

High frequency of contact allergy to gold in patients with endovascular coronary stents

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Summary

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Conflicts of interest

None declared.

Background Stent implantation is an effective method for treatment of atherosclerotic disease. Factors predisposing to in-stent restenosis are still largely unknown. Contact allergy to metal ions eluted from the stent has been suggested to be a risk factor.

Objectives To explore whether there is a possible induction of contact allergy to metals used in stents among patients with a stainless steel stent containing nickel (Ni stent) and patients with a gold-plated stent (Au stent).

Methods Adults ($n = 484$) treated with coronary stent implantation participated in the study with patch testing. The study design was retrospective and cross-sectional with no assessment of contact allergy before stenting. Age- and sex-matched patch-tested patients with dermatitis ($n = 447$) served as controls.

Results Of Au-stented patients, 54 of 146 (37%) were allergic to gold compared with 85 of 447 (19%) controls ($P < 0.001$). Within the stented population there were no statistically significant differences in contact allergy to gold or nickel between Ni-stented and Au-stented patients. In multivariate models where other risk factors for contact allergy to gold were considered, the Au stent showed a trend towards statistical significance (odds ratio 1.43, 95% confidence interval 0.95–2.16; $P = 0.09$).

Conclusions As the frequency of contact allergy to gold is higher in stented patients independent of stent type it suggests a previous sensitization. However, several pieces of circumstantial evidence as well as statistical analysis indicate the possibility of sensitization in the coronary vessel by the Au stent. Ni stents and Au stents should not be ruled out as risk factors for induction of contact allergy to these metals.

Percutaneous coronary interventions are commonly used to treat atherosclerotic coronary artery disease. The risk of restenosis could be greatly reduced by intravascular stenting but in-stent restenosis still remains a major clinical problem. The factors predisposing to in-stent restenosis are still largely unknown. Contact allergy to metal ions eluted from stainless steel stents, primarily nickel, chromate and molybdenum, has been suggested to be a factor contributing to in-stent stenosis, although this has never been confirmed.¹ We have recently shown a high prevalence of contact allergy to gold in patients given gold-plated stents.² Gold and nickel are metals that may cause contact allergy in a substantial number of exposed indi-

viduals.^{3,4} The aim of the present study was to evaluate the frequency of contact allergies to metals used in the stents, especially contact allergy to gold and nickel, in patients who had received one or both of two selected stent types. The stents were manufactured from the same stainless steel alloy but differed in that one stent type was gold plated whereas the other one was not. The results were also compared with those in a control population. Other aims of the study were to investigate a possible correlation between contact allergy to stent metals and restenosis, as well as the blood concentration of gold and nickel and the contact allergy pattern to nonmetal sensitizers. These results will be published elsewhere.

Materials and methods

Experimental design

The study was performed as a retrospective study of patients in southern Sweden who had been treated with percutaneous transluminal coronary angioplasty (PTCA) and stented at the Department of Thoracic Intervention, Blekinge Hospital, Karlskrona. Evaluation of restenosis frequency, defined as target lesion revascularization rate,⁵ had been performed by cardiologists before the study start in patients who had been admitted for new/deteriorating symptoms. The study consisted of a nonclinical part with patients who consented only to answer the questionnaire and a clinical part consisting of patients who agreed to give a medical history with standardized questions, a blood sample, and undergo a patch test. The questionnaire was sent out with the invitation letter. At the first visit (baseline) a short medical history was taken, blood was drawn and the patient underwent epicutaneous testing (Fig. 1). At the second visit the test was read. In case of a doubtful test reaction to specific metals, a retest was performed (Table 1).

Because of the large catchment area the patch testing was performed at five hospitals: in Malmö, Ljungby, Växjö, Karlskrona and Karlshamn from November 2003 to May 2004. The tests and readings were performed by the same personnel from the Department of Occupational and Environmental Dermatology in Malmö. The controls were all tested in Malmö.

