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# Local release of metal ions from endovascular metallic implants in the human biological specimens: An overview of *in vivo* clinical implications

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## Abstract

Cardiovascular heart disease is one of the leading healthcare problems in this present era and need much care to prevent from this problem. The main reason for this problem is the accumulation of fats or plaque that blocks coronary arteries of heart which in turn resist the flow of blood to the heart walls and cause serious complications. The advancement in biomedical engineering and fabrication technology along with implantation technique made it possible and convenient to minimize the problems of coronary heart diseases. Small medical implantable metallic devices are used in contemporary cardio logical practice. Metals constitute the main components of these cardiovascular medical devices. A complication to the intervention and especially to bare metal stents is in-stent restenosis. Furthermore, limited information is available regarding the condition of stent surfaces and their interaction with vascular tissue following implantation. Corrosion of stents presents two main risks: release of metal ions into tissue and bodily fluids and deterioration of the mechanical properties of stents which may contribute to fracture. Release of metal ions could alter the local tissue environment leading to up-regulation of inflammatory mediators and promote in-stent restenosis. In this article we have reviewed studies that have characterized *in vivo* corrosion of cardiovascular metallic devices which is associated with release of metal ions into tissue and bodily fluids. This review further reports a possible association between stents and metal contact allergy. Potential clinical consequences of these observations are discussed.

**Keywords:** Coronary heart disease; Endovascular metallic implants; Stent corrosion; Metal contact allergy; *In vivo* metal ion release; Biological fluids and tissues

## 1. Introduction

Cardiovascular heart disease is the greatest cause of death worldwide and is one of the leading healthcare problems in this present era and need much care to prevent from this problem. The main reason for this problem is the accumulation of fats or plaque that blocks coronary arteries of heart which in turn resist the flow of blood to the heart walls and cause serious complications. The advancement in biomedical engineering and fabrication technology along with implantation technique made it possible and convenient to minimize the problems of coronary heart diseases. Medical devices for assisting cardiac function and closing patent cardiac defects, as well as coronary stents, artificial cardiac valves, pacemakers, bioprostheses for transcatheter aortic valve replacement, closure devices for patent foramen ovale and trialseptal defects, defibrillators, and left ventricular active devices are used in today's clinical practice. Although they have proved to be life-saving devices, their use is associated, occasionally, with daunting and devastating thrombosis. All these devices have scaffold parts that contain metals.

Cardiovascular disease continues to be the leading cause of mortality and morbidity in the industrialized world [1,2], with a vast majority of these deaths attributed to obstructive coronary artery disease [3]. Depending on the severity of

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the disease, the main interventional options for revascularization include angioplasty, stent deployment and in severe, diffuse occlusions, bypass graft surgery [3]. Narrowed coronary arteries were originally treated percutaneously with balloon angioplasty; the technique was called "percutaneous transluminal coronary angioplasty" [4]. However, it became soon evident that this technique had drawbacks, specifically restenosis, which is an iatrogenic process leading. Clinical complications including abrupt vessel closure from elastic recoil in the short term and significant neointimal hyperplasia limited the applicability of this intervention. Almost ten years later, Sigwart et al. [5] introduced a new device to treat stenoses in the coronary arteries: self-expanding stent. Improved results were observed following the insertion of an additional intravascular mechanical support, cylindrical metal scaffolds. This device, a metallic cylindrical net-shaped prosthesis left in place during the dilatation of the artery, proved to be superior to balloon-only angioplasty in reducing the occurrence of restenosis, as it provided additional scaffolding to the dilated vessel wall. The first balloon expandable stents were designed from surgical grade stainless steel, and aimed to provide additional mechanical support, limiting vessel recoil and preventing acute occlusion [6]. Broad use of these stents began worldwide. Moreover, with the technical development of stent design, leading to stents with lower crossing profile, more flexible and more easily tractable in the coronary vasculature, interventional cardiologists progressively treated more complex anatomical settings. However, restenosis (re-narrowing) was not abolished and still remained an issue. Moreover, another problem peculiar of the metallic stent arose: stent thrombosis, i.e. the formation of a clot inside the stent, potentially leading to its occlusion. In addition, the corrosion of metallic stents occurs *in vivo* which is associated with release of heavy metal ions into vascular wall.

