other metal alloys Patients with autoimmune diseases Patients with immunosuppressive diseases Patients receiving immunosuppressive medications Patients with severe skin lesions that would interfere with patch test results	Skin patch test
Thyssen <i>et al.</i> [6]	Denmark	European	149	Patients without PCI Patients with PCI, without stent	Skin patch test
Aliağaoğlu <i>et al.</i> [16]	Turkey	European	61	Acute coronary syndrome Active eczema Immune-suppressive drugs or having a patch test before study inclusion	Skin patch test

PCI, percutaneous coronary intervention.

allergy to stent material is confirmed by a skin patch test. (c) ISR is identified by coronary angiography or other objective methods.

Exclusion criteria

A study was excluded if it fulfilled any criteria below: (a) contact allergy was confirmed by a medical report or other methods instead of by a standard skin patch test. (b) Restenosis was confirmed by symptoms of coronary stenosis rather than by a coronary angiography. (c) The data could not be extracted. (d) If similar data had been published twice, then only the latest data would be used.

Study selection and data extraction

Two reviewers independently screened the abstracts and titles of the search results, and articles were eliminated if they did not investigate the association between metal allergy and ISR. The same two reviewers evaluated studies independently for eligibility on the basis of the predefined set of eligibility criteria. Information from each study was extracted independently by the two investigators using a standardized data extraction form. Available general characteristics of the study (author, year of publication, country, time of study, study design, exclusion criteria, race of patients), characteristics of the ISR group and the non-ISR group (age, sex, BMI), and results (sample size, allergic patients) were recorded and double-checked. Discrepancies in data extraction between reviewers were resolved by discussion.

Statistical analysis

We compared the difference in allergic rates between the ISR group and the non-ISR group with odds ratio (OR) with a 95% confidence interval (95% CI) by meta-analysis using STATA 11 (Stata Corp., College Station, Texas, USA).

Heterogeneity between the results of different studies was examined using the I^2 -test ($I^2 > 50\%$: significant heterogeneity; $I^2 < 25\%$: insignificant heterogeneity). On the one hand, if no significant heterogeneity was found, a fixed-effect model will be chosen to carry out this meta-analysis. On the other, if significant heterogeneity is found, a random-effect model will be chosen.

To confirm our results, we plan to carry out a sensitivity test on our meta-analysis by excluding one study with the highest weight and observe whether the result will be altered by this test.

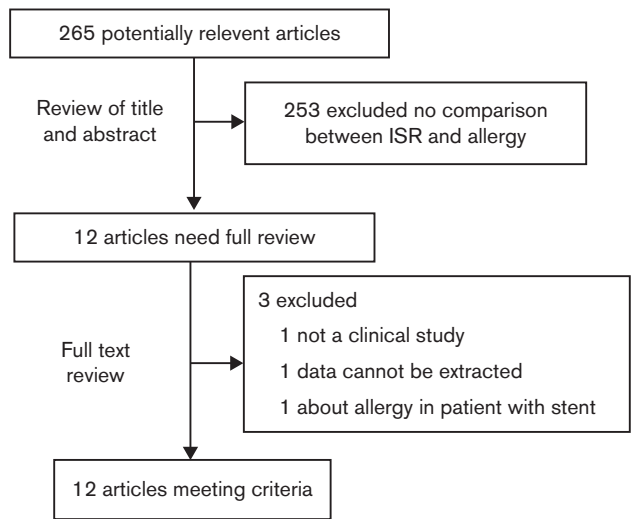
Results

Search results

We obtained 265 studies from both electronic and manual retrieval. Of these studies initially identified, we excluded 253 that did not examine the relationship between allergy to stent material and ISR. Of the 12 studies selected for further evaluation, one study, which was not a clinical study [7], and another study, which did not describe extractable data, were excluded [8]. A third study was excluded as it was actually an article

investigating whether patients with a stent implanted have a higher risk of developing contact allergy [9]. Finally, nine studies [5,6,10–16], including 1223 patients,

Fig. 1



Selection of studies. ISR, in-stent restenosis.

were included in the meta-analysis. Table 1 shows the characteristics of all nine studies included in our analysis.

We carried out a quality evaluation on all of the studies included according to the STROBE statement. All of the studies included were of high quality and no study was excluded in the meta analysis on the basis of quality (Fig. 1).

