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Corrosion and metal release from overlapping arterial stents under mechanical and electrochemical stress – An experimental study

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ABSTRACT

Intra-arterial stenosis due to atherosclerosis is often treated with endovascular balloon dilatation with a metal stent. Restenosis is common and is frequently treated with a new stent placed inside the existing one or the stents are placed with overlap to cover a larger area of the vessels. Observations of stent fractures, stent compression, accumulation of immunocompetent cells around stents have suggested the possibility of immunologic reactions to substances released from stents.

An accelerated corrosion model was developed to study corrosion behaviour of commonly used surgical peripheral stents. Single nitinol stents ($n = 6$), connected stents of the same material (stent-in-stent, both nitinol, $n = 7$) and connected stents of dissimilar alloys (Nitinol with stainless steel stent inside, $n = 7$) were investigated. The stents were subjected to mechanical pulsatile radial strain (up to 8% strain at 1 Hz) and electrochemical stress (+112 mV vs. SCE). The release of nickel and titanium ions was compared. Scanning electron images were obtained.

There was a higher release of nickel when combining two similar (range: 1382–8018 $\mu\text{g/L}$, $p = 0.0012$) and dissimilar (range: 170–2497 $\mu\text{g/L}$, $p = 0.0023$) stents compared to single stents (range: 0.4–216 $\mu\text{g/L}$). The concentration of titanium was low (range: 1.6–98.4 $\mu\text{g/L}$) with only a difference between the single and two similar stents ($p = 0.0047$). Deposits of corrosion products were clearly visible after fretting and pitting corrosion mainly on the Nitinol stents. Several mesh wires were fractured.

The study demonstrated that mechanical strain combined with weak electric potential resulted in pronounced corrosion and fracture of stents, especially with overlapping stents. Single stents after pulsatile load released the lowest amount of ions. The combination of stents of the same material (Nitinol) had the highest release of metal ions.

1. Introduction

Endovascular treatment of atherosclerotic lesions of the arteries has totally changed peripheral and thoracic vascular surgery. In most cases the first-choice treatment is percutaneous balloon dilatation (PTA) with or without stent implantation. Restenosis is the main complication. The frequency of restenosis varies from type of vessel and length of lesion. Restenosis is often treated with a new endovascular recanalization. Frequently a new stent is placed in an existing one or the stents are placed overlapping to cover a larger area of the vessels. Many factors have been suggested to contribute to restenosis in intra-arterial stents.

Observations of stent fractures (Nikanorov, 2008; Nikanorov, 2013; Rits, 2008), stent compression and accumulation of immune competent cells around the stents (macrophages, histiocytes, eosinophils and T-lymphocytes) has suggested the possibility of immunologic reactions to stents and the importance of stent design (Schillinger, 2002). Patients with positive skin patch-test reactions to nickel had higher frequency of in-stent restenosis than patients without hypersensitivity (Köster, 2000; Saito, 2009). A prevalence of nickel contact allergy in the population is 4–20%, highest in females (Veien et al., 2001). However, the potential association between skin metal allergy and intra vessel immune reactions remains uncertain (Thyssen, 2011). Association with localized

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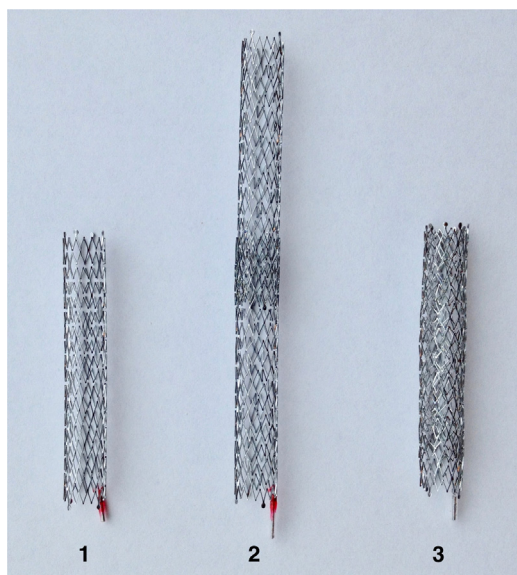


Fig. 1. 1. Single stent, type ev3™ EverFlex+™ (Nitinol), 6 × 40 mm, self-expandable, n = 6. 2. Stent-in-stent, both type ev3™ EverFlex+™ (Nitinol), 6 × 40 mm with 1.5 cm overlap, n = 7. 3. Stent-in-stent galvanic. Combination of ev3™ EverFlex+™ (Nitinol), 6 × 40 mm, with ev3 Visi-pro™, 7 × 37 mm (316 L SS) inside (full overlap), n = 7.

hypersensitivity and in-stent neoatherosclerosis has been suggested (Yamaji, 2014).

