

Original research

Nickel hypersensitivity and endovascular devices: a systematic review and meta-analysis

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ABSTRACT

Objective Nickel allergy is common; endovascular specialists are often confronted with nickel allergic patients ahead of the implantation of endovascular devices, many of which are nickel-containing. Our aim was to elucidate whether nickel hypersensitivity is significantly associated with worse or adverse outcomes after placement of a nickel-containing endovascular device.

Methods Inclusion criteria were: endovascular and transcatheter procedures for coronary, structural heart, neurovascular and peripheral vascular pathology involving nickel-allergic patients. All adverse outcomes were included as defined by included studies. A systematic review and meta-analysis were undertaken using a random-effects model. Searches of MEDLINE and EMBASE were conducted for articles published 1947–2019.

Results 190 records were identified, 78 articles were included for qualitative synthesis and 15 met criteria for meta-analysis. Patch-test confirmed nickel allergy was associated with an increased risk of adverse outcomes following implantation of a nickel-containing endovascular device (n=14 articles, 1740 patients; OR 2.61, 95% CI 1.41 to 4.85). This finding further was observed in coronary (n=12 articles, 1624 patients; OR 1.94, 95% CI 1.16 to 3.23) and structural heart subgroups (n=2 articles, 83 patients; OR 52.28, 95% CI 1.31 to 2079.14), but not in the neurovascular subgroup (n=1 article, 33 patients; OR 3.04, 95% CI 0.59 to 15.72) or with a patient-reported history of nickel allergy (n=2 articles, 207 patients; OR 2.14, 95% CI 0.23 to 19.70).

Conclusions Patch-tested nickel allergy is associated with an increased risk of adverse outcomes following endovascular device implantation and alternative treatment options should be considered. Specialists faced with patients' self-reporting nickel allergy should consider proceeding to diagnostic patch-testing.

that nickel allergy may be associated with an increased risk of adverse outcomes following device implantation, such as in-stent restenosis (ISR).² However, there is no clear consensus whether hypersensitivity to nickel is a contraindication to implantation of a nickel-containing device. This systematic review aims to elucidate whether nickel hypersensitivity is significantly associated with adverse outcomes after the placement of a nickel-containing endovascular device.

METHODS

This systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. There is no available written protocol for this review.

Search strategy

Searches of the online databases MEDLINE and EMBASE were performed on 10 January 2021 for all articles published since 1947. The search was not performed for unpublished studies.

There were no restrictions imposed on the search regarding publication type or language. Search terms included 'nickel', 'metal', 'allergy', 'hypersensitivity', 'endovascular', 'device', 'coil' and 'stent'. The full search string can be seen in online supplemental file 1. References and appendices of all included articles were also screened to identify any further eligible articles.

As a systematic review and meta-analysis, it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Inclusion criteria

Inclusion criteria were: all endovascular/transcatheter procedures for coronary, structural heart, neurovascular and peripheral vascular pathology involving patients with nickel hypersensitivity (table 1). All adverse outcomes were included as defined by eligible studies, for meta-analysis these were: ISR (defined as >50% diameter stenosis at the stent site), re-ISR, 'device syndromes' and 'fish-mouthing' (table 2). Articles identified by the search were independently screened using the title and abstract initially, then using the full text against the a priori inclusion criteria by two reviewers (AMG, AA-B). Any discrepancies were discussed between the two reviewers. If no agreement could be found, a third author (JS) arbitrated selection. Due to the sparsity of eligible articles, quality/rigour

INTRODUCTION

Endovascular devices are routinely used to treat vascular pathologies. The majority of these devices are composed of metallic alloys containing nickel. Nickel is a common hapten and hypersensitivity to the metal is prevalent in the adult population (17% in females and 3% in males).¹ As a result, endovascular specialists frequently face the scenario of implanting a nickel-containing device in a nickel-allergic patient. This is a cause for concern as severe reactions to nickel-containing intravascular devices are reported.² Furthermore, it has been conjectured



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Table 1 Inclusion and exclusion criteria relating to the systematic review and meta-analysis

Inclusion criteria	Exclusion criteria
<i>Systematic review</i>	
Clinical medicine	Non-human and in vitro
Endovascular and transcatheter procedures	Open and 'non-endovascular' procedures
Coronary, structural heart, neurovascular and peripheral vascular (including venous) pathology	Gynaecological clips and coils, orthopaedic prostheses, electrophysiological and circulatory support devices
Nickel hypersensitivity including as the constituent of an alloy (such as stainless steel, cobalt chromium and nitinol)	Non-nickel metal hypersensitivity
Nickel hypersensitivity and allergy, allergy induction, allergy prevention, allergy avoidance, allergy reduction, allergy treatment	Hypersensitivity to device or implant adjuncts such as eluents or polymers in drug-eluting stents
<i>Meta-analysis</i>	
Any study design	All other types of articles
Nickel allergy confirmed on patch test	Non-specific metal allergy on patch test
History of nickel allergy (including 'history of metal allergy')	'Hybrid' control groups: mixture of non-allergic on patch test/history
Defined adverse outcome(s)	

was not assessed prior to exclusion. Risk of bias assessment was performed after selection using the GRADE tool (online supplemental file 4).

Meta-analysis

Heterogeneity was assessed by the I^2 statistic using RevMan 5 software (Cochrane, UK). Dichotomous data (usually summarised as ORs) for the incidence of 'adverse events' were pooled across the included studies. Meta-analysis was performed using RevMan 5 using a DerSimonian and Laird random-effects model, the results were combined by the Mantel-Haenszel method.

Qualitative synthesis

A qualitative content analysis method was used to synthesise findings from the 78 articles included in the review's qualitative synthesis.

RESULTS

Study selection is summarised in the PRISMA flowchart (figure 1). A total of 190 records were identified in our initial search; 78 articles were included in this review's qualitative synthesis; 14 studies were included in a quantitative synthesis (meta-analysis). The characteristics of the included articles by specialty are summarised in tables 2 and 3 and online supplemental file 2. The funnel plot of included articles is symmetrical suggesting low reporting bias (online supplemental file 3). A pooled meta-analysis was performed examining the relationship between patch test confirmed nickel allergy and adverse outcomes following coronary, structural heart and neurovascular interventions. Heterogeneity between studies was moderate ($p=0.03$, $I^2=44\%$) (figure 2). Subgroup analyses by specialty revealed that the structural heart subgroup was the most heterogeneous ($p=0.06$, $I^2=72\%$) and the coronary subgroup the least ($p=0.29$, $I^2=16\%$). Further subanalysis of the coronary studies by adverse outcome (de novo ISR vs repeat ISR) showed minimal heterogeneity in the de novo ISR group ($p=0.68$, $I^2=0\%$) and

re-ISR group ($p=0.64$, $I^2=0\%$) (figure 3). In the meta-analysis of study arms investigating the relationship between history of metal/nickel allergy and adverse outcomes, heterogeneity was substantial ($p=0.1$, $I^2=63\%$) (figure 4).

The pooled meta-analysis of all specialties suggested that nickel allergy confirmed on a skin patch test may be associated with an increased risk of adverse outcomes following implantation of a nickel-containing endovascular device ($n=14$ articles, 1740 patients; OR 2.61, 95% CI 1.41 to 4.85) (figure 2). This finding was further observed in coronary ($n=12$ articles, 1624 patients; OR 1.94, 95% CI 1.16 to 3.23) and structural heart subgroups ($n=2$ articles, 83 patients; OR 52.28, 95% CI 1.31 to 2079.14), but not in the neurovascular subgroup ($n=1$ article, 33 patients; OR 3.04, 95% CI 0.59 to 15.72). Further subanalysis of the coronary studies by adverse outcome suggested that confirmed nickel allergy may increase the risk of re-ISR ($n=2$ articles, 193 patients; OR 5.00, 95% CI 2.11 to 11.85), but not de novo ISR ($n=10$ articles, 1431 patients; OR 1.38, 95% CI 0.83 to 2.30) (figure 3). In the history of nickel/metal allergy meta-analysis, no significant increase in risk of adverse outcome was observed ($n=2$ articles, 207 patients; OR 2.14, 95% CI 0.23 to 19.70) (figure 4).

DISCUSSION

Our pooled meta-analysis suggests that nickel allergy confirmed on a patch test may be associated with an increased risk of adverse outcomes following implantation of a nickel-containing endovascular device (OR 2.61, 95% CI 1.41 to 4.85).

Unsurprisingly for a pooled analysis of multidisciplinary studies with different interventions and mixed 'adverse outcomes', the heterogeneity of studies was significant ($p=0.03$, $I^2=44\%$); however, subgroups were, for the most part, more homogenous. Thus, it is more valuable to discuss results of the meta-analysis for each specialty/subgroup in turn, incorporating our qualitative synthesis of the reviewed literature.