This paper presents an overview of going research regarding the potential related adverse biological effects associated with local toxicity attributed to elevated trace metal ions released from endovascular metallic implants, based on the available *in vivo* clinical studies. This review further reports a possible association between stents and metal contact allergy. *In vitro* testing of metallic endovascular cardiovascular implants with a combination of electrochemical and mechanical tribo-corrosion conditions for assessing the bio-corrosion properties of metals used in implanted metal appliances was not considered. Furthermore, the systemic effects of elevated metal ions were not evaluated in any of the included studies, and as such were not commented on this review.

## 2. Vascular metallic devices

The use of metals as cardiovascular stent materials has become common practice in the field of cardiology [7]. The metal alloys used to produce bare metal stents (BMS) are fundamentally incompatible with the vasculature, promoting thrombosis due to their inherent surface properties, while exerting no inhibitory effect on smooth muscle cell hyperproliferation. Although providing intra-arterial support with BMS dramatically improves the angiographic and clinical outcome of patients to a restenosis rate of 20-30%, in-stent restenosis still remains a major limitation for this approach with exaggerated intimal hyperplasia. As a result of the inadequacies of BMS, different kinds of materials, designs, and techniques have been explored to further optimize stent design. Coronary stents developed to date can be grouped in four categories: bare metallic stents - 316L stainless steel (316L SS), platinum-iridium (Pt-Ir) alloy, tantalum (Ta), Nitinol (Ni-Ti), cobalt-chromium (Co-Cr) alloy, and titanium (Ti), coated metallic stents, biodegradable metallic stents - pure iron (Fe) and magnesium (Mg) alloys, and drug-eluting stents (DES). BMS are made from surgical grade metal alloys, initially 316 L stainless steel, but more recently evolving to cobalt chromium and platinum alloys [8].

A principal requirement for biomedical alloys in device implantation is *in vivo* corrosion resistance, combined with optimal mechanical properties at implant interface. Cobalt and chromium also exhibits improved corrosion resistance. At present, 316 SS, Ti and its alloys (shape memory alloys), Co-Cr alloys are the most frequently used metallic implant materials for stents in cardiology [9]. These alloys are prone to various extents of corrosion. The alloys have found applications with blood contact in pacing leads, AAA stent grafts and self-expanding stents for over a decade. The driving force to select these super alloys as laser-cut commercially available cardiovascular stents is due in parts to, reduced strut thickness for improved deliverability and reduced total stent volume (without compromising radial strength or radiopacity), combined with acceptable biological response *in vivo*. Cobalt-chromium based biomaterials are covered by several ASTM (American Society for Testing and Materials) approved specifications, with ASTM F75 Co-28-6-Mo and ASTM F90 Co-20Cr-10Ni, predominant forecast alloys and wrought alloys respectively [10]. The ideal stent material will be fully corrosion resistant, biocompatible, fatigue resistant, and visible with X-ray/MRI methodology.

## 3. *In vivo* corrosion of metallic vascular devices

The *in vitro* test methods can provide significant insight into the corrosion susceptibility of a given device. However, they are typically conducted under idealized and/or hyper-physiological conditions. Thus, while these tests enable comparisons between devices to be readily made, the extent to which *in vitro* performance correlates to corrosion

behavior *in vivo* remains unclear. This is primarily due to the scarcity of relevant *in vivo* data. In general, the electrochemical processes that drive corrosion lead to both dissolution of metal (as ions) as well as surface deposition (which can be called a corrosion product). Additionally, based on the solubility of the dissolved ions, it is possible for the ions to precipitate out to form additional corrosion products. The surface deposition products are localized to areas near the corrosion location, corrosion precipitates are generally found on the device or in adjacent tissue, while the dissolved ions can be found systemically. The spread of corrosion products throughout the human body made definitive corrosion product studies a challenge; most rely on analyzing the surface deposited/precipitated products while others include local tissue response.

The extent of patient exposure to corrosion by-products has been characterized in a limited number of cases for metallic cardiovascular devices. Assessment of systemic exposure to pitting corrosion by-products is typically limited to evaluating serum and urine levels of metal ions, due to the relative ease of measurement. For example, elevated serum and urine levels of nickel have been reported in patients receiving certain Nitinol septal occluders [11-14]. *In vivo* localized corrosion by-products in stainless steel and explanted Nitinol coronary and peripheral stents, in single and overlapped conditions, have also been characterized [15,16]. However, these studies did not have matched controls to definitively distinguish *in vivo* corrosion from pre-existing features of the manufacturing process. The authors found elevated levels of nickel and chromium ions in arterial tissue surrounding stainless steel stents. Elevated levels of nickel and titanium ions were also observed in tissue surrounding Nitinol stents. Corrosion by-products have been though to increase the risk of in-stent restenosis. Recent research [17,18] investigating whether nickel ions were elevated systemically or in local tissue due to corrosion in Nitinol stents. While no increase in nickel ion levels in blood or urine were observed in swine 6 months after implantation, there was evidence of increased nickel levels in local arterial tissue for corroded stents. Although the clinical ramifications of corrosion by-products in local vasculature are unclear, corrosion by-products have been thought to increase the risk of in-stent restenosis [15]. These results provide direct evidence that corrosion of stents occurs *in vivo*, and is associated with release of metal ions into vascular wall.