Study sample

Consecutive patients ($n = 715$) who had been treated with PTCA and stented in Karlskrona during 1997–2002 were asked to participate. Of these, 628 (87.8%) agreed to participate in some level of the study and 484 (77.1%) agreed to the full protocol including patch testing (Fig. 2). An age- and sex-matched cohort of 447 (344 men and 103 women) consecutively patch-tested patients with dermatitis at the Department of Occupational and Environmental Dermatology served as controls.

Stents

The patients each received one type of stent manufactured from the same stainless steel alloy, but differing in that one type was electroplated with 99.9% pure gold (NIRROYAL; henceforth referred to as Au stent) whereas the other type was not (NIR stent and a minority with a 316L stent of another type; henceforth called Ni stent). Gold plating is mainly used to improve stent visibility under fluoroscopy. Stainless steel 316L is an alloy containing known sensitizing metals and is commonly used by several manufacturers of stents (Table 2).⁶ Both NIRROYAL and NIR stents were manufactured by Medinol Ltd (Jerusalem, Israel). No clinical parameters directed the choice between the stents during the PTCA and stenting.

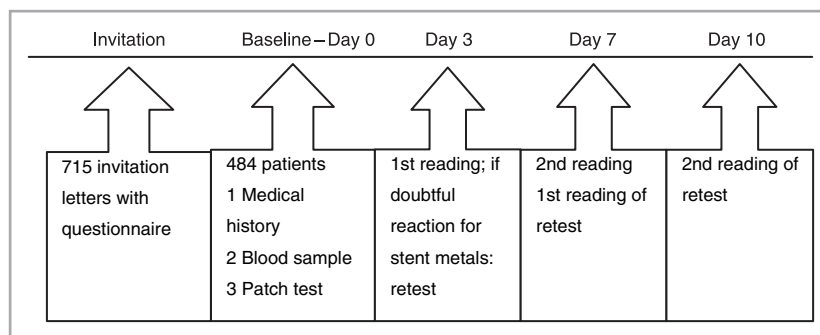


Fig 1. Logistics.

Table 1 Metal salt preparations tested in the stented patients

Test preparation	Concentration	Vehicle	Concentration at retest	Vehicle
Gold sodium thiosulphate ^{29a}	2.0% w/w	pet	5.0% w/w ^b	pet
Palladium chloride ^a	2.0% w/w	pet	No retest	
Molybdenum (V) chloride ^{30–32c}	0.5% and 0.25% w/w	pet	0.5%, 0.05%, 0.005% w/w	pet
Ammonium molybdate (VI) tetrahydrate ^{30–32c}	1.0% and 0.5% w/v	aq	1.0%, 0.1%, 0.001% w/v	aq
Nickel sulphate hexahydrate (ESS) ^a	5.0% w/w (ESS)	pet	30.0%, 15.0% w/v ^{33,34b}	aq
Potassium dichromate (ESS) ^a	0.5% w/w (ESS)	pet	No retest	
Cobalt chloride hexahydrate (SSS) ^a	0.5% w/w (SSS)	pet	No retest	

ESS, European standard series; SSS, Swedish standard series; aq, water; pet, petrolatum; w, weight; v, volume. ^aPurchased from Chemo-technique Diagnostics, Vellinge, Sweden. ^bPrepared at the Department of Occupational and Environmental Dermatology, Malmö, Sweden. ^cPurchased from Acros Organics, Labora, NJ, U.S.A.