Coronary endovascular interventions

Pooled analysis of coronary studies suggested a significantly increased risk of ISR/re-ISR in nickel-allergic patients (OR 1.94, 95% CI 1.16 to 3.23). This relationship was not observed for de novo ISR (OR 1.38, 95% CI 0.83 to 2.30); but for refractory ISR, nickel allergy was associated with a fivefold increase in risk (OR 5.00, 95% CI 2.11 to 11.85). This is consistent with the findings of the Iijima *et al* study.²

The pathophysiology of recurrent ISR is poorly understood and available treatments are of limited efficacy.² Our meta-analysis suggests that nickel allergy may have a pathophysiological role in some cases of recurrent ISR, although only two studies met eligibility criteria for inclusion.^{2,3} This is relevant to the issue of re-ISR as steroids and/or stent explantation may be offered to patients earlier. There are several case reports of potentially nickel-allergic patients affected by multiple episodes of re-ISR who became recurrence-free after courses of systemic steroid therapy.^{4,5} In other cases, stent removal⁶⁻⁹ was the therapeutic strategy.

Although the incidence of ISR has significantly reduced with the use of drug-eluting stents (DES), their binary restenosis rate at 2 years is still c. 5%–10%² and the stent struts frequently contain nickel. A Japanese study reported no difference in DES binary restenosis rate between a patch-tested metal allergic group compared with a non-allergic group (6.3% vs 6.5%, $p=0.98$).¹⁰ They concluded that sirolimus-eluting stents prevent ISR irrespective of metal allergy;¹⁰ however, this conclusion does

Table 2 Characteristics of studies included in the meta-analysis

Reference	Sample size	Study population characteristics	Confirmation of allergy	Outcome	Results
Coronary endovascular interventions (n=35)					
Studies (n=15, some presented below), Case reports (n=8, Supplements), Letters, editorials and reviews (n=12, Supplements)					
Aliağaoğlu <i>et al</i> (2012) ^{w51}	61	Patients who underwent reangiography after cobalt chromium stent implantation at >1 month due to persistent symptoms.	Skin patch test	ISR	OR 18.67, 95% CI 1.02 to 343.38, p=0.049
El-Mawardy <i>et al</i> (2011) ^{w52}	50	Reangiography for recurrent symptoms at >3 months following index stenting procedure.	Skin patch test	ISR	OR 3.12, 95% CI 0.12 to 80.40, p=0.49
Hillen <i>et al</i> (2002) ^{w53}	34 (only 27 evaluable)	Bare metal stent implantation and ISR on repeat angiography at >3 months.	Skin patch test	ISR	OR 1.00, 95% CI 0.08 to 12.76, p=1.00
Köster <i>et al</i> (2000) ^{w54}	131	Patients who underwent reangiography at 6 months after stenting for suspected ISR.	Skin patch test	ISR	OR 7.73, 95% CI 0.43 to 138.57, p=0.17
Morice <i>et al</i> (2001) ^{w55}	424	All patients undergoing PCI (2000 to 2001); asked to answer a questionnaire about nickel allergy and received a nickel patch test. They were followed for 6 months after dilatation.	Skin patch test	ISR	OR 0.85, 95% CI 0.25 to 2.90
Norgaz <i>et al</i> (2005) ^{w56}	43	Stent implantation and patch test the day after; angiogram at 6 months.	Skin patch test	ISR	OR 0.83, 95% CI 0.07 to 9.99, p=0.89
Slodownik <i>et al</i> (2018) ^{w57}	99	Bare metal stent implantation and ISR on repeat angiography at <2 years.	Skin patch test	ISR	OR 1.25, 95% CI 0.39 to 4.04, p=0.71
Svedman <i>et al</i> (2009) ^{w58}	338	Patients stented between 1997–2002 in a single centre. ISR evaluated if repeat angiography had been done.	Skin patch test	ISR	OR 1.54, 95% CI 0.67 to 3.58, p=0.31
Thyssen <i>et al</i> (2011) ^{w59}	149	Patch-tested dermatitis individuals who underwent stenting. This cohort was then evaluated for ISR defined as any subsequent PCI.	Skin patch test	ISR	OR 0.48, 95% CI 0.060 to 3.93, p=0.50
Iijima <i>et al</i> (2005) ²	174	Reangiography and patch-testing on a group of patients who had only undergone initial stenting and a group that had undergone dilatation for ISR.	Skin patch test + history of metal allergy	ISR arm and re-ISR arm	ISR arm OR 1.51, 95% CI 0.15–15.30, p=0.73 Re-ISR arm OR 7.06, 95% CI 1.29 to 38.56, p=0.02
Saito <i>et al</i> (2009) ³	128	ISR after initial stent placement requiring PCI and second instance of ISR on second angiogram at 6 months.	Skin patch test	Re-ISR	OR 4.43, 95% CI 1.62 to 12.08, p=0.004
Structural cardiac endovascular interventions (n=13)					
Studies (n=5, some presented below), case reports (n=5, supplements), letters, editorials and reviews (n=3, supplements)					
Rigatelli <i>et al</i> (2007) ¹⁷	46	Single-centre patients who underwent elective catheter-based closure of interatrial shunts. Mean age 35±28.8 years. Patch-tested before implantation; trans-thoracic echocardiography at 1, 6 and 12 months.	Skin patch test	'Device syndrome': chest discomfort, exertional dyspnoea, asthenia, mild leukocytosis.	OR 425, 95% CI 15.89 to 11364.17, p=0.0003
Wertman <i>et al</i> (2006) ¹⁸	37	Single-centre patients who underwent PFO/ASD closure with Amplatzer, where patch testing had been performed. Incidence of postclosure palpitations and chest discomfort was assessed by telephone interview and clinic visits.	Skin patch test	'Device syndrome': chest discomfort, palpitations, or migraine headache/aura	OR 9.69, 95% CI 1.07 to 87.44, p=0.043
Neuro-endovascular interventions (n=14)					
Studies (n=2, some presented below), case reports (n=8, supplements), letters, editorials and reviews (n=4, supplements)					
Kocer <i>et al</i> (2017) ²⁶	33	Patients with flow diverter fish-mouthing in a single centre were patch tested	History + skin patch test	Flow diverter fish-mouthing (device-specific type of in-device stenosis)	OR 3.04, 95% CI 0.59 to 15.72, p=0.18
Allergy induction (n=2)					
Studies (n=2, presented below), case reports (n=0), letters, editorials and reviews (n=0)					
Ekqvist <i>et al</i> (2007) ⁵⁰	314	Any patient stented in a regional catchment area between 1997–2002. These patients were then patch-tested.	Skin patch test	38 positive patch tests to nickel in nickel-stented group (n=314) compared to 40 positive patch tests in control group (n=447) (p=0.182)	
Ekqvist <i>et al</i> (2008) ⁴⁹	200	Any patient stented in a regional catchment area between 1997–2002. Blood samples were taken from these patients and analysed to detect concentration of gold and nickel. These patients were then patch-tested. 100 with gold stents and 100 with nickel stents were randomly selected for analysis.	Skin patch test	Median Blood Nickel concentration in Nickel allergy=0.862 (n=24), in no nickel allergy=0.598 (n=176) (p=0.14)	

Please see online supplemental file 2 for the characteristics of other studies, case reports, letters, editorials and reviews included in the qualitative analysis.

ASD, atrial septal defect; ISR, in-stent restenosis; n, number; PCI, percutaneous coronary intervention; PFO, patent foramen ovale.

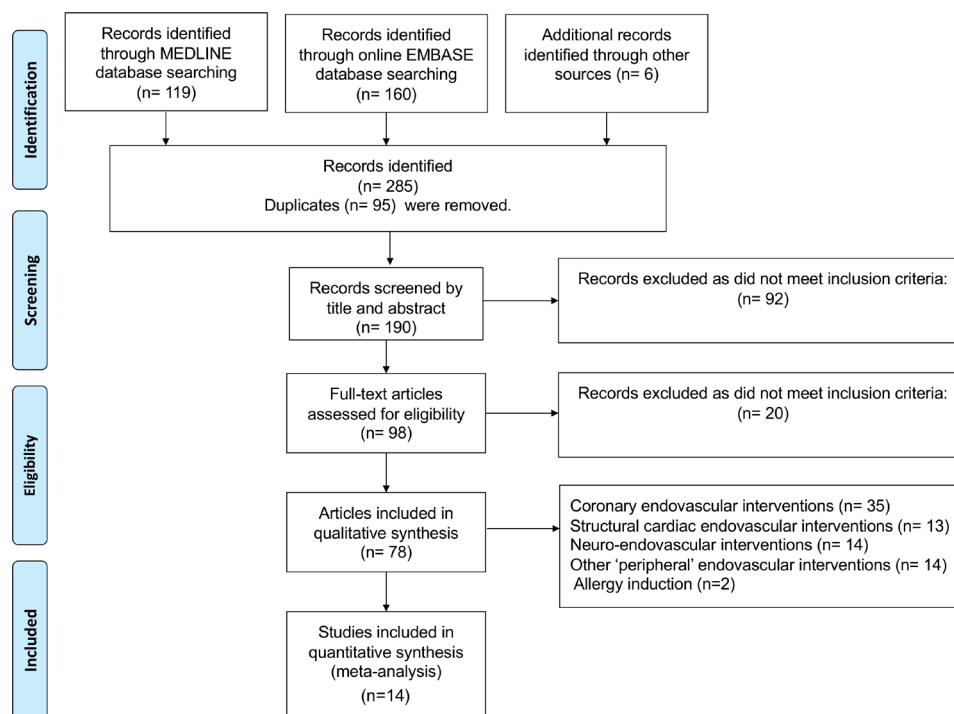


Figure 1 PRISMA flowchart illustrating article selection.