Biocorrosion of magnesium-based alloys is a new area of study for improving cardiovascular implant as an effective temporary system with inherent or hybrid local drug delivery functions. Though degradable stents seem to offer an ideal solution for the corrosion of stainless-steel device [19].

## 4. Cardiovascular Devices

Complications and adverse events associated with metallic cardiac and vascular implants often center on thrombus formation resulting from activation of coagulation cascades. Endothelium injury and foreign body placement lead to the activation of platelets at the site of the implant with recruitment of circulating leukocytes. Coagulation occurs through convergent extrinsic and intrinsic pathways, leading to generation of thrombin and fibrinogen, and conversion to fibrin [20]. Extensive crosstalk between coagulation, complement, and inflammation inherently couple outcomes from these pathways [21-23]. The ultimate biocompatibility of a device will be influenced by both inflammation and coagulation.

Metallic stents are good examples of cardiac devices that can be used to elucidate the interactions of device characteristics or features with coagulation processes. These devices can be manufactured using a variety of designs, expansion mechanisms, and metallic compositions including stainless steel, nickel, titanium, chromium and cobalt. Research studies have found that the adsorption of fibrinogen and platelet activation to Nitinol surfaces is dependent on surface chemistry and topography; specifically, titanium content enhanced the adsorption of fibrinogen [24,25]. In addition, nickel ions and particulates have been particularly well-studied for enhancement of platelet aggregation, through the induction of plasminogen activator inhibitor-1 (PAI1), and auto activation of factor XII [26-28]. Mechanistically guided strategies for coating devices with biomolecules, drugs, or polymers to strategically facilitate favorable responses are an active and continually developing area of investigation [29,30].

## 5. Cardiac and endovascular implants

Cardiac devices with metal elements include endovascular devices (coronary and other arterial stents), patent foramen ovale (PFO) occluders: pacemakers, and Implantable Cardioverter Defibrillators (ICDs).

### 5.1. Cardiovascular Stents

Cardiovascular stents are expandable mesh tubes with a circular cross section, implantable vascular scaffold devices, most commonly made from metal with a drug/polymer coating and have different design. These devices are designed to prevent vessel recoil by preserving the patency of the vascular lumen; they keep the walls of a blood vessel from becoming clogged or collapsing. Stents can be classified by their mechanism of expansion (self-expanding or balloon

expandable), their composition (stainless steel, cobalt-based alloy, Nitinol, inert coating, gold coating, active coating, no-coating, or biodegradable), and their design (mesh structure, coil, *etc.*). Metal alloys used for stents may include metals such as Ni, Ti, Cr and Co [31].

*5.1.1. Coronary stents*

Following vascular stent placement, approximately 10-15% of patients develops a narrowing of closing of the stented vessel referred to as in-stent restenosis (ISR) and may require repeated revascularization at some time after implantation. There have been questions whether metal-induced reactions (not just hypersensitivity) to vascular stents can cause implant failure in the form of restenosis, but the interpretation of available published evidence is somewhat muddled by the variety of stents (bare metal *vs.* drug-eluting, metal composition, *etc.*), small cohorts, and technical challenges of testing for metal reactivity. While much is known about the dermal response to metal allergens, determining metal hypersensitivity prior to the implant procedure or implant failure to metal hypersensitivity has proven to be a challenge in clinical settings [32].

Kőster and co-workers [33] were the first to demonstrate a higher incidence of ISR in patients with delayed hypersensitivity to metals, especially to nickel and molybdenum. Furthermore, some case reports and studies suggested an association between ISR and Ni sensitivity per patch testing [34,35]. Two years later, Hillen et al. [36] published a study that showed no significant differences in the incidence of restenosis in patients with hypersensitivity to metals, compared to patients without hypersensitivity to metals, although other studies have rejected an association [37]. Similarly, Iijima et al. [34] demonstrated that metal allergy was not associated with restenosis after initial stent implantation. However, metal allergy was frequently observed in patients with ISR recurrence.