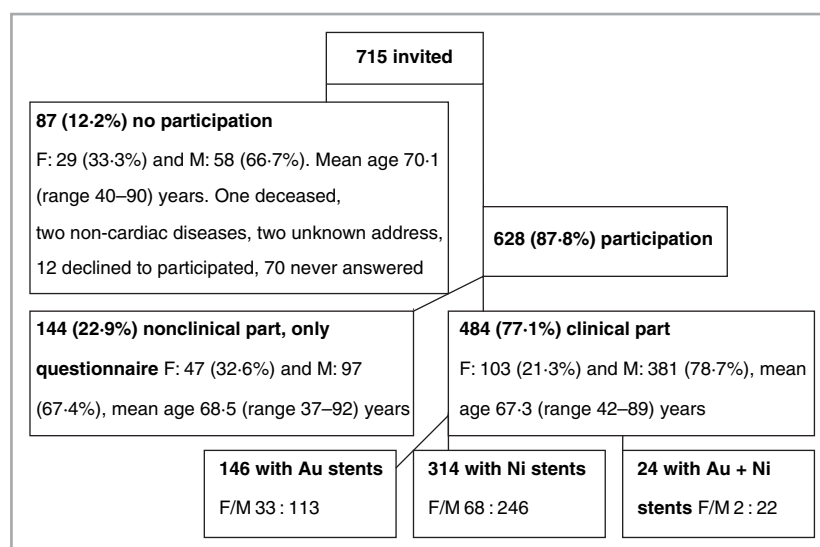


Fig 2. Study sample. F, female; M, male; Au, gold; Ni, nickel.

Table 2 Stainless steel 316L: chemical requirements for metals, heat analysis⁶

Element	Composition (%)
Manganese	2.00 max.
Chromium ^a	17.00–19.00
Nickel	13.00–15.00
Molybdenum ^a	2.25–3.00
Copper	0.50 max.
Iron ^b	Balance

^aThe compositional requirement shall meet the following: % chromium + 3.3 × % molybdenum ≥ 26.0. ^bApproximately equal to the difference between 100% and the sum percentage of the other specified elements. The percentage iron content by difference is not required to be reported.

Questionnaire

A questionnaire was sent out with the invitation to participate in the study. The questionnaire contained questions regarding dental gold restorations, medical and occupational exposure to gold as well as questions about nicotine habits and piercing. It also contained questions included in the Canadian Cardiovascular Society Angina Classification.⁷ The questionnaire was answered by patients who participated both in the nonclinical and in the clinical part (Fig. 2).

Medical history

A short standardized medical history was taken at the baseline visit from the patients who agreed to participate in the clinical part (Fig. 1). The participants had been told not to disclose any information about restenosis or stent type used. Information about risk factors for atherosclerotic disease, medication and skin disease was collected. The dermatologist who questioned the patients was unaware as to whether they had been

stented with an Au or an Ni stent and whether they had had a reintervention or infarction after the PTCA.

Patch testing

All 484 patients underwent epicutaneous patch testing with the European standard series (ESS)⁸ supplemented with test preparations representing metals, preservatives, plastics and corticosteroids. The metal salts were tested according to Table 1. The controls had been patch tested with the ESS supplemented with gold sodium thiosulphate 2.0% w/w pet, palladium chloride 2.0% w/w pet, preservatives, plastics and corticosteroids. The test technique used for controls was Finn Chambers[®] (EpiTest Ltd, Tuusula, Finland; diameter 8 mm, 15 µL on each patch unit for liquid preparations) on Scanpor[®] tape (Norgesplaster, Vennesla, Norway). The test technique used for the study population in the clinical investigation was IQ Chamber[®] (Chemotechnique Diagnostics, Vellinge, Sweden; 20 µL on each patch unit for liquid preparations) on Scanpor[®] tape. Clinical experience within the department has shown no difference in outcome between the two test techniques. For both controls and study population the patch tests were removed from the back after 48 h and readings were performed according to International Contact Dermatitis Research Group guidelines⁹ on day 3 and day 7.

The tests were read in a blinded way by a dermatologist unaware of cardiac symptoms and findings or the responses to the questionnaire. The patient was not informed of the test result until testing and readings were finished. If the test reaction on day 3 was doubtful to gold, nickel or molybdenum, i.e. redness without infiltration, infiltration not covering the whole test area, or a follicular reaction, the patient was retested with the metal(s) (Table 1). The retest patches were removed from the back after another 48 h (day 5) and retest readings were performed on day 7 and day 10 (Fig. 1). If the retest reaction was again doubtful, the result was considered negative. Ethical approval for this study was

given by the Ethics Committee of the faculty of Medicine, Lund University.