not take into account that after bare metal stent insertion, there seems to be no increased risk of de novo ISR in patients with nickel allergy (OR 1.38, 95% CI 0.83 to 2.30). Furthermore, the study's follow-up interval is limited to 8 months, which may not capture very late stent thrombosis (VLST) events that are reportedly more commonly seen in DES and—by definition—occur beyond 1 year.¹¹ It has been hypothesised that an allergic mechanism may underlie VLST in DES.¹¹ Allergologically, DES are more complex than bare metal stents in that they contain three potential allergens: the metallic struts, the biopolymer scaffold (reported to be the most allergenic component) and/or the eluent drug.¹¹ However, hypersensitivity to non-metal components of DES is beyond the scope of this review and this was part of our exclusion criteria. A pilot study by Hansen *et al* aimed to investigate allergy to metallic components of DES and whether there was an increased risk of VLST; however, none of the 10 VLST patients enrolled had a positive skin patch test to nickel.¹¹ Nonetheless, of the eight included case reports of allergic reactions to nickel-containing components of coronary stents in this review, five patients underwent DES implantation.^{6–9 12}

In addition to local intravascular effects of nickel hypersensitivity, systemic allergic reactions to nickel such as diffuse eczematous dermatitis,¹³ and urticaria with chest tightness and facial oedema¹² have also been reported following coronary stent placement. Furthermore, following stent implantation, nickel-hypersensitive individuals are at a theoretical risk of developing 'Kounis syndrome', an acute coronary syndrome occurring with an allergic reaction.¹⁴ Although there are no cases of Kounis syndrome reported in the literature after stenting per se, 'device syndromes' with features of acute coronary syndrome and thought to be of allergic aetiology (thus, by definition 'Kounis syndrome') are reported following the implantation of structural heart occlusion devices.¹⁵

Two studies included in this review examined the relationship between patients' self-reported history of nickel allergy and adverse outcomes following coronary stent implantation.^{2 16}

Neither study demonstrated any significant increase in the risk of adverse outcomes associated with a patient history of nickel or metal allergy.

Structural cardiac endovascular interventions

Chest pain and palpitations are characteristic of the hypersensitivity reactions reported following deployment of nickel-containing endovascular occlusion devices for patent foramen ovale or atrial septal defects (ASD), sometimes referred to as 'device syndrome'^{15 17 18} or, as previously discussed, 'Kounis syndrome'.¹⁵ Severe headache/migraine may also be a feature of these device syndromes.^{18 19} Two studies included in the meta-analysis defined chest pain and palpitations as the adverse outcomes for which they investigated the relationship with nickel allergy.^{17 18} Both studies report similarly high incidence of postoperative 'device syndrome' in nickel allergic groups: 89%¹⁷ and 90%,¹⁸ which is significantly higher than the incidence of adverse outcomes reported for any other type of device discussed herein. This may be the product of a reporting bias: device syndromes manifest early and obviously (unlike ISR for example); or perhaps, it is related to the size of the device (significantly larger than a stent) and therefore a larger 'dose' of nickel (although it is questionable whether nickel hypersensitivity is dose-dependent). Despite such a high complication rate, neither study concluded that nickel allergy is an absolute contraindication for nickel-containing occlusion devices because pharmacological treatment is usually effective at completely resolving symptoms.^{17 18} Note, however, that some reactions were reportedly refractory to medical therapy including debilitating migraines¹⁹ and systemic nickel hypersensitivity reactions such as eczematous dermatitis^{20 21} and one case of severe postoperative dyspnoea requiring intubation.²² In these cases, devices were invariably explanted by open operations at a median time of 4 months postinitial intervention (IQR 3.75–21).^{19–22}

Table 3 Characteristics of included peripheral endovascular subgroup case reports

Reference	Patient	Intervention	Reaction	Diagnosis
<i>Aortic</i>				
Kawatani <i>et al</i> (2018) ³⁵	78-year-old man No known allergy	Endovascular aortic aneurysm repair (rupture)	3 weeks postoperatively: pruritic eczematous rash on the trunk and both upper arms	Positive patch test
Gimenez-Arnau <i>et al</i> (2000) ³⁶	79-year-old woman	Endovascular aortic aneurysm repair (elective)	3 weeks postoperatively: diffuse pruritic eczematous skin rash	Positive patch test Skin biopsy
<i>Peripheral arterial</i>				
Joshi and Khan (2018), Guerra and Kirkwood (2017) ^{37 38}	44-year-old man No known allergy Background of lupus	Popliteal artery stent	2–4 weeks postoperatively: diffuse pruritic eczematous skin rash, worse on stented leg (left) In-stent restenosis	Positive patch test Skin biopsy
Jetty <i>et al</i> (2013) ³⁹	55-year-old man No known allergy	Superficial femoral artery stent	2 weeks postoperatively: diffuse pruritic eczematous skin rash, worse on stented leg (right)	Positive patch test Skin biopsy
Unvers <i>et al</i> (2018) ⁴¹	69-year-old man Known nickel allergy	Iliac artery stent	2 months postoperatively: diffuse pruritic eczematous skin rash, worse in stented groin (right)	Hypereosinophilia Histopathology of surgical specimen
Beecker and Pratt (2009) ⁴⁰	Known nickel allergy	Femoral artery stent	Systemic contact dermatitis	–
Guntani <i>et al</i> (2020) ⁴²	70-year-old woman	Iliac artery stent	'Shortly' (sic) postoperatively: diffuse pruritic eczematous skin rash, worse in the navel area	Positive patch test Histopathology of surgical specimen Energy-dispersed X-ray spectroscopy
<i>Venous</i>				
Stamm <i>et al</i> (2017) ⁴³	30-year-old man No known allergy	Gonadal vein embolisation	Day 1 postoperatively: Significant left lower quadrant pain that did not resolve over years	Positive patch test
Fahrni <i>et al</i> (2015) ⁴⁴	34-year-old woman No known allergy	Gonadal and internal iliac vein embolisation	Few days postoperatively: palpitations, fatigue, night sweats, feeling of heaviness in both legs and patchy dermatitis	Positive patch test
Jia <i>et al</i> (2015) ⁴⁵	67-year-old woman No known allergy	Implantation of inferior vena cava filter	Severe pruritus	Positive patch test
Hayashi <i>et al</i> (2019) ⁴⁶	45-year-old man No known allergy	Implantation of inferior vena cava filter	Eight days postoperatively: Extensive thrombus covering the filter and propagating past it	Hypereosinophilia
Morshedi and Kinney (2014) ⁴⁷	73-year-old woman Known allergy	Implantation of inferior vena cava filter	Nil postoperative issues	N/A

Please see online supplemental file 2 for the characteristics of other case reports, letters, editorials and reviews included in the qualitative analysis

Despite effective medical therapy,^{23 24} our meta-analysis demonstrates that individuals hypersensitive to nickel commonly develop occasionally dramatic allergic reactions to occlusion devices.^{17–19 23} With this in mind, and the fact that high-risk open-heart device explantation procedures are reported in the literature,^{20–22} it is reasonable to suggest that specialists select new generation occlusion devices which elute less nickel²⁴ when closing PFOs or ASDs in nickel-allergic patients. New occluder devices which elute less nickel are becoming available;²⁵ much lower incidence of reactions is reported with these.¹⁷

Neuroendovascular interventions

Similar concerns apply to the implantation of nickel-containing neuroendovascular devices in nickel-allergic patients regarding in-device stenosis/thrombosis^{26 27} and local organ dysfunction (neurological).