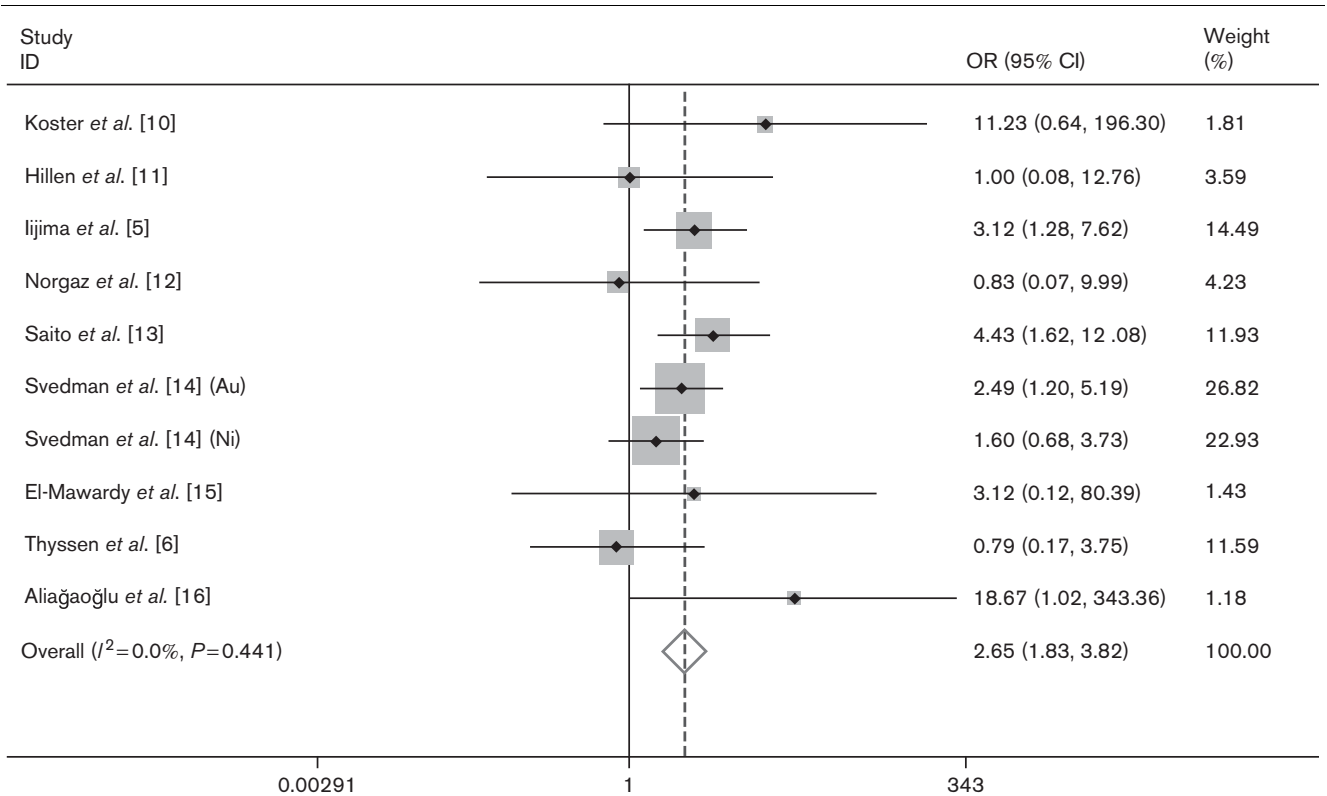
Statistical results

No statistical heterogeneity was found among these studies ($I^2 = 0.0\%$, $P = 0.441$). Thus, a fixed-effect model was used to carry out this meta-analysis. The result suggested that there might be a relationship between being allergic to stent material and ISR (OR = 2.65, 95% CI 1.83–3.82) (Figs 2 and 3).

Among these nine studies, four studies concluded that the risk of ISR was higher in allergic patients compared with nonallergic patients. The other five studies reported no statistical differences in this aspect.