A clinical study of patients receiving stainless steel coronary bare-metal stents demonstrated a higher frequency of angiographically-determined ISR of the initial stent in those with a positive patch test reaction to Ni or Mo versus patients with negative patch test results. Patch testing for metal allergies was performed on 131 patients with 171 stents undergoing repeat angiography for suspected coronary restenosis approximately six months after receiving stainless steel alloy 316L bare metal stents. Of these, 10 patients (8%) had positive patch reactions, and all of them were found to have ISR ($p = 0.03$). In contrast, only 65% of the patch-negative group had restenosis. No patients with an allergic reaction to the standard test substances had a positive reaction to the stainless-steel stents. All patients with positive results had recurrent angina pectoris and needed target-vessel revascularization. They concluded that "allergic reactions" to nickel and molybdenum released from stents may be one of the triggering mechanisms for in-stent restenosis [33]. In a retrospective study, Svedman et al. [35] aimed to evaluate the relationship between coronary stent material, contact allergy, and restenosis. All patients ($n = 484$) were patch tested for Ni and Au reactivity then received either a bare metal stainless steel (316L) stent ($n = 314$ patients), the same stent that was electroplated with 99.9% pure Au ($n = 146$ patients), or both kinds of stents ($n = 24$ patients). Pre-existing patch test positivity to nickel was similar in both stent groups (13.1% in the Ni stent group and 9.6% Au stent group, $p > 0.3$). The pre-existing patch test positivity to Au was also similar in both stent groups (32.5% in the Ni stent group and 39.0% Au stent group, $p=0.17$). Overall, the frequency of ISR in Au-stented patients was significantly higher compared to Ni stented patients (24.7% and 13.1%, respectively; $p = 0.0016$). In the Ni-stented group, there was no statistically significant difference in restenosis rate between allergic and non-allergic patients (17.8% and 12.3%, respectively). However, in the Au-stented group, there was a significant difference in restenosis rate between allergic patients and non-allergic patients (33.8% and 18.6%, respectively; $p=0.03$). Finally, it has been shown that the risk for restenosis was increased threefold in gold-sensitized patients who had gold-plated stents inserted. The Au-allergic patients with Au-plated stents had an increased degree of chest pain. When a multivariate logistic regression model where sex, age, and dental gold restorations was applied, a correlation ($p = 0.04$) between Au allergy, Au stent, and restenosis was demonstrated [35]. Some studies also noted a possible association between Ni sensitivity and recurrent coronary ISR (34,37]. As reported by Iijima et al. [34], the percentage of positive patch test results in patients having repeated coronary ISR was significantly higher than in those without recurrence of restenosis (39% *vs*. 12%; $p = 0.02$) and multivariate analysis further suggested that a positive patch test could be a significant predictor of recurrent ISR [34]. Gong et al. [38] carried out a meta-analysis of nine studies which evaluated the incidence of metal allergy in coronary patients with ISR *vs*. without ISR. An allergy to stent material was confirmed by patch testing, and ISR was identified by coronary angiography or other methods. A fixed-effect model-based analysis showed that being allergic to stent material increased the risk of ISR (OR=2.65, CI: 1.82-3.82); a race-based subgroup analysis suggested a higher risk for Asian patients compared to Europeans [38]. However, some clinical studies did not find statistically significant relationships between having a pre-existing nickel allergy metal allergy and higher risk for ISR [39,40] or other adverse outcomes after stenting [41,42]. Thus, the association between metal stents, metal allergy, and stent failure or cutaneous reactions is not clear.

Over the last several decades, a multitude of solutions to combat stenosis have been developed, which includes coronary bypass surgery, balloon angioplasty and more recently, development of coronary stents. However, due to the poor biocompatibility of bare metal stents (BMSs) and subsequent re-narrowing of the artery (restenosis), drug-eluting stents (DESs) have been considered a more viable option. Compared to BMS, DES have been regarded as a revolutionary change in coronary artery diseases (CADs) and provide a significant additional reduction in restenosis rates and the need for coronary re-interventions [43-46]. Releasing pharmaceutical agents from the stent surface was a promising progress in the realm of cardiovascular stents [31]. Most cell-derived histamine may also contribute to the hypersensitivity reaction underlying Kounis syndrome [47], a coronary syndrome in thrombosis and failure of metal coated or plated cardiovascular stents [48-51]. Of note, with regard to performance, possible side effects and possible hypersensitivity reactions regarding the most recent development in stents, among them drug-eluting metallic stent platforms, are still evaluated in studies [52-54]. The long-term safety of DES, however, is still under debate, with reported cases of delayed healing, late thrombosis and hypersensitivity demanding further evolution in this field. Despite the benefits of DES, there is still a role for BMS in the management of patients with CAD. Ultimately, the decision to implant a BMS is guided by both clinical and economic factors.