Two studies were included examining adverse outcomes following neuroendovascular intervention in nickel-allergic patients.^{26 27} In one study, one major procedural complication occurred (perioperative stroke) following implantation for cerebral aneurysm exclusion in 20 patients with a documented history of metal allergy.²⁷ The other study examined a possible relationship between 'fish-mouthing' (a specific type of in-device stenosis) following flow diverter implantation for the exclusion of giant or complex intracranial aneurysms.²⁶ The study showed

a statistically significant association between flow diverter fish mouthing and history of allergy to imitation jewellery (OR 6.00, 95% CI 1.13 to 31.70, $p=0.04$). No statistically significant association between flow diverter fish mouthing and a positive patch test was demonstrated (OR 3.04, 95% CI 0.59 to 15.72, $p=0.18$).

In addition to ischaemic/embolic complications, there are several reported cases of local cerebral inflammation secondary to nickel hypersensitivity.^{28–34} All cases reported hyperintense lesions on MRI following either coil embolisation or flow-diverter stenting of intracerebral aneurysms. In most cases reported, nickel allergy was confirmed by patch test,^{28–31 34} and in two cases, nickel allergy was presumed as the diagnosis of exclusion.^{28 32} Patients presented with focal neurological signs such as limb weakness,^{28–30} cranial nerve palsies,^{28 30} hemihypoesthesia, hemiparaesthesia,^{28–30} speech disturbance,^{29 30} visual disturbance³² and seizure;^{29 34} headache was also reported in two cases.^{29 32} These tended to occur within the first postoperative month with a median time of 21.5 days (IQR 20.5–28.5) to the first presentation of symptoms for the eight symptomatic cases reported in the literature.^{28–32} In one case, neurological symptoms (seizure) manifested much later, at 17 months.²⁹ Almost unanimously, these cerebral hypersensitivity reactions were treated with systemic steroid pulsed therapy^{28–31 34} with reported excellent symptom control, and at least partial

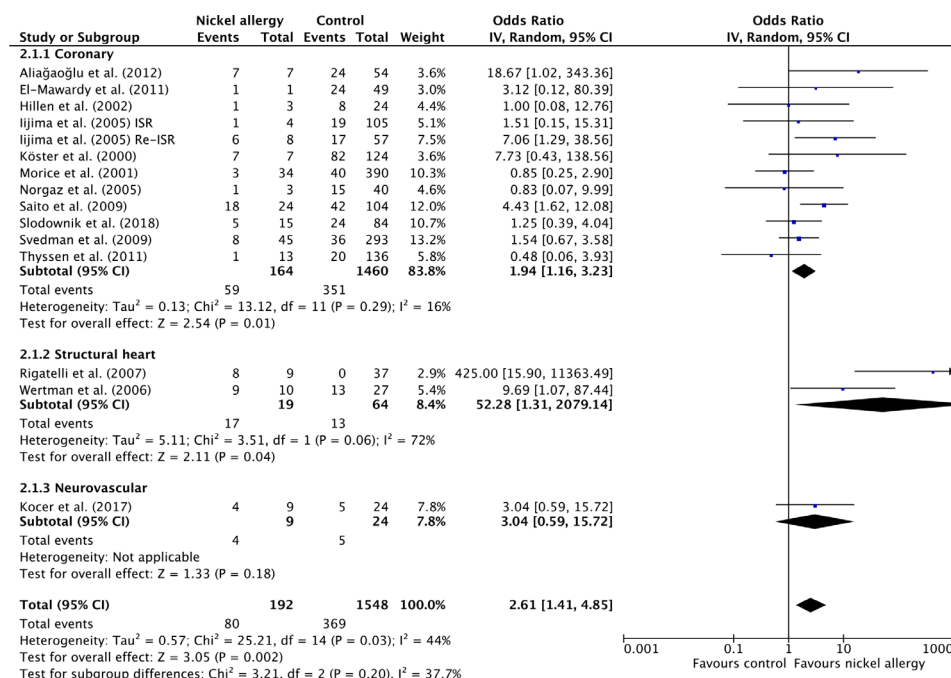


Figure 2 Pooled meta-analysis of the association between nickel allergy confirmed by patch test on diverse 'adverse outcomes' following coronary, structural heart and neurovascular interventions.

radiological resolution on repeat MRI.^{28–31 34} One patient was treated conservatively: their symptoms (headache and visual disturbance) resolved over 2–3 weeks and complete radiological resolution was observed at 6 months.³²

Other endovascular interventions

In the context of non-cardiac, non-cerebral, 'peripheral' endovascular interventions, there were 13 reported cases of allergic reactions to various nickel-containing devices including aortic grafts,^{35 36} lower limb arterial stents,^{37–42} venous embolisation coils^{43 44} and inferior vena cava (IVC) filters.^{45–47}

Most of the reactions reported are of the systemic allergic type characterised by a diffuse pruritic eczematous rash,^{35–41 44 45} presenting more severely at the site of device implantation in

some cases of lower limb arterial stenting.^{37–39 41 42} One patient is reported to have developed a device syndrome to venous embolisation coils with palpitations, fatigue, night sweats, a feeling of heaviness in both legs and patchy dermatitis.⁴⁴ In most of these systemic cases, nickel allergy was evidenced by patch test,^{35–39 43–45} occasionally combined with skin biopsy.^{36–39} Median time to first presentation of the rash was 21 days postprocedure (IQR 14–21 days)—similar to the neuroendovascular cases—and most were treated with systemic^{35 37–39 42} and/or topical³⁶ steroid therapy. In the two aortic graft cases, steroids were sufficient to satisfactorily control symptoms.^{35 36} In other cases, the urticaria was refractory to steroid treatment and resolution was only achieved with device explantation and vascular bypass^{37–41} or simple closure of the adventitia.⁴² One

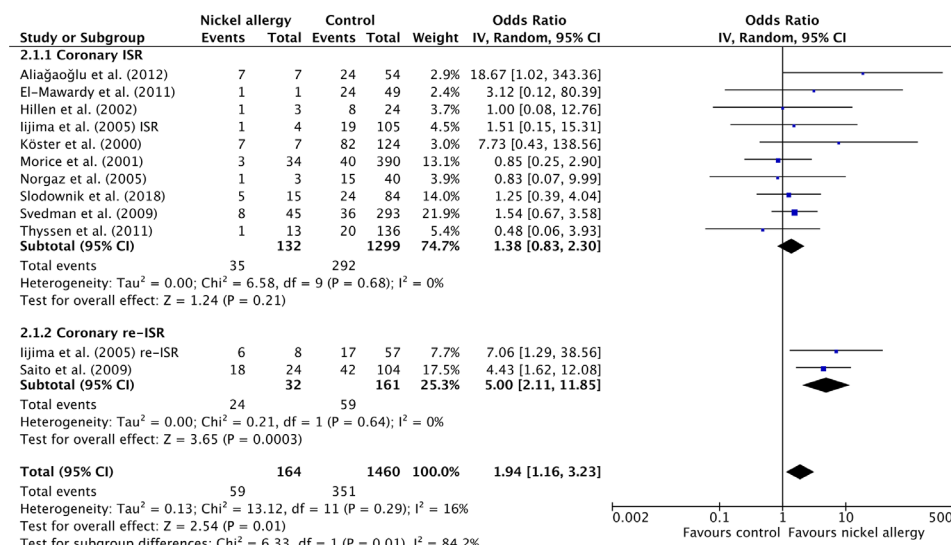


Figure 3 Coronary subgroup meta-analysis of the association between nickel allergy confirmed by patch test on ISR and re-ISR. ISR, in-stent restenosis; re-ISR, re-in-stent restenosis.

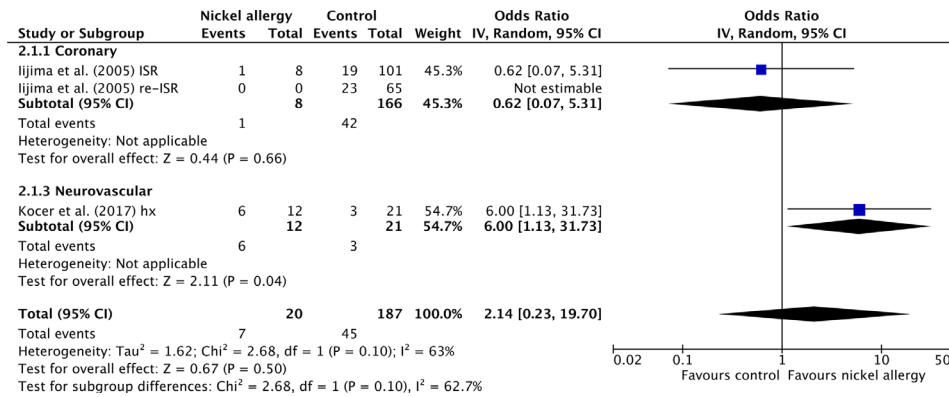


Figure 4 Pooled meta-analysis of the association between patient-reported history of nickel allergy and diverse adverse outcomes.

case required immunosuppression with mycophenolate mofetil and dupilumab.^{37 38} In the case involving venous embolisation coils, open hysterectomy and salpingoophorectomy with resection of the coil-containing pelvic varicosities and ovarian veins resulted in a resolution of symptoms.⁴⁴ Note also that there is a recognised postimplantation syndrome (PIS) following endovascular aneurysm repair characterised by a systemic inflammatory response with fever.⁴⁸ It has been conjectured that stent components, including nickel, may be associated with PIS. Polyester in endovascular aortic grafts has been shown to be significantly associated with a higher incidence of PIS when compared with expanded polytetrafluorethylene grafts;⁴⁸ however, no such relationship has been demonstrated with nickel.