There are few international standards for *in vitro* stent corrosion tests before clinical use (International Organization for Standardization, 2004; ASTM, 2008). Measurements of the long-term open circuit potential or applied potential in combination with mechanical loading can give information on the effect of mechanical, dynamic conditions on the electrochemical potential and corrosion behaviour. The purpose of this study was to find an *in vitro* test procedure to examine the corrosion and metal release from intra-arterial stents. Single stents, connected stents of the same material (stent-in-stent) and connected stent of dissimilar alloy material (stent-in-stent galvanic) were investigated and compared. The stents were tested with and without mechanical pulsative strain and electrochemical stress to mimic physiological conditions.

2. Material and methods

Three different stent combinations were tested: Single Nitinol stents (n = 6), connected stents of the same material (stent-in-stent, both Nitinol, n = 7) and connected stents of dissimilar alloys (Nitinol with stainless steel stent inside, n = 7), resulting in a total of 20 experiments (Fig. 1).

Each of the obtained stents was expanded according to the manufacturers' instructions. The distal stent marker was spot welded to a connection wire made of a NiTi. The welding spot of the stent was protected with three layers of polyurethane varnish (Lacomit) and the NiTi wire was covered by a thin plastic tube to avoid contact with the test medium. The stents were mounted on silicone plastic tubing and cyclically loaded at 1 Hz by air pressure causing expansion of the stent corresponding to a strain up to 8% (pneumatic valves: Festo, Esslingen, Germany). The specimens were immersed in an electrochemical test cell (Radiometer analytical, Villeurbanne Cedex, France) with 500 ml PBS (Gibco™ PBS tablet, Invitrogen Corporation, UK) at 37 °C with conditioning by 5% CO₂/air mixture keeping the pH constant at 7.4 (Fig. 2). The potential was recorded and measured versus a saturated calomel reference electrode (SCE) (Radiometer analytical, Villeurbanne Cedex, France). A platinum electrode (0.8 cm² flat solid area) was used as the counter electrode (Radiometer analytical, Villeurbanne Cedex, France).

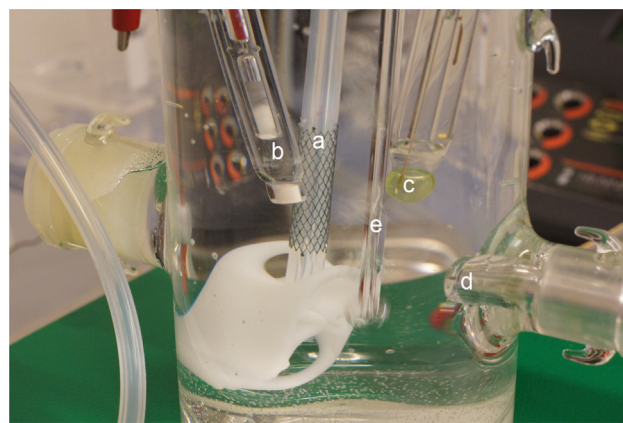


Fig. 2. The test cell with the sample (single stent) mounted on the silicone tube, blocked in the distal end with a clamp (a). Electrodes; SCE reference electrode (b), pH-electrode (c) and Pt-counter electrode (d). Bubbler conditioning the PBS-medium with 5% CO₂/air mixture (e).

First, the resting potential or open-circuit potential (E_{oc}) over the sample was recorded for 1 h. In the next hour 2.5% pulsative mechanical strain was applied. In the third hour at open-circuit, no strain was applied.

In the second part of the test scheme, a potentiostatic potential of +112 mV vs. SCE was applied to the stents with intervals of pulsed strain at two levels (2.5% and 8%), while the current was recorded by the potentiostat (Parstat 2253, Princeton Applied Research, USA). In total, 7600 pulses were applied to the stent. The complete test cycle is illustrated in Fig. 3.