Finally, evidence is not conclusive as to whether metal coronary stent implants increase metal sensitivity or whether pre-existing metal hypersensitivity leads to stent failure.

*5.1.2. Non-cardiac endovascular stents*

Several case studies have reported cutaneous reactions after implantation of metal stents into no cardiac arteries [55] described a case of an elderly nickel-allergic patient who developed a severe pruritus accompanied by eczematous erythema on the lower limbs three 3 weeks after abdominal aortic aneurysm repair with a nitinol endograft. Her age made her an unlikely candidate for revision, but antihistamines and topical hydrocortisone tolerably managed her symptoms. Two case reports have been published detailing a localized rash with pruritus involving the ipsilateral lower extremity after placement of a Nitinol stent in the femoral artery. Both patients were found to be allergic to nickel and had resolution of symptoms with stent removal [56,57]. Guerra and Kirkwood [58] reported a case of a severe full-body desquamating macularpapular, pruritic rash developing within one month of implanting a Nitinol stent into a popliteal artery after an embolus. The rash was resistant to high-dose oral prednisone and topical treatments. Subsequent patch testing was positive to nickel and the stent was explanted with resolution of most of the rash although the rash occasionally recurs. Another case report detailed the development of a diffuse rash consistent with a nickel reaction after placement of a stainless-steel stent placed in an iliac artery in a patient with a clinical history of developing an eczematous rash to sterna wires. While the white blood cell count was normal, the eosinophil fraction was 25.4% (a normal eosinophil fraction is 0 to 6%) suggesting a systemic allergic response or systemic hypersensitivity reaction [59]. Pacemakers and implantable cardioverter defibrillators

Pacemakers help to manage abnormally slow heart rhythms while ICDs detect abnormally fast heart rhythms and deliver a small electrical shock to restore normal heartbeat. Newer-generation ICDs may also serve as a pacemaker [60]. Implanted pacemakers and ICDs usually have two parts: a pulse generator placed near the collarbone and wires that are attached to the heart wall. Many generators are covered with a Ti capsule, while the alloy leads are insulated with polymers or silicone, and electrodes are typically made with platinum alloys. While many adverse reactions to cardiovascular devices are suspected to be due to Ni as a predominant cause, Ti (or its additives) has been implicated as the source for these reactions [61,62]. In addition, the variety of other materials used in these devices complicates determining the true cause of the reaction [63,64].

Contact dermatitis and delayed hypersensitivity-type reactions have been reported with pacemakers and ICDs; most reported localized reactions included cutaneous eruption, pruritus, pain, erythema, and swelling at the site of pacemaker insertion [65] while some cases included sterile pocket erythema [66], erosion, draining, and/or necrosis [61,64,67]. These cutaneous reactions usually present within 2 days to 24 months after implantation and are often mistaken as surgical infections. Treatment with corticosteroids (topical or oral) may resolve the symptom; however, in several cases, the symptoms recurred [65]. In many cases, removal of the device, followed by a replacement with a device made from different materials, is needed to resolve the clinical problem.

*5.1.3. Patent foramen ovale occluder*

Patent Foramen Ovale (PFO) occluders are used to close septal defects in the walls of heart chambers. Occluders are made of different materials and have different closure mechanisms. In addition to local cutaneous reactions [68,69], occluders have been reported to be associated with systemic reactions presenting as chest discomfort, dyspnea (difficulty breathing), fever, edema, palpitations, migraines, and/or pericarditis with effusion [70,71]. In one case, a patient with a known severe contact dermatitis to any metal jewelry presented with severe bronchospasm [72]. As in

several other cases, her symptoms resolved only after removal of the implant; in other less severe cases, symptoms resolved after courses of corticosteroids. Within a study of 46 patients evaluating the relationship between Ni hypersensitivity and unusual side effects after interatrial shunt device closure [73], a cohort of nine patients who were patch test positive to nickel and underwent implantation; eight developed what the authors referred to as a post-procedure "device syndrome" characterized by chest discomfort, exertional dyspnea, and asthenia that began within 24 hours of the procedure. In one, the syndrome resolved spontaneously after 5 weeks; the other seven were treated with 10 mg/day of prednisone and 75 mg/day of Clopidogrel plus usual dose of 100 mg/day of aspirin. All symptoms resolved after 1 week of treatment. The authors noted that none of the patch-test negative 37 patients who completed the procedure developed these symptoms.