Statistics

The statistical analyses were conducted using SPSS release 12.0.1 (SPSS Inc., Chicago, IL, U.S.A.). We regarded $P < 0.05$ as statistically significant. Differences in the prevalence of contact allergy between stented patients and controls and between patients carrying different types of stents (Ni stent only, Au stent only, or both) were tested using Fisher's exact test. Differences due to the metal used in the stent were investigated further using logistic regression, controlling for age, gender, dental gold and piercing. Differences in the prevalence of contact allergies in general between the patients and the controls were investigated by calculating the Z-score for the patient-control difference in prevalence for 33 contact allergens (metals excluded). A Z-score of > 1 in any direction was considered as a marked difference in prevalence. Differences in the proportions of marked positive (higher prevalence among patients) and marked negative Z-scores (higher prevalence among controls) were tested using McNemar's test for correlated proportions.

In statistical analyses between the controls and the stented population no retest results are included as the controls were not retested. The multivariate analysis within the stented population is performed with and without retest results.

Results

The questionnaire and medical history

When the group that only answered the questionnaire was compared with the patients included in the clinical part no marked/important differences were found regarding demo-

graphic data, angina classification, smoking habits or known exposure to gold (Table 3), nor were there any marked/important differences between the subgroups within the study population receiving different stents.

Patch test

The patch test results are given in Table 4. Contact allergy to gold was more frequent in the Au-stented patients than in the control group ($P < 0.001$). There was no statistically significant difference in contact allergy to nickel in the Ni-stented patients compared with controls. The frequency of nickel and palladium allergy was higher in the stented population and particularly in Ni-stented women compared with controls, but the difference was not statistically significant ($P = 0.07$ and $P = 0.06$, respectively). Chromium and cobalt allergy was statistically significantly more frequent in the controls compared with the whole stented population ($P = 0.03$ and $P = 0.02$, respectively). By using higher patch test concentrations for nickel and gold at the retest (Table 1), approximately 13% more contact allergy to each of the sensitizers, gold and nickel, was detected (Table 5).

When we calculated the Z-score for the difference in the prevalence for each of the 33 investigated contact allergens (metals excluded), 21 showed marked differences in prevalence. Of these, 17 were such that the controls had higher prevalence than the patients ($P = 0.007$; McNemar's test for correlated proportions).

There was no significant difference in contact allergy to nickel or gold between the Ni-stented patients and the Au-stented patients (Table 5). When looking at Ni-stented patients alone there was a statistically significant correlation between presence of dental gold and gold allergy [odds ratio (OR) 3.2, 95% confidence interval (CI) 1.8–5.9; $P < 0.001$]. Nickel and palladium allergy was higher in Ni-stented women

Table 3 Baseline patient characteristics from questionnaire and medical history

	Au stent (n = 146)	Ni stent (n = 314)	Au + Ni stent (n = 24)	Nonclinical part (n = 144)
Age in years, mean	66.4	67.4	70.8	68.5
Women, % (n)	22.6 (33/146)	21.7 (68/314)	8.3 (2/24)	32.6 (47/144)
Smoking, % (n) ^a	13.9 (20/144)	10.7 (33/307)	8.7 (2/23)	14.3 (20/140)
Diabetes mellitus, % (n) ^b	17.4 (23/132)	18.8 (57/303)	9.1 (2/22)	—
Any medication for cardiac disease, % (n) ^b	99.2 (121/122)	99.0 (291/294)	100.0 (19/19)	—
Medication for hypercholesterolaemia, % (n) ^b	91.5 (119/130)	87.9 (262/298)	90.9 (20/22)	—
Any skin disease, % (n) ^b	31.5 (41/130)	22.1 (66/299)	8.7 (2/23)	—
Any allergy, % (n) ^b	23.7 (32/135)	21.6 (65/301)	17.4 (4/23)	—
Ear piercing, % (n) ^a	15.1 (22/146)	14.2 (44/310)	8.7 (2/23)	13.6 (19/140)
Occupational gold exposure, % (n) ^a	0.7 (1/144)	1.0 (3/306)	0 (0/23)	0.7 (1/140)
Any gold medication, % (n) ^a	0.7 (1/145)	0.3 (1/306)	0	0.7 (1/140)
Dental gold restorations, % (n) ^a	57.9 (81/140)	64.7 (196/303)	60.0 (12/20)	61.0 (83/136)
CCS class 3 and 4, % (n) ^a	14.0 (20)	11.9 (36)	20.0 (4)	15.1 (20)

CCS class, Canadian Cardiovascular Society Angina Classification. ^aFrom questionnaire sent out with invitation letter. ^bMedical history at baseline visit.

