

No association between metal allergy and cardiac in-stent restenosis in patients with dermatitis—results from a linkage study

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Summary

Background. Percutaneous coronary intervention (PCI) with implantation of a metal stent is a common procedure performed in patients with symptomatic ischaemic heart disease. Intracoronary stents typically have a backbone of stainless steel, which contains nickel, chromium, and molybdenum, and it remains unclear whether individuals who are allergic to these metals have an increased risk of restenosis after PCI with stent implantation.

Objectives. To further evaluate whether dermatitis patients with nickel and/or chromium allergy had an increased risk of developing cardiac in-stent restenosis with stainless steel stents.

Methods. An individual-level linkage study was performed to identify dermatitis patients who had been patch tested with the European baseline series between 1979 and 2007 at Gentofte University Hospital ($N = 18\,794$) and who had also undergone PCI at some point in a Danish hospital.

Results. One hundred and forty-nine (0.8%) dermatitis patients who had undergone PCI with a metal stent were included. One hundred and forty-seven were patch-tested before undergoing PCI. Of the patients, 14.1% (21/149) had cardiac in-stent restenosis. Among patients with metal allergy, 2 (11.8%) had restenosis.

Conclusions. Nickel and/or chromium allergy in dermatitis patients does not appear to increase the overall risk of in-stent restenosis after PCI.

Key words: cardiology; chromium; in-stent restenosis; metal allergy; nickel.

Percutaneous coronary intervention (PCI) with implantation of a metal stent is a common procedure performed in patients with symptomatic ischaemic heart disease. Approximately 10–15% of patients develop restenosis of the stented coronary segment following intracoronary

stent placement, referred to as in-stent restenosis, and may require repeated coronary revascularization. Some years ago, the hypothesis was raised that subjects with contact allergy to metal compounds in coronary stents had an increased risk of restenosis, owing to an increased inflammatory response (1). It has so far been convincingly shown that gold-allergic individuals with gold composite stents have an increased risk of in-stent restenosis (2). Intracoronary stents typically have a backbone of stainless steel, which contains nickel, chromium, and molybdenum, and it remains unclear whether individuals who are allergic to these compounds have an increased risk of restenosis after PCI with stent implantation (3–5).

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A Danish patch test study showed that at least 10% of adult women and 1% of adult men from the general population were nickel-allergic, whereas only few were allergic to chromium (6). During the 1970s and 1980s, young European women and men were heavily exposed to nickel following cutaneous exposure to jewellery and other consumer items. Accordingly, up to 30% of women from this generation, who today are middle-aged, are nickel-allergic (7). It was recently proposed that middle-aged individuals might be at particular risk of developing complications following insertion of metallic devices, including cardiac stents, owing to their high level of sensitization (8). This study aimed to further evaluate whether dermatitis patients with nickel and/or chromium allergy had an increased risk of developing cardiac in-stent restenosis with stainless steel stents.

Materials and Methods

An individual-level linkage study using the unique personal identification number given to all Danish citizens was performed to identify dermatitis patients who had been patch tested with the European baseline series between 1979 and 2007 at Gentofte University Hospital ($N = 18\,794$) and who had also undergone PCI at some point in a Danish hospital. For this study, restenosis was defined as a repeated PCI at any time after the index procedure. Information about PCI was obtained from the Danish National Patient Registry (DNPR), with the Danish Health Care System classification codes KFNG (except for KFNG 02). The DNPR contains information on all hospital admissions in Denmark since 1978, and each hospitalization is registered with one primary diagnosis and, if appropriate, one or more secondary diagnoses, according to the International Classification of Diseases.

Patch testing

Patch testing was performed with the European baseline series, using Finn Chambers® (8 mm; Epitest Ltd, Oy, Finland) on Scanpor® tape (Norgesplaster A/S, Alpharma, Vennesla, Norway). Nickel sulfate and potassium dichromate were tested in petrolatum at concentrations of 5% and 0.5%, respectively, according to international standards. The patch tests were applied to the upper back and were occluded for 48 hr. Readings were performed on day 2, day 3 or day 4, and day 7, according to the recommendations of the International Contact Dermatitis Research Group (9). Metal allergy was defined as a positive patch test reaction to nickel sulfate and/or potassium dichromate.

Statistics

Comparisons between independent variables were made using the chi-square test. Fisher's exact test was used when the expected frequency in one of the cells was lower than five. Multivariable Cox proportional-hazard regression analysis was used to estimate risk of recurrent PCI procedure, adjusted for age, sex, calendar year of first PCI, and concomitant cardiac medication use. Associations were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical analyses were performed with SAS version 9.1.3 for Windows (SAS Institute, Cary, NC, USA).

Results

Eighteen thousand, seven hundred and ninety-four dermatitis patients were registered in the patch test database. The overall frequencies of chromium and nickel allergy were, respectively, 3.3% and 3.8% in male patients and 3.2% and 18.9% in female patients. A total of 149 (0.8%) dermatitis patients had undergone PCI with a metal stent at some point, and were included in the study. One hundred and forty-seven were patch-tested before undergoing PCI (median time from patch testing to coronary stenting was 4149 days; range 4124 days [interquartile range (IQR) 2106–6230]). The selection of the study cohort is shown in Fig. 1. The mean age of the study population was 63.5 years (± 10.3 years), and 58% were males. Baseline characteristics of the study

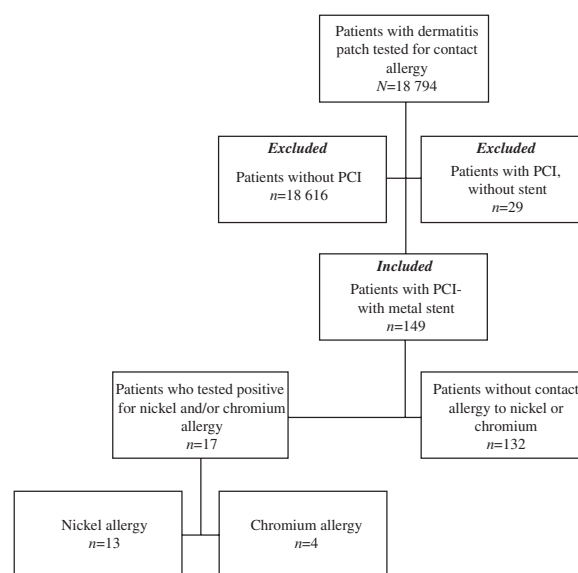


Fig. 1. Selection of the study cohort. PCI, percutaneous coronary intervention.