The released metal ions in the test medium were quantified by ICP-MS (Element 2, Thermo Finnigan, Bremen, Germany) after the complete test cycle. The samples were inspected with an optical microscope (Leica EZ4) and scanning electron microscope (SEM, JEOL JSM-7400F) after testing.

2.1. Statistical methods

The data was analysed using non-parametric statistical methods. Comparison between the metal ion-concentrations between stent-groups were analysed pair-wise by Mann-Whitney *U* test. The statistical significance was defined as $p < 0.05$. Statistical analyses were performed with GraphPad Prism version 8.0.1 for MacOS (GraphPad Software, San Diego, California USA, www.graphpad.com).

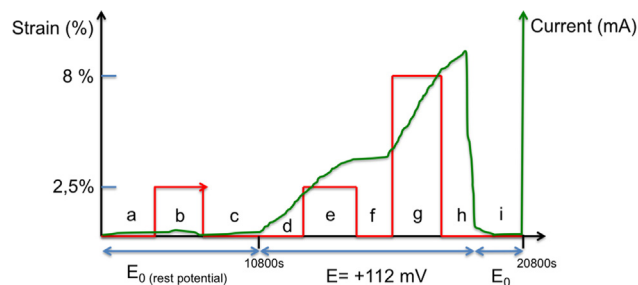


Fig. 3. The complete test cycle (time (s) versus pulsative strain (%) at rest potential (first 10,800 s) and with potentiostatic potential of 112 mV vs. SCE for the last 10,000 s. For illustration, the typical resulting current is overlaid (green line). Open circuit: a. No strain (0–3600 s), b. Strain, 2.5% (3600–7200), c. No strain (7200–10,800 s). Potentiostatic for the last 10,000 s (+112 mV vs. SCE): d. No strain, record current (10,800–12,800 s), e. Small strain, 2.5% (12,800–14,800 s), f. No strain (14,800–15,800 s), g. High strain, 8% (15,800–17,800 s), h. No strain (17,800–19,800 s), i. No strain, current off, rest potential (19,800–20,800 s).

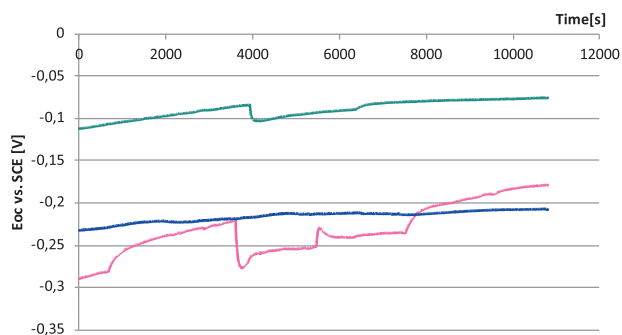


Fig. 4. Open circuit potential (E_{oc} , V) versus time (s) for 3 representative samples. Single stent (blue line), stent-in-stent (purple line) and galvanic stent (green line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

3. Results

After 3 h with open circuit potential applied to the stents, the E_{oc} changed to a more positive value (Fig. 4). During the mechanical strain, the potential dropped steeply, but recovered when pulsing ended. The single stents finished with a median potential of -101.5 mV (range: -208 to -78 mV), Stent-in-stent: -168 mV, (range: -191 to -114 mV), and galvanic: -143 mV (range: -260 to -12 mV), respectively.

When the potentiostatic condition was initiated, the current slowly started to rise (Fig. 5). It further increased when strain was applied. The current normally flattened out when pausing the strain for 1000 s, then continue to rise when applying 8% strain, but dropped when adjusting the potential back to E_{oc} for the last 1000 s of the test.

There was a higher release of nickel when two similar ($p = 0.0012$) and dissimilar (galvanic) ($p = 0.0023$) stents were combined compared to single stents (Fig. 6A). The highest corrosion was seen when two identical Nitinol stents were combined, where the current in some cases reached 3–4 mA. The highest Ni concentration detected was $8018 \mu\text{g/L}$, while the Ti concentrations were more moderate (highest conc. $98.4 \mu\text{g/L}$). The current profile closely correlated with the number of corrosion pits and the quantity of metal ions released from the stents. The Ti-release from stent-in-stents were higher than single stents ($p = 0.0047$). However, the galvanic stent combinations were not statistically different from those of single stents ($p = 0.45$) (Fig. 6B).