## 6. *In vivo m*etal ion release from metallic vascular devices

The discovery of relatively inert metallic and alloy biomaterials has led to their prolific use in biomedicine, such as in cardio logical practice. All metallic cardiac devices degrade to some extent over time, however, resulting in locally and systemically elevated levels of metal ions. Several modes of metal ion release exist, including passive dissolution, wear (mechanical), corrosion (electrochemical) and combined mechanical and electrochemical processes (i.e. fretting corrosion). Metal ion release from metallic cardiac implants has been reported *in vitro* as well as *in vivo*. Metal release can be measured locally, in periprosthetic tissue or, more relevantly, in the human biological specimens, i.e. blood, serum or urine, which show the local and systematic impact of metal release.

Several studies have shown that there is *in vivo* and *in vitro* nickel release and reported nickel allergy in patients in whom interatrial shunts were closed with Nitinol-containing devices [68,70].

Most physicians are reluctant to believe that current cardiovascular stents can corrode in the high-chloride environment of the human cardiovascular system and the release of nickel ions might influence human homeostasis milieu. In 2001, Heintz et al. [14] warned that the Nitinol stent wires of explanted endovascular grafts used for treatment of abdominal aortic aneurysm demonstrated severe corrosion in the platinum marker area and also at random positions of the metallic frame. The mean implantation interval for the endografts was 29.1 +/- 13.2 months (range 5-46). All examined explants, even those retrieved after only a few months in *situ*, showed pit like surface damage 10-25 microns in diameter. Presumably, the observed pitting and irregularly shaped corrosion defects are the precursors of material failure. They weaken the thin wire, which leads to stress cracks and eventually fracture of the stent wire under circulatory pulsation. Additionally, a decrease in the Ni concentration in the center of a defect, compared to the surrounding normal segment, confirmed that Ni ions were being released after initiation of corrosion [14].

Impacts of Ni ions released from corroded stents and stent grafts on the behaviors of monocytes and macrophages are still not well understood. Few reports so far, however, have properly focused on the relationship between Ni released by the corrosion process and monocyte activation. Shih et al. [74] examined the relationship between released (leached) Ni concentrations and monocyte behavior. This research focused on impacts of nickel ions released from a corroded cardiovascular stent on cytotoxicity and monocyte activation. The concentration of Ni (II) ions was reported to be 261 μM (14.4 μg $L^{-1}$) after short-term corrosion of Ni-containing alloys and 0.5 μM after long-term corrosion *in vitro*. In order to explore the effects of Ni concentrations from corroded Ni-containing alloys on monocyte behavior, a human promonocytic cell line, U937, was cultured with graduated concentrations of Ni (II) ions *in vitro*, while also monitoring the cytotoxicity and inflammatory activation of U937 cells. Their results demonstrated that a high concentration of Ni ions causes apoptotic cell death of circulating monocytes. They may also play different roles in vascular remodeling during the corrosion process following implantation of Ni alloy-containing cardiovascular metallic stents.

Recent analyses of human explanted stents suggest localized corrosion and metal ion release into the surrounding tissue and vasculature may occur in these cardiovascular devices. More recently, corrosion was also observed in explanted Nitinol coronary and peripheral stents in single and overlapped conditions [15,16]. *In vivo* localized corrosion by-products in stainless-steel and Nitinol cardiovascular metallic implants have been characterized. The authors found elevated levels of nickel and chromium ions (0.5-3.0 μg $cm^2$ stent) in arterial tissue surrounding stainless steel stents. However, these studies did not have matched controls to definitively distinguish *in-vivo* corrosion from pre-existing features of the manufacturing process. Elevated levels of nickel and titanium ions were also observed in tissue surrounding Nitinol stents. Corrosion in Nitinol can lead to a release of nickel ions which may illicit foreign body reactions and reduce the overall biocompatibility of the device. Metals ions from corrosion byproducts may be transported systemically by blood flow or remain locally within the vasculature. Corrosion by-products have been thought to increase the risk of in-stent restenosis.