Table 4 Contact allergy frequencies in the stented patients vs. controls including statistical comparisons^a

Stented population														
Test preparations/ groups	Au-stented		Ni-stented		Au + Ni-stented		All stented		Controls		Stented patients vs. controls			
	All 146		All 314		All 24		All 484		All 447					
	F 33		F 68		F 2		F 103		F 103					
	M 113		M 246		M 22		M 381		M 344					
	Contact allergy		Contact allergy		Contact allergy		Contact allergy		Contact allergy					
	n	%	n	%	n	%	n	%	n	%	P-value	P-value	P-value	P-value
Au														
All	54	37.0	89	28.3	7	29.2	150	31.0	85	19.0	< 0.001↑	0.003↑	0.286	< 0.001↑
F	18	54.5	25	36.8	1	50.0	44	42.7	27	26.2	0.005↑	0.175	> 0.3	0.002↑
M	36	31.9	64	26.0	6	27.3	106	27.8	58	16.9	0.001↑	0.008↑	0.243	< 0.001↑
Ni														
All	11	7.5	38	12.1	3	12.5	52	10.7	40	8.9	> 0.3	0.182	> 0.3	> 0.3
F	6	18.2	23	33.8	1	50.0	30	29.1	21	20.4	> 0.3	0.073	> 0.3	0.196
M	5	4.4	15	6.1	2	9.1	22	5.8	19	5.5	> 0.3	> 0.3	> 0.3	> 0.3
Co														
All	3	2.1	7	2.2	0	0	10	2.1	22	4.9	0.160	> 0.3	> 0.3	0.019↓
F	1	3.0	4	5.9	0	0	5	4.9	3	2.9	> 0.3	> 0.3	> 0.3	0.720
M	2	1.8	3	1.2	0	0	5	1.3	19	5.5	0.122	> 0.3	> 0.3	0.002↓
Cr														
All	5	3.4	13	4.1	0	0	18	3.7	32	7.2	0.118	0.088	> 0.3	0.028↓
F	0	0	3	4.4	0	0	3	2.9	8	7.8	0.198	> 0.3	> 0.3	0.214
M	5	4.4	10	4.1	0	0	15	3.9	24	7.0	> 0.3	0.154	> 0.3	0.198
Pd														
All	3	2.1	14	4.5	0	0	17	3.5	13	2.9	> 0.3	> 0.3	> 0.3	> 0.3
F	1	3.0	12	17.6	0	0	13	12.6	8	7.8	> 0.3	0.056	> 0.3	> 0.3
M	2	1.8	2	0.8	0	0	4	1.0	5	1.5	> 0.3	> 0.3	> 0.3	> 0.3

^aNo retest results included. Bold text indicates statistically significant P-values, ↑ in favour of stented, ↓ in favour of controls. F, female; M, male; Au, gold sodium thiosulphate; Ni, nickel sulphate hexahydrate; Co, cobalt chloride hexahydrate; Cr, potassium dichromate; Pd, palladium chloride.

compared with Au-stented women but the difference was not statistically significant ($P = 0.16$ and $P = 0.06$, respectively). A positive patch test reaction to molybdenum was observed in only one man.

In the multivariate model presented in Table 6 all patients are included irrespective of stent type. Retest results are not included. Dental gold, age, sex, ear piercing and Au stent (OR 1.5, 95% CI 1.0–2.4; $P = 0.04$) all had a statistically significant impact on the prevalence of contact allergy to gold. The corresponding calculation including retest results gave a somewhat weaker correlation between Au stent and Au allergy (OR 1.4, 95% CI 0.95–2.2; $P = 0.09$) (Table 7). A similar multivariate model without and with retest result for correlation between stent type and nickel allergy is given in Tables 8 and 9.