When compared with intracardiac or intracranial devices, peripherally sited endovascular devices can develop similar device-specific complications secondary to nickel hypersensitivity reactions, such as ISR,^{37 38} in-device thrombus formation⁴⁶ and clinically manifest local inflammation.⁴³ In the specific context of IVC filters, severe pruritus⁴⁵ secondary to nickel hypersensitivity is also reported. Morshedi and Kinney also describe implantation of an IVC filter in a patient with known nickel allergy who experienced no postprocedure complications.⁴⁷

Allergy induction

For the majority of studies and case reports reviewed thus far, patients were patch-tested after the suspicion of a nickel hypersensitivity reaction had been raised, rather than prior to device implantation. Frequently, the authors of these retrospective studies and case reports assume that a postimplantation patch test confirms a pre-existing allergy that may underlie the aetiology of an adverse outcome. However, this may be a bold assumption if one considers that the implantation of the device itself induces nickel hypersensitivity in certain patients. If this is the case, it would have important implications regarding the utility of preoperative nickel allergy screening, verbally or by patch-test, as it would mean that a proportion of 'non-allergic patients' may unpredictably develop nickel allergy and associated adverse outcomes. Furthermore, it would call into question the validity of many retrospectively designed studies in which the aforementioned assumption is key; these studies currently make up most of the scientific literature on this topic.

Although evidence for allergy induction by intravascular devices is limited, it has been demonstrated in gold stents that, in situ, these increase circulating blood concentrations of gold, correlating significantly with patch-test intensities.⁴⁹ However, this has not been demonstrated when comparing blood nickel concentrations and patch test reactions.⁴⁹ Another study by the

same group suggested that gold and nickel stents may sensitise individuals to their constituent metals from within coronary vessels although, by their own admission, the evidence was circumstantial.⁵⁰

Limitations

As discussed, overall heterogeneity between studies was moderate ($p=0.03$, $I^2=44\%$). The structural heart subgroup was the most heterogeneous ($p=0.06$, $I^2=72\%$) and the coronary subgroup the least ($p=0.29$, $I^2=16\%$). The coronary subgroup

Key messages

What is already known on this subject?

- Our systematic search of EMBASE and MEDLINE databases identified one systematic review of outcomes in nickel-allergic patients confined to percutaneous coronary interventions. We only included articles related to clinical medicine with endovascular or transcatheter procedures on human subjects dated 1947–2021. To our knowledge, this is the first comprehensive systematic review and meta-analysis of its kind examining nickel allergy in multiple endovascular disciplines. The evidence reviewed was limited by heterogeneity and level; there were no available randomised controlled trials.

What might this study add?

- Our meta-analysis demonstrates a significant increase in risk of an adverse outcome associated with patch-test confirmed nickel allergy following insertion of a nickel-containing endovascular device (OR 2.61, 95% CI 1.41 to 4.85). These findings underline the need for randomised and prospectively designed research treating this issue. Currently, there is no clear consensus on whether nickel allergy is a relative or absolute contraindication to implantation of a nickel-containing device.

How might this impact on clinical practice?

- Endovascular procedures with device implantations are undertaken in large and rising numbers worldwide. In light of these findings, endovascular specialists should seriously consider nickel patch-testing when deciding whether to insert nickel-containing devices in patients self-reporting nickel allergy. If available to them, they should also consider alternative devices that contain less or no nickel.

had the largest sample size ($n=1624$), to best support the relationship observed; other subgroups had quite small sample sizes: structural heart ($n=175$) and neurovascular ($n=33$). All studies included in the meta-analysis were case-control studies, which are subject to recall bias.

CONCLUSION

Hypersensitivity reactions to nickel-containing endovascular devices are reported and, when they occur, the burden of morbidity is significant. Our meta-analysis suggests that nickel allergy confirmed on patch testing is associated with a greater than twofold increased risk of adverse outcomes following implantation of a nickel containing endovascular device. This relationship was not observed with self-reported history of nickel/metal allergy. Further work is necessary to confirm these findings, including large-scale and prospectively designed research that also considers allergy induction. In the meantime, specialists faced with patients self-reporting a history of nickel allergy should consider cutaneous patch-testing and alternative treatment options.

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Supplement 1: Full Search String

Search on 10/01/2021

#	Database	Search term	Results
1	Medline	((nickel OR metal*) ADJ3 (allerg* OR hypersensitiv* OR sensitiv*)).ti,ab	5089
2	Medline	NICKEL/	23086
3	Medline	HYPERSENSITIVITY/	48952
4	Medline	(2 AND 3)	362
5	Medline	(1 OR 4)	5201
6	Medline	((((neuroendovascular OR endovascular OR intrasaccular OR intra-saccular) ADJ3 (treatment* OR intervention* OR procedure* OR therap* OR device* OR surgery)) OR EVT).ti,ab	28659
7	Medline	(stent*).ti,ab	103445
8	Medline	exp STENTS/	79035
9	Medline	"EMBOLIC PROTECTION DEVICES"/	563
10	Medline	"BLOOD VESSEL PROSTHESIS"/	29877
11	Medline	(6 OR 7 OR 8 OR 9 OR 10)	158465
12	Medline	(5 AND 11)	78
13	Medline	(coil* OR hydrocoil* OR Guglielmi* OR GDC*).ti,ab	62142
14	Medline	ENDOVASCULAR PROCEDURES/	20036
15	Medline	VASCULAR SURGICAL PROCEDURES/	31600
16	Medline	(clip* OR microsurg*).ti,ab	54309

17	Medline	(emboli?at*).ti,ab	49442
18	Medline	EMBOLIZATION, THERAPEUTIC/	32578
19	Medline	(6 OR 7 OR 8 OR 9 OR 10 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18)	336774
20	Medline	(5 AND 19)	119
21	EMBASE	((nickel OR metal*) ADJ3 (allerg* OR hypersensitiv* OR sensitiv*).ti,ab	5756
22	EMBASE	"NICKEL HYPERSENSITIVITY"/	1336
23	EMBASE	(21 OR 22)	6161
24	EMBASE	((((neuroendovascular OR endovascular OR intrasaccular OR intra-saccular) ADJ3 (treatment* OR intervention* OR procedure* OR therap* OR device* OR surgery)) OR EVT).ti,ab	43440
25	EMBASE	(stent*).ti,ab	174408
26	EMBASE	(coil* OR hydrocoil* OR Guglielmi* OR GDC*).ti,ab	80693
27	EMBASE	(clip* OR microsurg*).ti,ab	75435
28	EMBASE	(emboli?at*).ti,ab	73735
29	EMBASE	exp "ARTIFICIAL EMBOLIZATION"/	52617
30	EMBASE	exp "VASCULAR SURGERY"/	495716
31	EMBASE	exp ANEURYSM SURGERY/	28109
32	EMBASE	BLOOD VESSEL PROSTHESIS/	8991
33	EMBASE	(24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32)	804291
34	EMBASE	(23 AND 33)	160

Supplement 2. All other articles included in review and meta-analysis

Coronary endovascular interventions [n=35]				
<i>Studies [n=15], Case reports [n=8], Letters, editorials and reviews [n=12]</i>				
Studies [n=15]				
Reference	Sample size	Study population characteristics	Confirmation of allergy	Results
Nakazawa et al. (2008) ¹⁰	88	PCI with sirolimus-eluting stents and re-angiography at 8 months. Patch testing at re-angiography.	Skin patch test	<i>Unable to separate nickel from other metals in this study</i> Metal allergy=14/88 Nickel allergy=4/14 Manganese/chromium allergy=11/14 Binary restenosis rate 6.3% in positive patch test group versus 6.5% in control group (p=0.98)
Romero-Brufau et al. (2012) ¹⁶	279	Self-reported metal allergy individuals who underwent stenting. Outcomes included death, myocardial infarction and target lesion revascularisation.	Patient history	<i>Unable to separate nickel from other metals in this study</i> Metal allergy=29/279 Nickel allergy=26/29 Chromium allergy=9/29 Long-term outcomes: Death rate: 12% allergic versus 13% control (HR 1.08, 95% CI 0.52-3.69, p=0.72) Target lesion revascularisation rate: 13% allergic versus 17% control (HR 0.76, 95% CI 0.25-2.26, p=0.76)
Hansen et al. (2010) ¹¹	10	Very late stent thrombosis after drug eluting stent implantation and ST elevation myocardial infarction.	Skin patch test	0 patients positive [10]