At a public FDA meeting, the cardiovascular implant industry expressed the need for better methods to assess the presence of local and/or systemic allergic reactions to determine the true rate of metal ion allergy-induced adverse events [17]. The U.S. Food and Drug Administration (USFDA) published guidance documents with recommendations to medical device manufacturers for safety assessments of Nitinol devices. In particular, a recent draft guidance document was published that provides Nitinol-specific technical recommendations and covers the following areas: manufacturing, mechanical testing, corrosion, nickel ion release, and biocompatibility of Nitinol devices. Important assessment outlined in the Nitinol guidance document is immersion testing to quantify nickel ion release over time under physiologically relevant conditions. This testing quantifies the elution (release testing) of metal ions such as nickel over time and soluble or insoluble nickel compounds as part of a toxicological risk assessment. However, more studies are needed to help definitively identify the consequences of corrosion in Nitinol implants.

Local exposure to corrosion by-products was evaluated in patients receiving Nitinol occluders [11,13]. Ries et al. [11] conducted a prospective study in 67 patients in whom the Amplatzer septal occluder was used for transcatheter closure of atrial septal defects (ASD) and patent foramen ovale for a period of one year with no history of nickel sensitivity. Blood samples were taken 24 h before, i.e. at baseline and 24 h, 1 month, 3 months, and 12 months after occluder implantation. They found after 2-4 weeks implantation serum and urine nickel concentrations were up to 6 μg $L^{-1}$ and 20 μg $L^{-1}$, respectively. These values were substantially higher compared to reference values for humans of 1.1 μg $L^{-1}$ in serum and 4.4 μg $L^{-1}$ in urine [75]. These authors claimed that localized mechanical stress or friction caused by the movement of the heart could damage the surface layer on the device and that the duration of nickel release might be extended until endothelialization around the device was complete [11]. In another study by Burian et al. [13] blood and urine samples were obtained from 24 patients with ASD before occluder implantation (baseline) and during a 12-month post closure period, with antiplatelet drug being administered for the initial 6-month period post implantation. Mean baseline concentrations of nickel in serum and urine were found to be within the normal range, with values of 0.6 ± 0.2 μg $L^{-1}$ and 3.1 ± 1.2 μg $L^{-1}$, respectively. During the 6-week postclosure period, the nickel levels in serum increased up to 5-fold ($P$<0.01 *vs*. baseline), because that is the time needed for the formation of neointima on the surface of the graft. Mean concentrations in serum and urine returned to baseline levels within 4-6 months post implantation. None of the patients had any complications throughout the 12-month follow-up. It was concluded on the basis of these results that the nickel release from the Amplatzer device in the beginning did not pose any specific cardiovascular risk. In similar study conducted by Badran et al. [76] the blood samples for serum nickel levels were taken from 31 patients, aged 4-59 years who underwent transcatheter closure, before and 1 day, 1 week, 1 month, and 3 months after implantation. There was no significant difference in serum nickel levels before and after implantation. Another prospective longitudinal observational study was conducted at a public hospital, and percutaneous ASD occlusion with the Cocoon Septal Occluder device has shown that during the initial period of endothelization after the procedure there was no significant nickel release into the bloodstream in ten patients, with a mean age of 34.4 years (range 5-60 years). Serum nickel levels did not show any significant change and remained within the normal range for the population within 3 months of the procedure.

The Amplatzer septal occluder is a nickel-titanium alloy (Nitinol) device which is the commonly implanted device for the transcatheter closure of ASDs. Controversies still exist regarding the release of nickel from these devices and the allergy and other ill effects of nickel and also the duration of antiplatelet therapy to aid endothelization of the device [74,75]. Narayana et al. [77] followed a total 25 patients in whom the platinum-coated Nitinol-containing Amplatzer septal occluder was used for transcatheter closure of ASD for a period of one year. Blood nickel levels were estimated before and 24 h after the procedure and later at 1 month, 3 months, and 6 months post procedure. A value of <2 μg $L^{-1}$ was considered to be normal. The blood nickel levels at mean baseline, 24 h, 1 month, 3 months, and 6 months postprocedure were 1.05, 1.39, 0.98, 0.79, and 0.74 μg $L^{-1}$, respectively. A transient rise in nickel levels was noted in seven patients, which returned to normal levels in six patients at 3 months and in one patient at 6 months. The transient rise was found mostly at 1 month postprocedure; thereafter, the values declined. Though there is a transient rise of serum nickel levels during the initial months of post implantation, the values decline to normal by 6-12 months. Percutaneous ASD closure using Nitinol devices can be carried out safely without any significant ill effects related to nickel release. In another study by Elkiran et al. [78] it was examining the serum nickel and titanium release after transcatheter implantation of Amplatzer device used. In 38 pediatric patients with no history of nickel sensitivity, blood samples were drawn 24 hours before and 24 hours, 1, 3, 6, and 12 months after implantation of Amplatzer occluder. The median serum nickel level which was 0.44 μg $L^{-1}$ before the implantation increased to 1.01 μg $L^{-1}$ 24 hours after implantation and 1.72 μg $L^{-1}$ one month after implantation. The maximum level was detected 3 months after implantation, with a median level of 1.96 μg $L^{-1}$. During follow-up, the nickel levels decreased to those measured before implantation. Serum nickel levels at the 24th hour, 1st month, and 3rd month following implantation were found to have increased significantly. No patients showed a detectable serum titanium level. In the concerned study, the highest nickel level was established in the first month following implantation of the Amplatzer occluder. None of the patients experienced any side effects or showed any allergic signs associated with nickel allergy over the follow-up period.