Discussion

In the present study we have found a statistically significantly higher frequency of gold allergy in the stented population vs.

controls. This confirms our previous result from a pilot study where 10 of 22 (45%) patients with a gold-plated stent had a contact allergy to gold.² We have also found an approximately 20% higher contact allergy frequency, although not statistically significant, to nickel and palladium in stented patients vs. controls. Basically, the three most plausible explanations to the higher frequencies of contact allergy are that the stented patients (i) have a high frequency of contact allergy in general before stenting, or (ii) have a high frequency of contact allergy to specific metals before stenting or (iii) are sensitized in the coronary vessel. In order to investigate this, several factors must be considered.

Firstly, in order to elucidate whether the stented patients in this retrospective study had a high frequency of contact allergies in general before stenting, the preferable method would be to compare the frequency of contact allergy with that in a general population matched for age and sex. In this study, for practical reasons, the controls were chosen from a population of patients with dermatitis. Due to the dermatitis the controls are expected to have a higher frequency of contact allergies

Table 5 Contact allergy frequencies within the stented population^a

Test preparations/ groups	Stented patients									
	Au-stented		Ni-stented		Au + Ni-stented					
	All 146		All 314		All 24					
	F 33		F 68		F 2					
	M 113		M 246		M 22					
							Within stented population			
	Contact allergy		Contact allergy		Contact allergy		Au vs. Ni	Au vs. Au + Ni	Ni vs. Au + Ni	
	n	%	n	%	n	%	P-value	P-value	P-value	
Au										
All	57	39.0	102	32.5	11	45.8	0.173	> 0.3		0.186
F	18	54.5	26	38.2	1	50.0	0.139	> 0.3		> 0.3
M	39	34.5	76	30.9	10	45.4	> 0.3	> 0.3		0.232
Ni										
All	14	9.6	41	13.1	4	16.7	> 0.3	0.290		> 0.3
F	6	18.2	23	33.8	1	50.0	0.159	> 0.3		> 0.3
M	8	7.1	18	7.3	3	13.6	> 0.3	> 0.3		> 0.3
Co										
All	3	2.1	7	2.2	0	0	> 0.3	> 0.3		> 0.3
F	1	3.0	4	5.9	0	0	> 0.3	> 0.3		> 0.3
M	2	1.8	3	1.2	0	0	> 0.3	> 0.3		> 0.3
Cr										
All	5	3.4	13	4.1	0	0	> 0.3	> 0.3		> 0.3
F	0	0	3	4.4	0	0	> 0.3	> 0.3		> 0.3
M	5	4.4	10	4.1	0	0	> 0.3	> 0.3		> 0.3
Pd										
All	3	2.1	14	4.5	0	0	0.290	> 0.3		> 0.3
F	1	3.0	12	17.6	0	0	0.055	> 0.3		> 0.3
M	2	1.8	2	0.8	0	0	> 0.3	> 0.3		> 0.3
Molybdenum (V) chloride										
All	1	0.7	0	0	0	0	< 0.3	< 0.3		< 0.3
F	0	0	0	0	0	0	< 0.3	< 0.3		< 0.3
M	1	0.8	0	0	0	0	< 0.3	< 0.3		< 0.3
Ammonium molybdate (VI) tetrahydrate										
All	1	0.7	0	0	0	0	< 0.3	< 0.3		< 0.3
F	0	0	0	0	0	0	< 0.3	< 0.3		< 0.3
M	1	0.8	0	0	0	0	< 0.3	< 0.3		< 0.3

*Retest results included. F, female; M, male; Au, gold sodium thiosulphate; Ni, nickel sulphate hexahydrate; Co, cobalt chloride hexahydrate; Cr, potassium dichromate; Pd, palladium chloride.

^aRetest results included. F, female; M, male; Au, gold sodium thiosulphate; Ni, nickel sulphate hexahydrate; Co, cobalt chloride hexahydrate; Cr, potassium dichromate; Pd, palladium chloride.

