

Immunology Devices Panel Advisory Committee Meeting

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COOK MEDICAL

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Introduction to Cook Medical

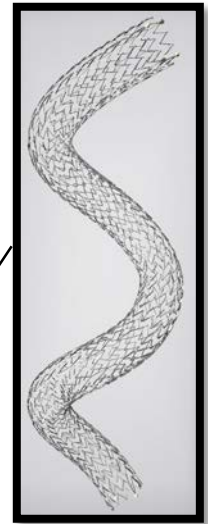
- Family-owned group of medical device companies, founded in 1963
- Develops, manufactures and distributes minimally invasive medical devices globally
 - Over 10,000 products for more than 40 medical specialties
 - Approximately 12,000 employees



Cook has substantial experience (>40 years) with metal implants

Implant	Year	Metal	Comment
Embolization Coils	Starting 1977	Stainless Steel	Cook's first metal implants
Bird's Nest Vena Cava Filter	FDA Approved 1989	Stainless Steel	First Cook PMA approval
Coronary Artery Stent	FDA Approved 1993	Stainless Steel	First to be approved in US
Zenith AAA Endograft	FDA Approved 2003	Stainless Steel and Nitinol	Nitinol approval 2006
Drug-Eluting Femoral Artery Stent	FDA Approved 2012	Nitinol	First to be approved in US

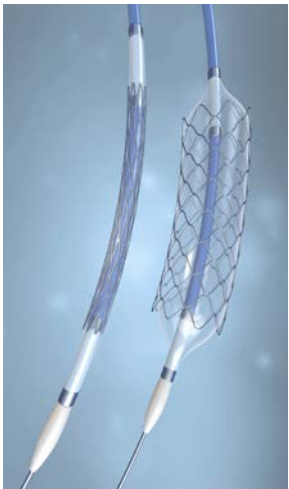
Many other devices such as, hemostasis clips; vena cava filters; venous, ureteral, esophageal, colonic and tracheobronchial stents. Includes some other metals (e.g., cobalt, chromium, platinum).



Metal implants benefit millions of patients each year, including

Cardiovascular

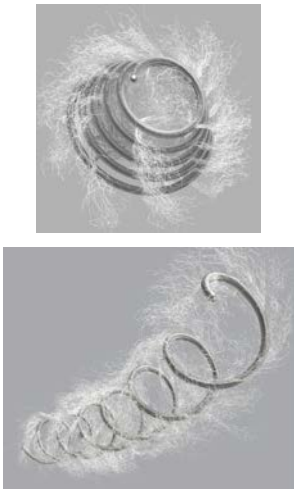
Example
balloon-expanded
coronary stent



Example
self-expanding
peripheral stent



Example
embolization coils



Orthopedic



Dental



Coronary artery and peripheral vascular stents

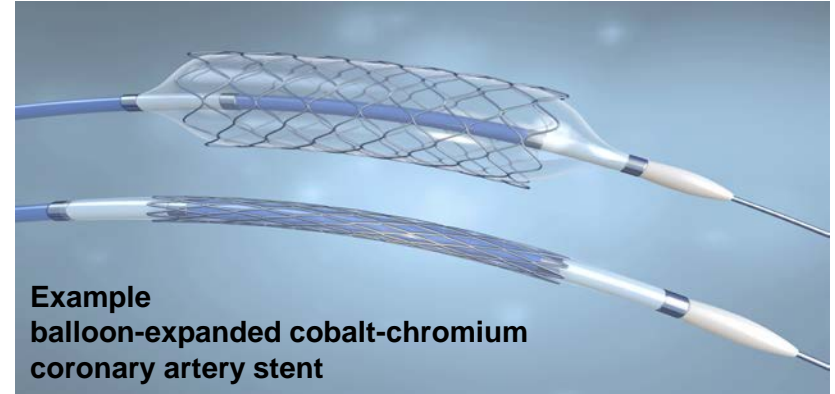
- More than one million coronary and 0.5 million peripheral stents placed each year in the US
- Approximately 50% improvement for coronary artery and femoral artery stents compared to balloon angioplasty (e.g., reduced procedural failure and recurrence) ^[1-4]
 - **Saves lives**
 - **Saves limbs** (e.g., reduced amputations)
 - **Improves quality of life** (e.g., reduced pain, increased exercise tolerance)