There is a scarcity of data regarding metal ion levels locally surrounding Nitinol cardiovascular devices. One study observed significant levels of nickel and titanium ions in tissue surrounding two explanted Nitinol stents [15]. Although these studies provided insight into local and systemic exposure from Nitinol corrosion by-products, the clinical ramifications of corrosion remain unclear for cardiovascular devices. With regard to cardiovascular stents, the studies performed in this field are mainly retrospective studies, and show somewhat disparate results. In the study by Svedman et al. [79], two patient groups and a control material (dermatitis patients) were studied. The stented population had been stented with anatomically identical stents where one subgroup was gold-plated. The two stents, identical but for the gold plating [42] have been analyzed *in vitro*, and it was shown that the stents did release the metals: nickel and gold [79,80]. In the study, it was found a relationship between gold stent and contact allergy to gold and a numerically however not statistically significant higher frequency of nickel allergy in the stainless steel (i.e. alloy containing nickel)-stented group. There was, as has previously been found, an association between dental gold and contact allergy to gold. Adjusting for this association in a multivariate analysis, there was still found an increased frequency of gold allergy in the gold-stented population [80]. When the blood drawn from the patients with gold-plated stents was analyzed, it was found a higher concentration of gold in the circulation [81] indicating a continuous release of gold and thus a circulating hapten from the stent.

Many alloys used in cardiovascular device applications contain high levels of nickel, which if released in sufficient quantities, can lead to adverse health effects. While nickel release from these devices is typically characterized through the use of *in vitro* immersion tests, it is unclear if the rate at which nickel is released from a device during *in vitro* testing is representative of the release rate following implantation in the human body. To address this uncertainty, Saylor et al. [82,83] have developed a novel biokinetic model that combines a traditional toxicokinetic compartment model with a physics-based model to estimate nickel release from an implanted cardiovascular device. They use the model to predict local and systemic nickel exposure due to passive release from Nitinol devices produced using a wide range of manufacturing processes, as well as general relationships between release rate and exposure. These relationships suggest that peri-implant tissue and serum levels of nickel will remain below 5 μg $g^{-1}$ and 10 μg $L^{-1}$, respectively, in patients who have received implanted Nitinol cardiovascular devices provided the rate of nickel release per device surface area does not exceed 0.074 μg $cm^2$ $d^{-1}$ and is less than 32 μg $d^{-1}$ in total. Their model address the potential for local and systemic metal ion exposure due to a medical device and can serve as a basis for future efforts aimed at other metal ions and biomedical products.

## 7. Conclusion

Cardiovascular heart disease is one of the leading healthcare problems in this present era and need much care to prevent from this problem. Coronary stenting represents the standard of care for percutaneous revascularization of symptomatic coronary artery disease. Small medical implantable metallic devices are used in contemporary cardio logical practice; metals constitute the main components of these cardiovascular medical devices. Potential health risks are associated with local release of *in vivo* heavy metal ions into human biological specimen's circulation after implantation of the cardiovescular metallic implants. Release of metal ions could alter the local tissue environment leading to up-regulation of inflammatory mediators and promote in-stent restenosis. We overview studies that have characterized *in vivo* localized corrosion of cardiovascular metallic implants, and the extent to which metal release from cardiovascular active devices *in vivo* has potential biological effects, in terms of elicitation of a metal allergic reactions or induction of sensitization. Despite of the benefits of drug-eluting stents (DESs), there is still a role of bare-metal stents (BMSs) in the management of patients with coronary artery disease (CAD), and that BMS are still used in contemporary cardio logical practice. The main benefit of stents was reduction of acute closure due to dissection or recoil and, some years later, reduction of restenosis. It might be hard to get away from stenting, even in small vessels where stents have been less effective [84]. Ultimately, the decision to implant a BMS is guided by both clinical and economic factors.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

All authors declare no conflicts of interest associated with this manuscript.

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