Table 6 Multivariate model for the association between stent type and contact allergy to gold^a

Dependent variable: contact allergy to gold	P-value	OR	95% CI
Au stent vs. Ni stent	0.04	1.55	1.01–2.37
Dental gold	< 0.001	2.39	1.52–3.77
Age	0.01	1.03	1.01–1.05
Ear piercing	0.03	1.82	1.05–3.16

^aNo retest result included. Au, gold; Ni, nickel; OR, odds ratio; CI, confidence interval.

Table 7 Multivariate model for the association between stent type and contact allergy to gold^a

Dependent variable: contact allergy to gold	P-value	OR	95% CI
Au stent vs. Ni stent	0.09	1.43	0.95–2.16
Dental gold	< 0.001	2.35	1.53–3.63
Age	0.07	1.02	0.99–1.04
Ear piercing	0.13	1.52	0.88–2.61

^aRetest result is included. Au, gold; Ni, nickel; OR, odds ratio; CI, confidence interval.

Table 8 Multivariate model for the association between stent type and contact allergy to nickel^a

Dependent variable: contact allergy to nickel	P-value	OR	95% CI
Ni stent vs. Au stent	0.07	1.98	0.94–4.15
Ear piercing	0.05	2.45	0.99–6.09
Gender (F vs. M)	0.001	4.20	1.73–10.19
Age	0.09	0.97	0.94–1.00

^aNo retest result included. Ni, nickel; Au, gold; F, female; M, male; OR, odds ratio; CI, confidence interval.

Table 9 Multivariate model for the association between stent type and contact allergy to nickel^a

Dependent variable: contact allergy to nickel	P-value	OR	95% CI
Ni stent vs. Au stent	0.15	1.63	0.84–3.17
Ear piercing	0.06	2.35	0.97–5.70
Gender (F vs. M)	0.008	3.13	1.35–7.27
Age	0.10	0.97	0.94–1.01

^aRetest result included. Ni, nickel; Au, gold; F, female; M, male; OR, odds ratio; CI, confidence interval.

than the stented patients, provided the stented patients were not more prone to have contact allergies. We already have data on the general frequency of contact allergy in the stented population vs. controls.¹⁰ The analysis gave no indication that the stented population had a high frequency of contact allergy in general.

Secondly, with regard to a population with a previous contact allergy to specific metals one must consider the significance of known risk factors for metal sensitization and the possibility of cross-reactions/simultaneous contact allergies as well as exposure differences. For the metals investigated the major known difference in exposure is by the stent. Of the metals tested, gold, nickel and palladium yielded higher allergy rates than in the controls, while cobalt and chromium yielded lower (Table 4). Thus, there is no general higher contact allergy burden to all metals. Yet, can the contact allergy rates to nickel, palladium, and particularly gold, be explained by nonstent-related conditions? It is well known that there is a clear relationship between ear piercing and induction of nickel allergy,^{11–13} and nickel allergy is more common in women. As expected, there was a significant association between ear piercing and nickel allergy in our stented patients (Tables 8 and 9).

An association has previously been found between positive patch test reactions among transition metals. Concomitant reactions between nickel and palladium are frequent.¹⁴ It has also been argued that sensitization to one metal ion should increase the risk to be sensitized to another. Whether this should be due to concurrent exposure or to concomitant responses due to similar chemical properties of the metals is

not known.¹⁵ There was an approximately 20% higher contact allergy frequency to nickel and palladium in the stented patients vs. controls, while the allergy rates to cobalt and chromium were statistically significantly more frequent in controls. This does not follow the expected association pattern of concomitant reactions between transition metals. Thus, in the stented population and the controls, where apart from the stent procedure the metal exposure could be regarded as similar, there is a difference in the expected patch test pattern. Could one explanation for our finding be sensitization through different exposure routes?¹⁶