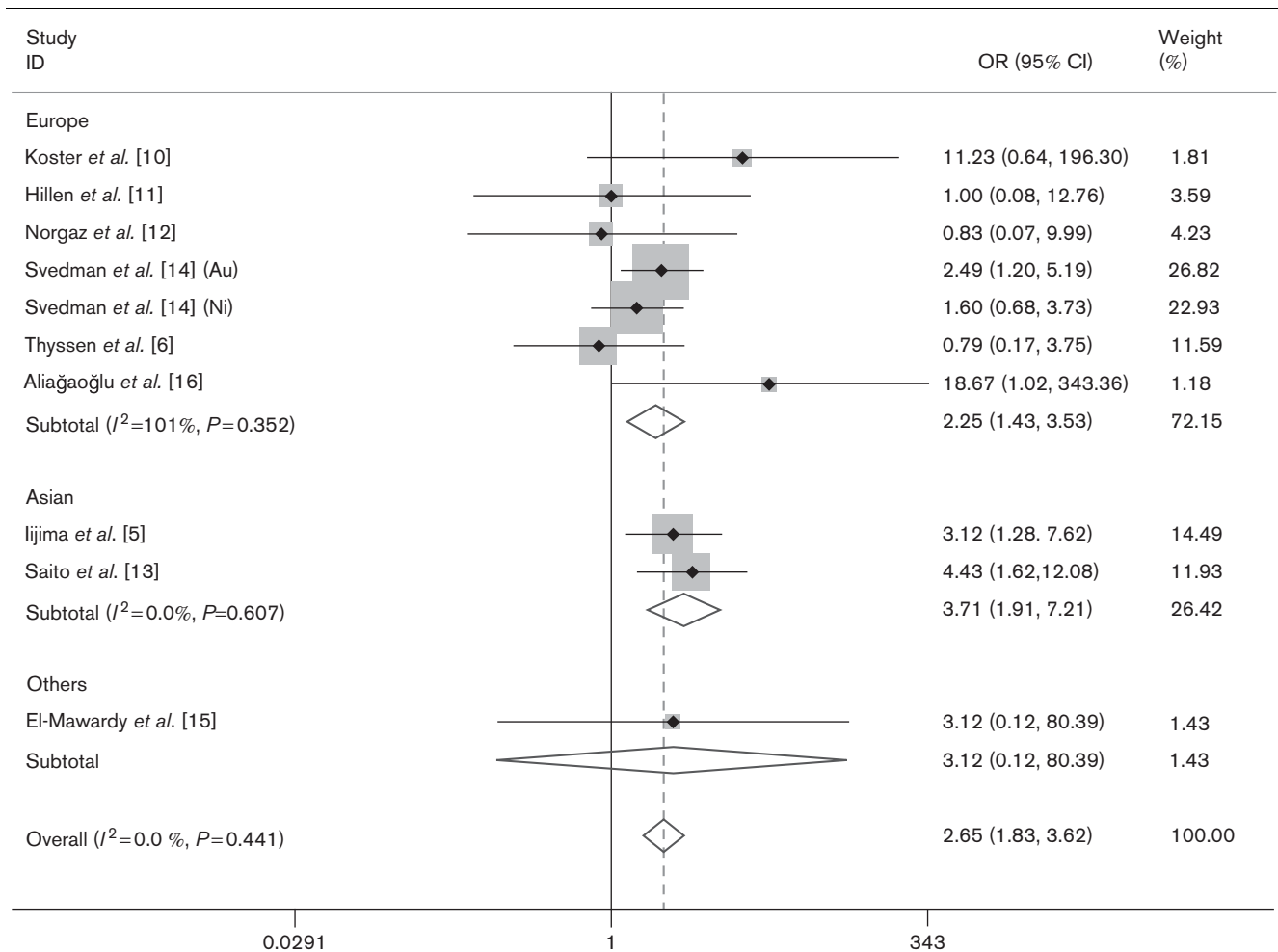
Six studies investigated the relationship between being allergic to stent material and ISR in a European population. We carried out a fixed-effect meta-analysis because no statistical heterogeneity was confirmed among these studies ($P = 0.352$, $I^2 = 10.1\%$). In these

Fig. 2



OR between ISR patients and non-ISR patients. CI, confidence interval; ISR, in-stent restenosis; OR, odds ratio.