Deposits of corrosion products were clearly visible nearby wires where pitting corrosion had taken place (Fig. 7 B and C). Corrosion products also deposited on the underlying SS-stent unaffected by pitting (Fig. 7C). Frequently, wires were fractured near the corrosion attacks (Fig. 7 A and C). Corrosion products are most probably precipitated titanium dioxide. Some of the corrosion products sedimented to the bottom of the electrochemical cell. The measured concentration of

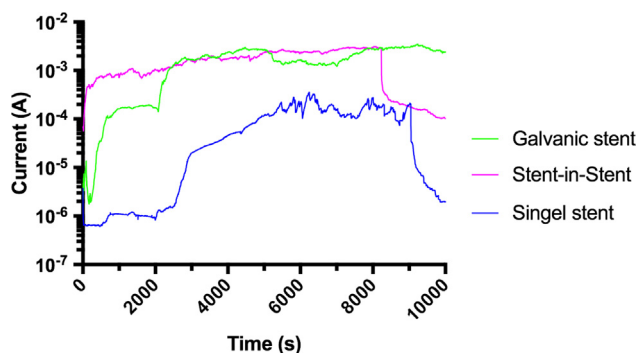


Fig. 5. Plot of current (A, log scale) vs time (s) under different strain (2.5% and 8%) and constant potential. Comparison of the 3 different stent combinations.

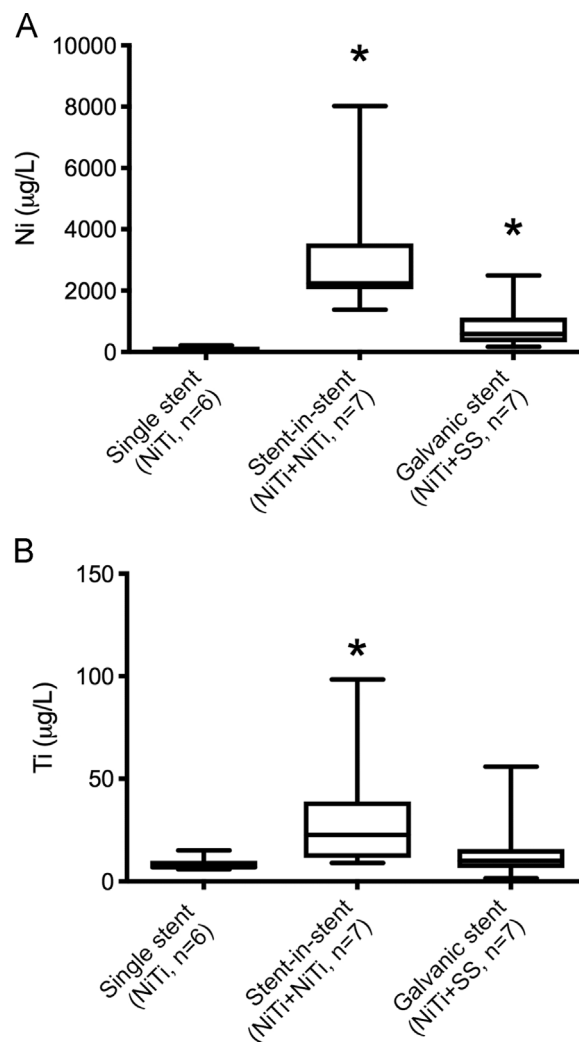


Fig. 6. Boxplots (quartiles and range) showing Ni (A) and Ti (B) release ($\mu\text{g/L}$) after complete test cycle involving mechanical strain and potentiostatic loading. * $p < 0.05$ versus single stents.

titanium in the medium might be lower than the released amount due to the precipitated titanium oxides.