Lim et al. (2007) ⁶⁰	128	6-month follow-up angiography in patients randomly assigned to 'arthos inert stent' or 'arthos stent'. At 3 months subjects were patch tested.	Skin patch test	<i>Unable to separate nickel from other metals in this study</i> 9 positives in ISR group [n=16], 20 positives in control group [n=41]; (OR 1.35, 95% CI 0.42-4.31 p=0.61)
Case reports [n=8]				
Reference	Patient	Intervention	Reaction	Diagnosis
Konishi et al. (2015) ⁴	43 year old female	Bare metal coronary stent to LAD for acute anterior MI	Recurrent in-stent restenosis and ACS (x5) at 12, 24, 36, 40 and 41 months At 12 months post-operatively: Repeated immediate in-stent thrombosis requiring aspiration x10. Eventually recurrence halted with balloon angioplasty and heparin substitution with abogatran (suspected HIT).	Positive patch test
Jurado-Román et al. (2016) ⁶	64 year old female Known nickel allergy	Everolimus-eluting stents to RCA and LAD for ACS	In-stent restenosis at 24, 30, 36 and 38 months in both vessels CxA also involved at 36 and 38 months At 38 months post-operatively: NSTEMI and cardiogenic shock	Positive patch test
Konishi et al. (2016) ⁵	66 year old male	PCI and stent insertion to RCA for acute antero-lateral MI	Immediate in-stent thrombosis; resolved with multiple balloon angioplasties and insertion of an intra-aortic balloon pump At day 1 post-operatively: Acute in-stent thrombosis and ACS	Histopathological analysis of day 1 thrombi revealed large numbers of eosinophils with fibrin and erythrocytes Positive patch test

Perkins (2017) ¹³	58 year old male	Cardiovascular disease requiring stents	Diffuse eczematous dermatitis (ongoing for 2 years) covering the majority of the trunk and extremities; refractory to topical/oral steroids and light therapy	Histopathological analysis of skin biopsy revealed spongiotic dermatitis Serum IgE was significantly elevated Positive patch test
Tuzer et al. (2018) ¹²	53 year old male Known nickel allergy	DES to posterior descending artery	Anti-histamine resistant chronic urticaria Episodes of urticarial flares with chest tightness and face oedema 4 times a month	 Positive patch test
Granata et al. (2015) ⁹	65 year old male	DES to RCA for STEMI	At 3 months post-operatively: Unstable angina secondary to ISR and <i>de novo</i> lesion At 22 months post-operatively: STEMI due to in-scaffold thrombosis of the BVS in DES and <i>de novo</i> lesion	 Positive patch test
Eda et al. (2016) ⁷	58 year old female	DES to LAD for ACS	At 3 years post-operatively: Had had 4 episodes of ISR presenting with angina	Positive patch test Histopathological analysis of surgical specimens revealed invasion of macrophages and eosinophils around the stents
Jimba et al. (2020) ⁸	81 year old female	DES to LCx and LAD for STEMI	At 8 months post-operatively: NSTEMI due to diffuse ISR at both stent sites	PET-CT Cardiac MR

		At 12 months post-operatively: NSTEMI due to 2 nd episode of ISR at LAD stent site	Presumed hypersensitivity to cobalt-chromium alloy (c. 10% nickel)
		At 15 months post-operatively: 3 rd episode of ISR at LAD site	
Letters, editorials and reviews [n=12]			
Reference	Article type	Results/message	
Koniari et al. (2016) ⁶¹	Editorial	Metal components of stents may cause hypersensitivity reactions leading to in-stent restenosis and thrombosis. Before implanting coronary prostheses, clinicians should always elicit any history of metal hypersensitivity and consider lymphocyte transformation studies to detect material hypersensitivity.	
Kounis et al. (2008) ⁶²	Letter to the editor	DES are not exempt from hypersensitivity-related in-stent thrombosis, MI and paradoxical vasoconstriction. Monitoring of inflammatory mediators (especially arachidonic acid products), antibody testing and macrophage/T-cell activation studies can provide valuable additional information compared to patch-testing alone to establish causal relationships.	
Nakazawa et al. (2008) ⁶³	Letter (reply)	DES contain at least three possible allergens: metal, drug and polymer. Although Nakazawa et al. demonstrated in their study that there was no relationship between metal allergy and neointimal formation, this does not exclude the fact that local hypersensitivity reactions to the stent may have taken place. In the study period no patient suffered an overt systemic reaction and angiography alone may not have been sensitive enough to detect early remodelling changes secondary to hypersensitivity reactions. These may lead to clinical sequelae in months/years underlining the importance of long-term follow-up for these patients.	
Schalock (2018) ⁶⁴	Conference abstract	Pre-implant screening is appropriate for patients reporting prior dermatitis reactions. Nickel is commonly used in medical devices and has the highest prevalence of reactions of all metals. It may be an important cause of hypersensitivity to medical endoprostheses.	
Lall et al. (2011) ⁶⁵	Conference abstract	Electronic record review of patients seen in a private American allergy and a cardiology practice between January 2008 and December 2009. Evaluating symptoms, temporal correlation, and response to treatment, 7 patients were identified who had hypersensitivity reactions to DES.	

		Symptoms included skin rashes (5/7), fatigue, dyspnoea, arthritis and chest pain, all beginning within one month of stent insertion. Most patients responded well to medical treatment (i.e. antihistamines, steroids) over one year. However, there was a subset of patients that failed to improve and requested stent removal.
Basko-Plluska et al. (2011) ⁶⁶	Review	Reviewed 7 studies evaluating relationship between coronary ISR and metal allergy. Allergic contact dermatitis (ACD) and device failure may occur in response to implanted intravascular metal exposures. Most information regarding putative sensitivity reactions to endovascular metal implants are based either on anecdotal case reports or on data gathered from relatively small cohorts. Very few prospective data are available. In the majority of cases, the removal of the allergenic metal device results in clearing of the skin condition. Based on these data, we recommend that patients who develop a cutaneous eruption months to years after receiving a metal implant should be patch-tested with an appropriate series of metals. If relevant allergens are identified and corticosteroid therapy is insufficient to clear the eruption, removal of the implant may be considered.
Teo and Schalock (2016) ⁶⁷	Review	Intravascular devices such as coronary stents, perforated foramen occluders, pacemakers, and implantable cardioverter defibrillators contain several metals and may cause hypersensitivity reactions. A review of the existing literature reveals an ostensible lack of consensus on the evaluation and management of possible metal hypersensitivity reactions. This is in part due to the lack of strong evidence-based understanding of the relevance of these reactions to the viability of implants. More extensive and controlled research needs to be carried out to elucidate the exact relationship between metal hypersensitivity reactions and the survival of metallic implants.
Schalock et al. (2011) ⁶⁸	Review	Hypersensitivity reactions to intravascular devices occur. In-stent restenosis (ISR) arises in bare-metal stents and metal hypersensitivity may play a role in its pathophysiology. Patch testing is the gold standard for evaluation of type IV hypersensitivity reactions. Appropriate and extensive patch testing is indicated in patients with implanted metal devices and suspected metal hypersensitivity reactions.
Honari et al. (2008) ⁶⁹	Review	The majority of current data regarding putative sensitivity reactions to endovascular and other cardiovascular biomaterials is based either on anecdotal case reports or data gathered from small cohorts. A spectrum of responses, varying from benign reactions to excessive inflammation and systemic hypersensitivity reactions are reported. The role of lymphocyte proliferation tests and intradermal testing is not well defined. Recommendations are made for evaluation of a patient with putative stent or other cardiac device allergies. Includes thorough history and patch-testing.