Fig. 3



Subgroup analysis by race. CI, confidence interval; OR, odds ratio.

six studies, the OR between the ISR group and the non-ISR group showed a significant difference (OR 2.25, 95% CI 1.43–3.53). This result might suggest that there was a relationship between being allergic to stent material and ISR.

Two studies, 237 patients in total, examined the association in an Asian population. A fixed-effect meta-analysis was carried out as no statistical heterogeneity was evident among these studies ($P = 0.607$, $I^2 = 0.0\%$). The OR between the ISR group and the non-ISR group showed a significant difference (OR = 3.71, 95% CI 1.91–7.21), which was even higher than that in the European ones. This result might suggest that compared with European patients, Asian patients who are allergic to stent material are at a higher risk of ISR if they undergo stent implantation.

To confirm our study, we carried out a sensitivity test on our study. We excluded the study with the highest

weight. Exclusion of this study yielded results similar to previous OR (OR = 2.76, 95% CI 1.74–4.39).

Discussion

The results of our study suggest an association between being allergic to stent material and ISR. However, it did not fully explain why being allergic to stent material has an adverse effect on the outcome of stent implantation. To our knowledge, metal can only cause a contact allergy in an ionized state [17]. A stent may give rise to ions as a result of the formation of a galvanic cell, which is caused by constant mechanical damage to the surface. Finally, this may lead to sensitization and cause inflammation and proliferation within the vessel in which a stent is implanted [18]. This mechanism may explain why a drug-eluting stent can improve the prognosis significantly [19]. A recent study [20] shows that eosinophilic cationic protein (ECP), which is a highly sensitive biomarker of eosinophil activation, is an indicator of

clinical outcome in patients undergoing bare metal stent implantation. This may suggest that allergy-mediated inflammation plays a very important role in adverse reactions of coronary stent implantation. Even preintervention plasma ECP levels can indicate prognosis after coronary stent implantation [21], suggesting that the state of high eosinophil activation may contribute toward cardiovascular adverse events even if this state is not induced by stent implantation. Further study is warranted to show whether ECP is a pathogenic factor or just a marker of side effects.

We found that Asian individuals have a higher risk of ISR if they are allergic to stent material than their European counterparts. However, studies on Asians are quite different from those on Europeans. One study only included those patients who already had ISR, and the paper discussed the risk of re-restenosis in patients who had undergone a stent implantation for ISR. Thus, there might be bias.

In the study of Svedman and colleagues it was found that patients had a higher risk if they were allergic to gold and had been implanted with a gold stent. However, they found that there was no statistically significant difference if the patient was allergic to nickel. Limited by the small sample sizes, we have not carried out a meta-analysis on Au-stent patients and Ni-stent patients separately. A further well-designed study is required to determine whether a nickel stent may have a better prognosis than a gold stent in allergic patients.

The study carried out by Svedman and colleagues has confirmed that being allergic to stent material will increase the risk of ISR. These results differ from those obtained from studies carried out by Koster, Hillen, and some others. The latter suggests that being allergic to stent material is not associated with ISR. This lack of an association may be because of a small sample size and selection bias arising from the study by Thyssen *et al.* [6].

A study by Brunetti *et al.* [22] suggests that a history of allergy is an indicator of poor prognosis in patients with unstable angina undergoing coronary angioplasty. Confounding bias may exist here as being allergic to stent material could be part of a history of allergy. Further study should be carried out on the basis of excluding patients with a known history of allergy to eliminate the effect of history of allergy and determine the relationship between allergy to stent material and ISR.

From our study, we can conclude that in clinical practice, patients with an allergic reaction to stent material should be followed up more frequently to prevent potential cardiovascular adverse events as early as possible because they have a higher risk of developing ISR. Moreover, physicians should be more cautious when considering stent implantation in patients who are known to be allergic to stent materials.

Our findings are based on available information on ISR and allergy to stent materials. Limited by the current studies published, studies included in this meta-analysis are all case-control ones, without a single prospective study. We have not yet found any unpublished article.

However, as many kinds of bias may occur in a meta-analysis, to ensure objectivity, we carried out and reported this analysis according to the guidelines of the Meta-Analysis of Observational Studies in Epidemiology Group. A sensitivity test was also used to ensure that the result was not affected by one high-weighted study. Although we believe that our study is objective, further well-designed, large sample size prospective study is still required to confirm such a relationship.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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