[1] N Engl J Med. 1994;331:489-495

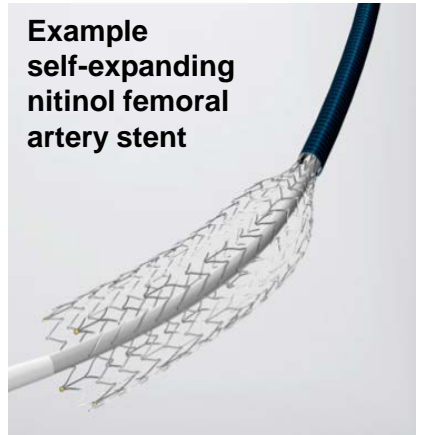
[2] N Engl J Med. 2003;349:1315-1323

[3] N Engl J Med. 2006;354:1879–1888

[4] Circ Cardiovasc Interv. 2010;3:267–276



Example
balloon-expanded cobalt-chromium
coronary artery stent



Example
self-expanding
nitinol femoral
artery stent

The incidence of metal allergy appears very low with the types of metal implants Cook supplies, for example

- **Zero (0) cases** of metal allergy were observed in 1-5 year follow-up of over 2700 patients with over 4000 **nitinol femoral artery stents in clinical studies**^[5]
 - Over the 7 years since US approval, the **reported adverse events** of possible metal allergy is approximately **one per hundred thousand sold** (i.e., 0.001%)^[5]
- Over the past 10 years, the rate of **reported adverse events** of possible metal allergy to **embolization coils** is **less than one per hundred thousand sold** (i.e., approximately 0.0007%)^[5]
- For comparison, other published rates include
 - Anaphylaxis during **general anesthesia** is at least **7X higher** at approximately 0.007%^[6-7]
 - Allergy to **iodinated contrast media** is at least **100X higher** at approximately 0.1%^[8]
 - Allergy to **latex** is at least **4000X higher** at >4%^[9]

[5] Data on file at Cook (FS190375)

[6] Br J Anaesth. 2018;121:159-171

[7] Anesthesiology 2009;110:759-765

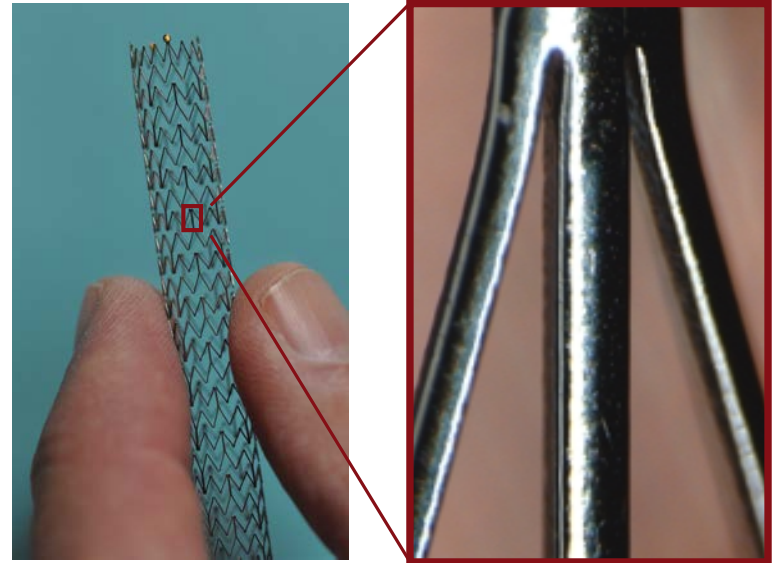
[8] Perm J. 2018;22:17-072

[9] J Occup Health. 2016;58:138-144



Why the low incidence of metal allergy with these types of implants?