Thyssen and Menné (2010) ¹	Review	Coronary in-stent restenosis has been associated with nickel allergy in some studies, whereas others have not been able to confirm such an association.		
		Metal allergy remains prevalent. The pattern of exposure has changed over the decades, mainly as result of regulatory interventions and increased work hygiene. Metal allergy remains of medical importance, lately illustrated by device failure.		
Gong et al. (2013) ⁷⁰	Review and meta-analysis	Reviewed 9 studies evaluating relationship between coronary ISR and metal allergy.		
		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.		
		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.		
		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.		
Jukema et al. (2012) ⁷¹	Review	Hypersensitivity to one or more components of the implanted stent is a rare, but nevertheless important, problem. Nickel allergy is a proposed mechanism triggering the development of restenosis, although not confirmed by all studies. Hypersensitivity reactions to DES, especially to the drug-carrying polymers, have also been reported, but are mainly associated with stent thrombosis and not restenosis.		
Structural cardiac endovascular interventions [n=13]				
<i>Studies [n=5], Case reports [n=5], Letters, editorials and reviews [n=3]</i>				
Studies [n=5]				
Reddy et al. (2009) ²⁵	95	Single-centre patients who underwent PFO/ASD closure were interrogated for potential history of nickel allergy. Self-reported hypersensitive patients underwent skin patch test. Patch test patients were treated with Helex device. Non-allergic patients were treated with Helex (1%)/Amplatzer (99%).	Skin patch test/ history	8 patients reported a history of allergy.
				6 patients had a positive patch test.
				In the positive patch test group: 1/6 patients developed chest pain
				In the 'control group': 11/89 patients developed chest pain

				Nil significant difference between allergic and 'non-allergic' groups for multiple adverse symptoms.
Thanopoulos et al. (2014) ⁷²	92	Multi-centre patients who underwent elective ASD closure with a cocoon septal occluder; Median age 10.5 years (range 3–61 years)	Skin patch test	Device-related complications: none observed
Lertsapcharoen et al. (2008) ⁷³	60	Single-centre patients who underwent patent ductus arteriosus closure with a self-expanding platinum-coated nitinol device. 18 patients had serial blood samples for serum nickel analysis taken before and at 1, 3 and 30 days after device implantation.	N/A	The devices were successfully deployed in all 60 patients. There were no serious procedural complications. There was no evidence of nickel release or nickel reaction after device implantation.
Case reports [n=5]				
Reference	Patient	Intervention	Reaction	Diagnosis
Khodaverdian and Jones (2009) ²²	27 year old female Known metal allergy	Amplatzer septal occluder insertion for ASD (initially presenting as stroke)	Shortness of breath immediately after recovering from anaesthesia refractory to aggressive medical treatment and requiring intubation	History of metal allergy Diagnosis of exclusion
Vincent et al. (2003) ²¹	? year old male (paediatric study population median age 5 year old)	HELEX septal occluder insertion for ASD	Itching skin and soreness of the feet	Positive patch test
Anselmino et al. (2009) ⁷⁴	41 year old female	Amplatzer septal occluder	No complications and/or allergic reactions ensued	Positive patch test

	Known nickel allergy	insertion for ASD		
Bělohávková et al. (2011) ²⁰	40 year old female No known nickel allergy	Amplatzer septal occluder insertion for PFO	At 3 days post-operatively: Severe generalised exanthema	Positive patch test
Fernandes et al. (2019) ¹⁹	16 year old male No known allergy	Amplatzer septal occlude insertion for ASD	At 3 days post-operatively: Severe migraine-type headache	Positive patch test
Letters, editorials and reviews [n=3]				
Almpanis et al. (2010) ¹⁵	Letter to the editor	Nickel is prevalent in the metal struts of many endovascular and intracardiac devices, they may cause intracardiac and intracoronary mast cell activation resulting in Kounis hypersensitivity coronary syndrome. Before implantation clinicians should take a careful history of any metal allergy and efforts should be made such that future devices have better biocompatibility.		
Bissessor (2015) ²³	Review	Nickel allergy with current ASD devices remains a significant side effect with device extractions reported in the literature.		
Jalal et al. (2016) ²⁴	Review	After ASD closure using an ASO, an increased incidence of migraine headache has been observed during the post- procedural course and was shown to be correlated with nickel hypersensitivity. Discomfort in the chest, rash/urticaria, difficulty breathing, fever, or pericardial effusion with tamponade after ASD closure have also been described as possible symptoms related to nickel release. Nickel hypersensitivity-related symptoms might persist for several months but usually respond to medical therapy, including antihistamines, steroids, or the addition of clopidogrel for 3 months. In rare cases in which medical management fails, surgical removal of the device may be considered. In patients with documented nickel hypersensitivity, ASO implantation is not a contraindication; however, other devices may be considered if available. In particular some of the new devices such as HELEX which elute less nickel do not seem to be associated with nickel hypersensitivity reactions.		
Neuro-endovascular interventions [n=14]				

<i>Studies [n=2], Case reports [n=8], Letters, editorials and reviews [n=4]</i>				
Studies [n=2]				
Reference	Sample size	Study population characteristics	Confirmation of allergy	Results
Wallace et al. (2019) ²⁷	20	Patients with metal allergy who underwent pipeline embolization device treatment in a single centre	History/device patch test	<i>Not nickel-specific, 'metal allergy'</i> 20 patients 23 devices 26 aneurysms One major procedural complication occurred (5%, 1/20) in which a stroke was caused by perioperative pipeline embolization device thrombosis. Complete aneurysm occlusion rate of 88% (23/26). Asymptomatic in-pipeline stenosis occurred in 2 cases (10%, 2/20), resulting in 65% and 50% parent artery stenosis, respectively.
Case reports [n=8]				
Reference	Patient	Intervention	Reaction	Diagnosis
Park et al. (2017) ²⁸	64 year old female No known allergy	Elective stent-assisted coil embolisation of left ICA aneurysm	21 days post-operatively: Right hand weakness MRI demonstrated multifocal white matter lesions in the left cerebral hemisphere	Presumed allergy (diagnosis of exclusion)
Park et al. (2017) ²⁸ and Nakagawa et al. (2019) ³⁴	52 year old female	Elective stent-assisted coil embolisation of right vertebral artery aneurysm	18 days post-operatively: abducens nerve palsy, right facial palsy, dysphagia, and left-sided sensory disturbance MRI demonstrated multifocal right-sided white matter lesions involving the medulla, pons, thalamus, and corpus callosum	Positive patch test

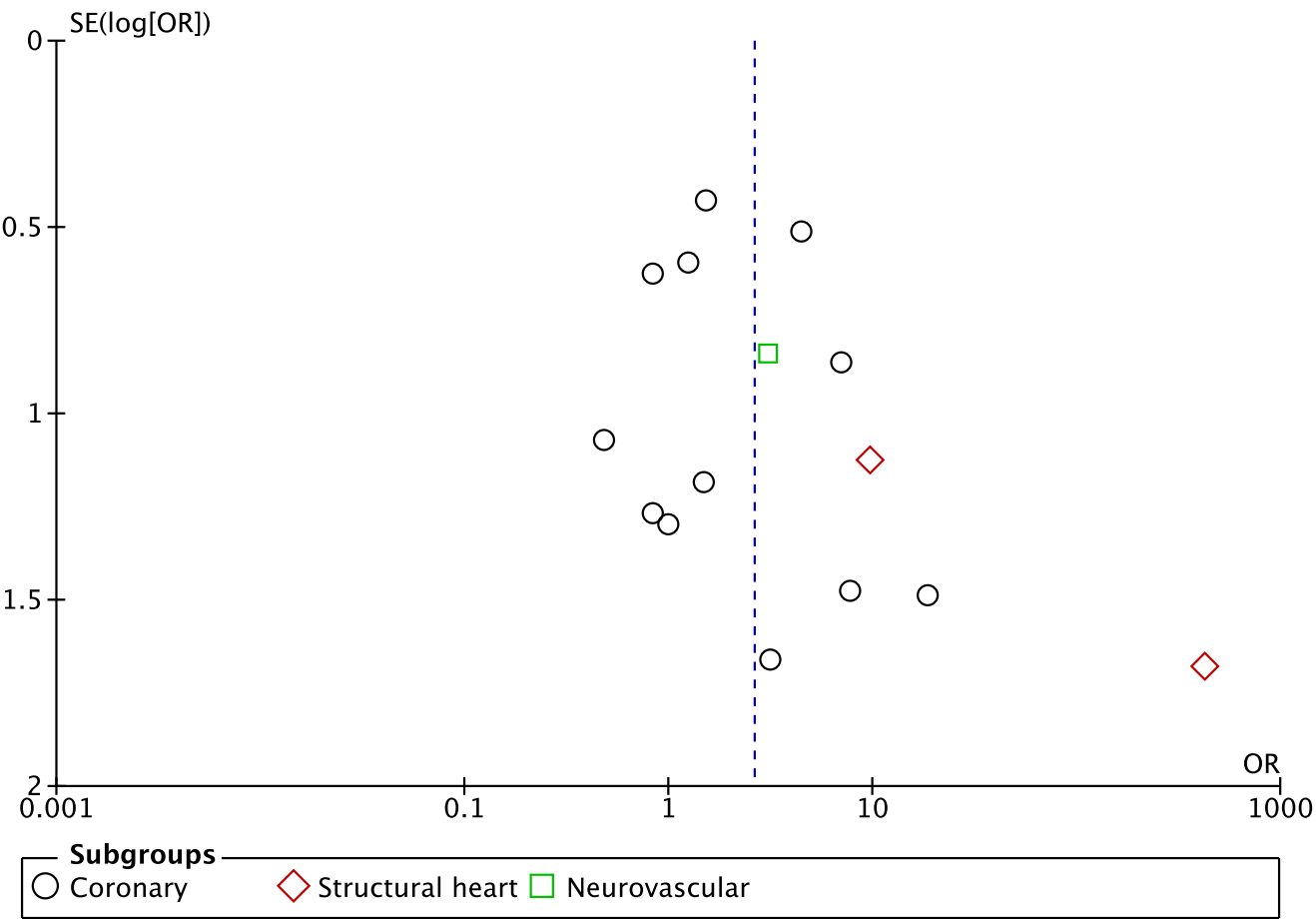
Shotar et al. (2016) ²⁹	45 year old male Penicillin allergy	Coil embolisation of ruptured right AComA aneurysm	28 days post-operatively: Right-sided hypoaesthesia and headache progressing 10 days later to speech disturbance, right arm weakness, and seizure MRI demonstrated multiple leptomeningeal, cortical and subcortical micronodular and annular enhancing lesions in the territories of the right ACA, left ACA, and left MCA with peri-lesion oedema	Negative patch test Foreign body reaction as suggested cause
	54 year old female No known allergy	Elective coiling of right ICA and flow-diverter stent deployment	12 months post-operatively: Asymptomatic with MRI changes 17 months post-operatively: Seizure MRI at 12 months demonstrated multiple regions of right hemisphere subcortical oedema. MRI at 17 months demonstrated extension of hyperintense lesions and leptomeningeal and cortical enhancements in the territories of the right MCA and possibly right PCA	Positive patch test Cerebral biopsy at 21 months: non-specific lymphocytic inflammatory infiltration, minimal eosinophilic leukocytoclastic vasculitis, no foreign body emboli and no giant cells
Tonetti et al. (2018) ⁷⁵	68 year old female Known nickel allergy	Elective exclusion of left ICA aneurysm with flow diverter stent	2 years post-operatively: Nil evidence of systemic inflammation or allergic reaction Angiography at 1 year No residual aneurysm filling or in-stent stenosis	Positive patch test
	66 year old female Known nickel allergy	Elective exclusion of left ICA aneurysm with flow diverter stent	3 years post-operatively: Nil evidence of systemic inflammation or allergic reaction Angiography at 1 year Persistent aneurysm filling, but no in-stent stenosis Angiography at 3 years (after re-stenting)	Positive patch test