4. Discussion

Intrarterial stenosis due to peripheral atherosclerotic arterial disease (PAD) is usually treated with endovascular procedures with or without stents. Restenosis is very frequent and a great clinical problem at vascular surgical clinics (Stettler, 2007). The pathology of in-stent restenosis is complex. One reason is the progression of PAD. Another factor is the traumatic reaction of the artery to the trauma of endovascular dilatation and to the stent (Zdanowski, 1999). In clinical practise stents are often placed in arteries where there is abundant bending and stretching. The stents remain in the same place for the rest of the patients' life. Studies on cadaveric femoropopliteal arteries have demonstrated that constant bending and compression results in a high rate of stent fractures (Nikanorov, 2008; Scheinert, 2005). Clinical observations in humans have demonstrated stent disintegration such as stent fractures and stent deformities in the same region (Scheinert, 2005; Park, 2012). In the literature the incidence of fractures varies between 2% and 65% (Rits, 2008; Pelton, 2008). Clinical investigations have demonstrated that placement of several adjacent stents and inside each other resulted in an increased frequency of stent fractures (Park, 2012). There is no generally accepted method to study the corrosion behaviour

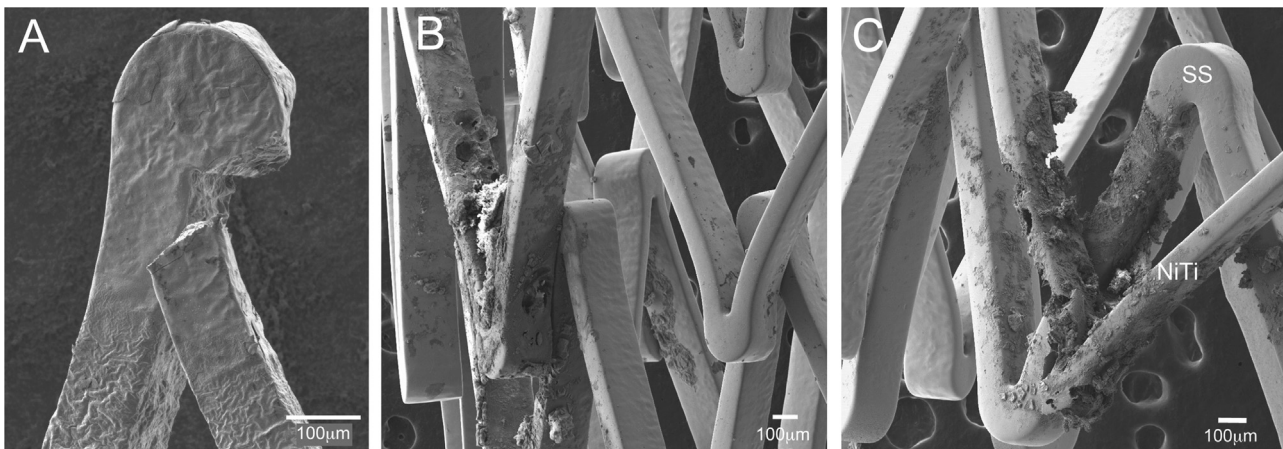


Fig. 7. A: Wire fracture of a single Nitinol stent. B: Evidence of localized corrosion (pitting) at the junction between two overlapping identical Nitinol stents. Corrosion deposits on both stents are visible where corrosion has taken place. C: Massive pitting corrosion and fracture of outer Nitinol stent (NiTi) and signs of fretting wear of the inner stainless steel stent (SS) at the contact area.

and biological response of the stents before clinical application.

Mechanical destruction of stents, inflammatory reactions and allergy to stent metals have been suggested to contribute to restenosis after stent implantation in arterial vessels. The metal stents are mainly composed of different alloys consisting of iron, nickel, molybdenum, titanium, cobalt or chromium. In this study, similar (Nitinol) and dissimilar (Nitinol + 316 L stainless steel) stents were connected under mechanical and electrochemical stress and the release of nickel and titanium were measured.

Closed contact of dissimilar metals can cause formation of a galvanic corrosion which is further worsened due to constant mechanical damage of the surface, termed fretting corrosion. Stress and fatigue corrosion are also possible mechanisms. Another process that can weaken the protective oxide surface in chloride rich medium is pitting corrosion. All corrosion processes may cause release of metal ions and result in sensitization and local inflammation (Anderson, 2004; Basko-Plluska et al., 2011). The present *in vitro* study suggests that combination of stents lead to fretting corrosion with sharply increased release of metal ions when a stent was placed into another, compared to the single stents. The breakdown of the stents came quickly under experimental conditions and surprisingly Nitinol-stents inside identical stents resulted in worse corrosion than Nitinol in combination with stainless steel. In a study of cp titanium and stainless steel fracture plates, the combination of dissimilar screws and plates did not result in higher weight loss or metal release, than the combination of single-material constructions made of cp titanium (Høl et al., 2008). A reason might be that stainless steel has a more resilient layer of chromium rich oxide. In another *in vitro* study, a significant decrease in breakdown potential of overlapping stents was found after an axial fatigue test (Trépanier, 2006). However, unlike the stents in this study, the stents in that study were not simultaneously tested under mechanical and electrochemical stress. The authors believe that cyclic stress with metal fretting wear and potentiostatic loading reduces the corrosion resistance even more.