The frequency of contact allergy to gold was statistically significantly higher in stented patients vs. controls, not only in the Au-stented patients but also in the Ni-stented patients, which supports the theory of a previous sensitization to gold before stenting in stented patients in general. Gender and age, which are known risk factors for gold allergy, were controlled in the present study. Common frequencies of contact allergy to gold in published materials are 5–10% in patch-tested patients with eczematous diseases.^{4,17} As age increases so does the frequency of contact allergy to gold, which partly explains the rather high frequency in the controls as well as in both the Ni- and Au-stented patients. Contact allergy to gold can be induced by ear piercing.^{18,19} In our stented population there was a statistically significant correlation between ear piercing and contact allergy to gold (Table 6). Dental gold is known to correlate with contact allergy to gold^{20,21} which was once more shown in the present study, with a statistically significant correlation between dental gold and gold allergy (Tables 6 and 7). The high frequency of gold allergy in the Ni-stented patients confirms the significance of dental gold for sensitization. Dental gold restoration could thus be part of the explanation for the high frequency of contact allergy. Why, then, should these patients have such a high frequency of dental gold? Previous periodontitis has been suggested to be a risk factor for coronary heart disease.^{22,23} If so, this could be an explanation to why we find so many patients with dental gold, being a marker for poorer dental status.

Thirdly, are there any prerequisites pointing towards a possible induction of contact allergy mediated by the metal stent? The important factor for sensitization and elicitation of metal allergy is not the concentration of the individual metal in the alloy but the rate of formation of allergenic ions as the alloy corrodes.^{24,25} Thus, the stent metal in itself is inert, but it has been found that nickel, chromium and molybdenum ions are eluted from stainless steel stents in *in vitro* studies.²⁶ The action of blood, saline, proteins and mechanical stress can increase the release of these ions.²⁷ It has to be taken into account that as the stent is left in the vessel, it is expanded and the surface of the stent is partly broken. In the Au stent this leads to exposure of the underlying stainless steel. This might lead to a galvanic coupling with a possible increase of ion leakage.²⁵ Thus, the tissue around the stent is exposed to potentially sensitizing metals. Furthermore, to enable sensitization there must be dendritic cells/antigen-

presenting cells present in the intima which indeed also have been demonstrated.²⁸ Thus, basic immunological prerequisites for induction of sensitization seem to be present in the vessel wall. Regarding contact allergy to nickel, there were numerically more contact allergies in the Ni-stented patients compared with controls, but not statistically significantly. However, the multivariate model indicates that Ni stents could be a factor of importance concerning nickel allergy. On the other hand, regarding contact allergy to gold, where there were statistically significantly higher frequencies in Au-stented patients compared with controls, induction through the Au stent seemed initially to be a likely explanation. However, also in the Ni-stented patients there was a high frequency of contact allergy to gold, indicating sensitization to gold before stenting in all stent patients. Dental gold restorations have already been mentioned as a significant factor for induction of gold allergy.^{20,21} Yet, the Au stent itself was strongly indicated to be an independent risk factor, when a multivariate analysis was performed considering Au stent, dental gold, age and ear piercing, as there was a statistically significant correlation between Au stents and contact allergy to gold (Table 6). However, when retest results to gold were included in the analysis the correlation was somewhat weaker (Table 7).

In conclusion, in this study we have not been able to prove an induction of allergy through alloys implanted in the vessel but many pieces of circumstantial evidence as well as statistical analysis suggest an induction of gold allergy through a gold-plated stent implanted in the coronary vessel. We have found a high frequency of contact allergy to gold in the stented population. Dental gold, age and ear piercing are all independent risk factors for contact allergy to gold and the possibility remains of a sensitization due to the Au stent. Concerning nickel, the higher contact allergy frequency indicated for Ni-stented women vs. controls did not reach statistical significance. It has to be taken into consideration that the controls were a dermatitis population with an overall higher contact allergy burden when looking at the result, which was close to statistical significance. Furthermore, when all risk factors are considered in the multivariate model, the result indicates that the Ni stent should not be ruled out as a risk factor for induction of contact allergy to nickel. In order to investigate this further, and to demonstrate the Au stent as a risk factor for gold allergy, a prospective longitudinal study would have to be performed.

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