			No residual aneurysm filling or in-stent stenosis	
Lobotesis et al. (2015) ³⁰	60 year old female Known nickel allergy	Elective coil embolisation of ICA aneurysm	19 days post-operatively: 2 episodes of sudden-onset left arm numbness and clumsiness lasting 30 minutes each 34 days post-operatively: Multiple further episodes of stereotypical transient left arm weakness, along with new, persisting left facial weakness and dysarthria. MRI demonstrated multifocal hyperintense lesions in MCA and ACA territories	Positive patch test
Marcos-Gonzalez et al. (2016) ³¹	45 year old female	Elective exclusion of right ICA aneurysm with flow diverter stent	21 days post-operatively: Recurrent left-sided paraesthesia MRI at 3 weeks demonstrated hyperintense lesions and surrounding oedema downstream of the stent	Positive patch test
Ulus et al. (2012) ³²	41 year old female	Elective stent-assisted coil embolisation of left MCA aneurysm	1 month post-operatively: Headache and visual disturbance MRI at 1 month demonstrated multifocal hyperintense lesions in the left frontal, parietal, temporal, and occipital lobes	Presumed allergy (diagnosis of exclusion)
Narata et al. (2018) ⁷⁶	-	Elective flow-diverter stent placement in MCA-ICA	Reversible localised contrast enhanced lesions considered nickel allergy or foreign body reaction on MRI	-
Nakagawa et al. (2019) ³⁴	39 year old female	Elective stent-assisted coil embolisation of left ICA aneurysm	22 days post-operatively: Seizure	Positive patch test
Letters, editorials and reviews [n=4]				
Reference	Article type	Results/message		

Jeswani and Alexander (2011) ⁷⁷	Editorial	No significant data exist to show a causal relationship between coronary artery restenosis following stenting in patients with nickel allergies. For patients with significant known nickel allergies, the decision to place an intracranial nitinol stent must be considered carefully.
Pinto and de Souza (2015) ⁷⁸	Letter	Regarding Lobotesis et al. ³⁰ : It is not possible to make a diagnosis of nickel hypersensitivity reaction in the setting of a cortico-responsive syndrome. In addition to the pre-procedure patch test, histopathologic confirmation of brain lesions is also necessary. Author response: they agree that it is not possible to say with certainty that the case was due to nickel hypersensitivity. This seemed most likely when compared to similar, previously described cases; also the timing and spatial distribution of the lesions strongly suggested a relationship with the previous coiling.
Majersik (2015) ⁷⁹	Letter	Regarding Lobotesis et al. ³⁰ : this case highlights the need for clinicians to have heightened suspicion of a systemic metal reaction in patients with an unusual postprocedural complication, including symptomatic, multifocal, cerebral hyperintensities after a catheter-based procedure.
Chun et al. (2018) ⁸⁰	Review	9 studies included, all case reports. Neurologic complications related to nickel in cerebral aneurysm treatments are rare but remain concern owing to the high prevalence of nickel allergy in the population. Surgeons and interventionists should consider the metal allergy history and its potential clinical significance in managing nickel-allergic patients with aneurysms.
Other 'peripheral' endovascular interventions [n=14]		
<i>Studies [n=0], Case reports [n=13], Letters, editorials and reviews [n=2, Supplements]. N.B. One review and report are the same reference</i>		
Reference	Article type	Results/message
Spanos et al. (2015) ⁸¹	Letter	Physicians should routinely inquire about nitinol allergy prior to stent procedures and to perform skin testing prior to interventions when this is indicated.

Morshedi and Kinney (2014) ⁴⁷	Literature review	Most authors agree that nickel allergy is unlikely to be a true contraindication to placement of a nickel-containing device. There are no reported incidents of nickel allergy to IVC filter placement to date despite the high prevalence of nickel allergy in the general population and large numbers of filters placed. Placing nickel-containing IVC filters as medically indicated in patients regardless of nickel allergy history does not appear to be contraindicated. Use of retrievable IVC filters in these patients is recommended because such filters potentially can be removed in the event of an allergic reaction, which appears to resolve symptoms in nearly all reported cases of allergic reaction to implantable metallic devices.
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Supplement 3. Funnel plot



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Supplement 4. GRADE Summary of evidence table

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Patch-test proven nickel allergy		Risk with Control	Risk difference with Patch-test proven nickel allergy

Coronary In-stent Restenosis (timing of exposure: range 1 months to 2 years)

132 cases 1299 controls (10 observational studies)	serious 1,2,3,4,5,6,7,8,9,10,11,a	not serious	not serious	not serious	none	⊕○○○ VERY LOW	132 cases 1299 controls	OR 1.38 (0.83 to 2.30)	Moderate	
									229 per 1,000	62 more per 1,000 (from 31 fewer to 177 more)

Coronary Re-In-Stent Restenosis (timing of exposure: median 6 months)

32 cases 161 controls (2 observational studies)	serious ^{2,3,a}	not serious	not serious	not serious	none	⊕○○○ VERY LOW	32 cases 161 controls	OR 5.00 (2.11 to 11.85)	High	
									430 per 1,000	360 more per 1,000 (from 184 more to 469 more)

Structural heart 'Device Syndromes' (timing of exposure: range 6 months to 12 months)

19 cases 64 controls (2 observational studies)	serious ^{12,13,a}	not serious	not serious	not serious	none	⊕○○○ VERY LOW	19 cases 64 controls	OR 52.28 (1.31 to 2079.14)	Moderate	
									361 per 1,000	606 more per 1,000 (from 64 more to 638 more)

Neurovascular adverse outcomes (fish-mouthing)

9 cases 24	serious ^{14,a}	not serious	not serious	not serious	none	⊕○○○	9 cases 24 controls	OR 3.04	Moderate	
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Supplement 4. GRADE Summary of evidence table

Certainty assessment							Summary of findings			
controls (1 observational study)						VERY LOW		(0.59 to 15.72)	273 per 1,000	260 more per 1,000 (from 92 fewer to 582 more)
Pooled 'adverse outcomes' as defined by the studies (timing of exposure: range 1 months to 2 years)										
192 cases 1548 controls (14 observational studies)	serious 1,2,3,4,5,6,7,8,9,10,11,12,13,14,a	not serious	not serious	not serious	none	⊕○○○ VERY LOW	192 cases 1548 controls	OR 2.61 (1.41 to 4.85)	Moderate	
									258 per 1,000	218 more per 1,000 (from 71 more to 370 more)

CI: Confidence interval; OR: Odds ratio

Explanations

a. Risk of reporting bias and small sample sizes

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