During open circuit potential and mechanical stress, a sharp drop was observed to a more negative potential. Electrochemical potential shifts in metallic biomedical implants occur *in-vivo* due to a number of processes including mechanically assisted corrosion. This has been shown to cause cell death (apoptosis) near implant surfaces where electrochemical redox reactions take place (Haeri, 2012).

Allergic reactions to stent materials have mostly been studied in patients with coronary atherosclerotic diseases (Hillen, 2002). Köster et al. suggested that patients with allergic patch test reactions to nickel and molybdenum had a higher frequency of in-stent restenosis than patients without hypersensitivity (Köster, 2000). Other studies has supported that metal allergy can contribute to in-stent restenosis

(Romero-Brufau, 2012; Khan, 2007). However, there are other publications that have not been able to confirm this (Thyssen, 2011). It has been difficult to correlate metal allergy from skin test to stent occlusions. Development of localized hypersensitivity may play a role for stent thrombosis. Eosinophilic cationic protein (ECP, sensitive biomarker of eosinophil activation) may be a predictor of clinical outcome in patients after bare metal stent implantation (Niccoli, 2011). In a meta-analysis, encompassing 1223 patients, Gong et al. found that allergy to stent material worsened the prognosis of the patients (Gong, 2013). Post-implantation syndrome following endovascular treatment of aortic aneurysm is considered an inflammatory response to the endovascular equipment. The patients have fever, leucocytosis, increased C-reactive protein indicating inflammatory reaction following an infection - but the blood cultures are negative. An allergic component in this reaction has been discussed (Nebeker, 2006).

Limitations with the study: Despite a relatively low sample number in the current study, there were clear statistical differences between stent groups. Another potential limitation of the study could be the difference in surface area and overlap between the stent combinations. Arterial restenosis in patients is often treated with a new stent in an existing one. Usually the area of stenting is extended, and different types of stents are used, similar to the *in vitro* design in this study.

The corrosion at open circuit potential was low, but it is uncertain if it can be compared to *in vivo* settings (Kazimierzak, 2013; Sullivan, 2017). No evidence was found for significant galvanic corrosion when two endovascular implants (stent-grafts) made from different metal composition were used in the same procedure tested at resting potential (Kazimierzak, 2013). *In vivo* experiments in minipigs showed signs of pitting already six months after implantation in some types of Nitinol stents, probably due to the stents surface finish and oxide layer thickness (Sullivan, 2015; Sullivan, 2017). The reason for applying an elevated constant potential over the stents together with the mechanical strain in this study was to challenge the materials by disturbing the surface protection and simulate long-term effects. The level of applied potential could be questioned; it was sufficient to create corrosion of the Nitinol stent highlighting the differences with the various combinations. The potentiostatic loading was still lower than the breakdown potential reported in the literature (Trépanier, 2006; Sullivan, 2017) and generally much lower than test conditions performed in other similar studies (1–3.5 V vs SCE) (Paprottka, 2015; Siddiqui, 2017). Our belief is that only testing at resting potential would have required a much longer test period, as performed in a study by Kazimierzak et al., where tests were performed for two years (Kazimierzak, 2013).

The clinical implication of metal exposure from arterial stents needs to be clarified.

5. Conclusion

This new *in vitro* test procedure demonstrated that mechanical strain with simultaneous application of electric potential caused pronounced corrosion, especially with overlapping stents. Corrosion occurred mostly in places with direct contact. The combination of stents of the same material (Nitinol) had the highest release of metal ions. The test procedure is considered a realistic provocation condition to predict long-term behaviour.

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Conflict of interest

The authors declare no conflict of interests.

Declaration of interest

None.

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