Table 1. Baseline characteristics of dermatitis patients who underwent percutaneous coronary intervention (PCI) at some point as compared with all Danish patients undergoing PCI in Denmark 1997–2006

	All Danish patients undergoing PCI (N = 41 581)	Total cohort (N = 149)	Without metal contact allergy [†] (n = 132)	Positive for nickel and/or chromium allergy (n = 17)	p-value*
Age [years (±SD)]	63.6 (±11.5)	63.5 (±10.3)	63.8 (±10.3)	61.7 (±10.4)	0.45
Sex, no. (%)					
Males	29 928 (72.0)	87 (58.4)	80 (60.6)	7 (41.2)	0.13
Females	11 653 (28.0)	62 (41.6)	52 (39.4)	10 (58.8)	
Concomitant cardiovascular pharmacotherapy, no. (%)					
Antithrombotics	34 988 (84.1)	91 (61.1)	78 (59.1)	13 (76.5)	0.17
Beta-blocker	30 275 (72.8)	72 (48.3)	62 (47.0)	10 (58.8)	0.36
RAS inhibitor	17 068 (41.1)	65 (43.6)	57 (43.2)	8 (47.1)	0.76
Statin	33 516 (80.6)	109 (73.2)	97 (73.5)	12 (70.6)	0.80
Loop diuretics	7923 (19.1)	17 (11.4)	15 (11.4)	2 (11.8)	0.96
Glucose-lowering drugs	3989 (9.6)	14 (9.4)	14 (10.6)	0 (0)	0.16

RAS, reticular activating system; SD, standard deviation.

*For the comparison of patients with and without metal contact allergy.

[†] Metal allergy was defined as contact allergy to nickel sulfate and/or potassium dichromate.

cohort are shown in Table 1. The frequencies of nickel and chromium allergy in different subgroups are shown in Table 2. Among the 149 patients, 11.4% (17/149) had metal allergy (defined as contact allergy to nickel and/or chromium) and 14.1% (21/149) had cardiac in-stent restenosis [median time from coronary stenting to in-stent restenosis was 287 days; range 853 days (IQR 147–1000 days)]. Among patients with metal allergy, the number of patients with restenosis was 2 (11.8%). The multivariable Cox proportional-hazard analysis did not demonstrate any significant increase in the risk of in-stent restenosis associated with having metal allergy (HR 1.57; 95% CI 0.13–19.4; $p = 0.72$).

Discussion

This study found no association between being nickel-allergic and/or chromium-allergic and having in-stent restenosis after PCI in a subgroup of dermatitis patients (Table 2). The strengths of the study include its unique

design, with the use of a large database of patch-tested individuals, individual-level linkage of interventions with data retrieved from a national registry, and long-term follow-up. Contact allergy to chromium and/or nickel preceded PCI in most patients, as 147 of 149 patients were patch tested prior to PCI. The study, however, also had several weaknesses. First, the study power was low, owing to the small number of cases in the patch test database who underwent PCI. Second, we had no information about patch test reactivity to molybdenum, an allergen that has previously been associated with in-stent restenosis (1), or to other stent components, for example the drug and drug-eluting polymer of drug-eluting stents (10). Third, as a result of the retrospective study design, we analysed contact allergy status on only one occasion. It is possible that this limitation resulted in misclassification, as some patients with negative patch test results may have developed metal allergy in the period between patch testing and coronary stenting or in-stent restenosis. Fourth, and perhaps most importantly, we used repeated

Table 2. Nickel, chromium and metal allergy* stratified by patient status

	Nickel allergy, % (n)	Chromium allergy, % (n)	Metal allergy*, % (n)
Adults from the general population (n = 3460) (6)	5.9 (204)	0.1 (5)	5.9 (205)
All patients (n = 18 794)	13.4 (2514)	3.2 (610)	15.4 (2897)
Non-PCI patients (n = 18 616)	13.4 (2499)	3.3 (606)	15.4 (2879)
PCI patients (n = 149)	8.7 (13)	2.7 (4)	11.4 (17)
PCI patients with in-stent restenosis (n = 21)	4.8 (1)	4.8 (1)	9.5 (2)
PCI patients without in-stent restenosis (n = 128)	9.5 (12)	2.3 (3)	11.7 (15)

PCI, percutaneous coronary intervention.

*Defined as nickel sulfate and/or potassium dichromate allergy.

PCI as a surrogate of in-stent restenosis, but we were not able to assess whether the repeated intervention was targeted at the originally stented coronary segment; that is, the repeated PCI could also represent disease progression in previously non-stented arteries. Finally, we did not ascertain whether the repeated PCI was performed for in-stent thrombosis rather than restenosis.

We conclude that nickel and/or chromium allergy in dermatitis patients did not appear to increase the overall risk of in-stent restenosis after PCI in our retrospective study. However, it remains possible that, in selected cases, restenosis could be caused by a delayed-type hypersensitivity reaction. Large prospective studies are warranted to address this important research question.

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