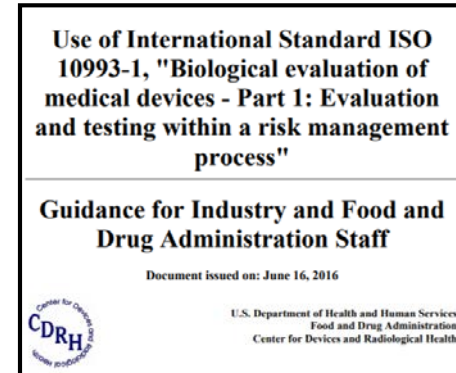
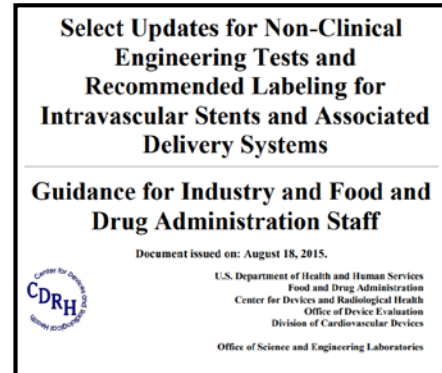
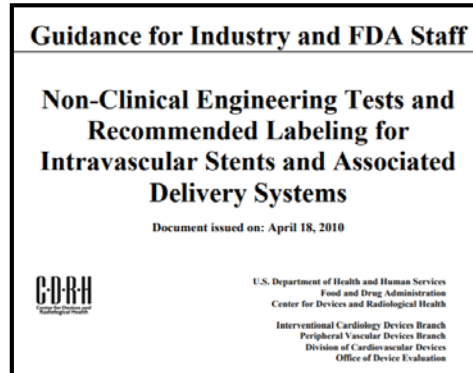
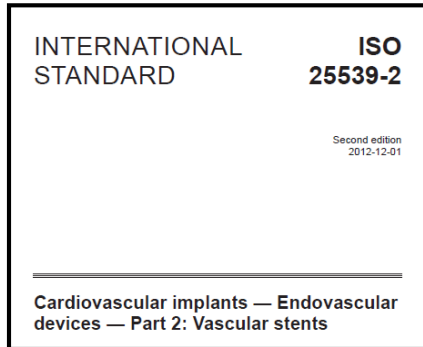
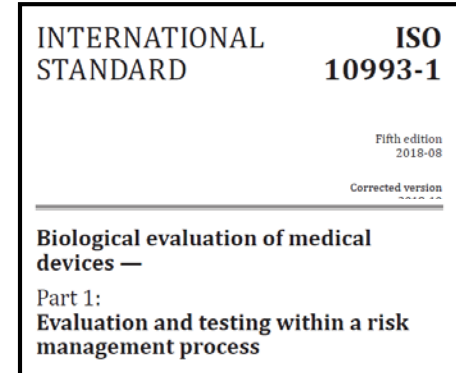
- **Relatively small amounts of metal:** stents, for example, contain 1,000 – 10,000 times less metal than some other common implants
- **Established surface finish:** the nitinol femoral artery stent, for example, has
 - An established electropolished and protective oxide layer surface finish
 - Has not exhibited release of metal particles in clinically relevant animal implantation studies, even with overlapping stents
 - In confirmatory testing, releases only extremely minute traces of nickel (less than 0.2% of levels in FDA guidance)^[10]



[10] Data on file at Cook (FS190369)

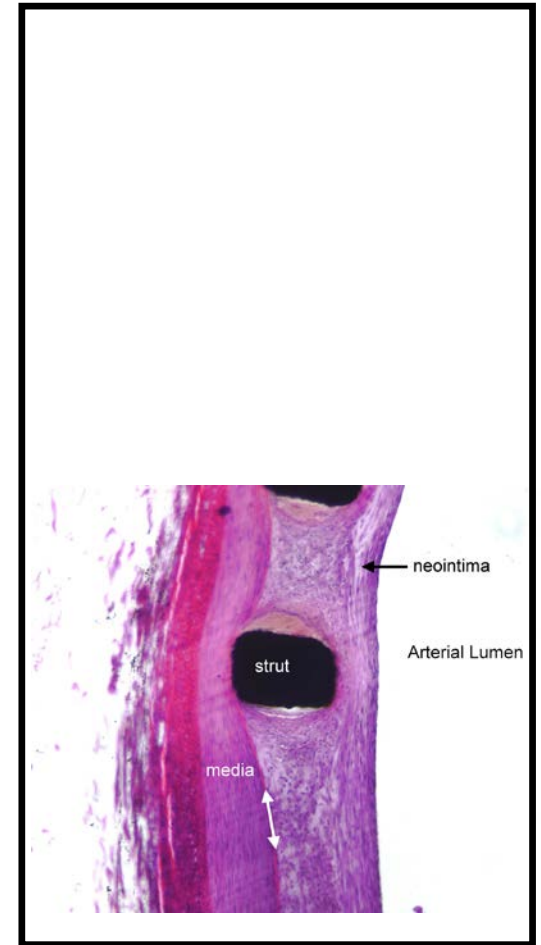
Why the low incidence of metal allergy? (continued)

- **Extensive nonclinical testing**
- Consistent with FDA guidance and international standards
- Thousands of devices in hundreds of tests, including
 - Chemical characterization testing
 - Biocompatibility testing



Extensive nonclinical testing (continued)

- **Clinically relevant in vivo testing** of the nitinol femoral artery stent included **over 500 stents in over 200 swine** with follow-up from one month to one year [11-12]
 - In-life observations were normal
 - Whole-body necropsies showing no adverse regional (downstream limb) or systemic effects (e.g., no adverse bloodwork changes, no organ damage)
 - Histopathology of the stented vessels showing appropriate healing and no adverse local reactions



[11] J Vasc Interv Radiol. 2011;22:603–610

[12] Data on file at Cook

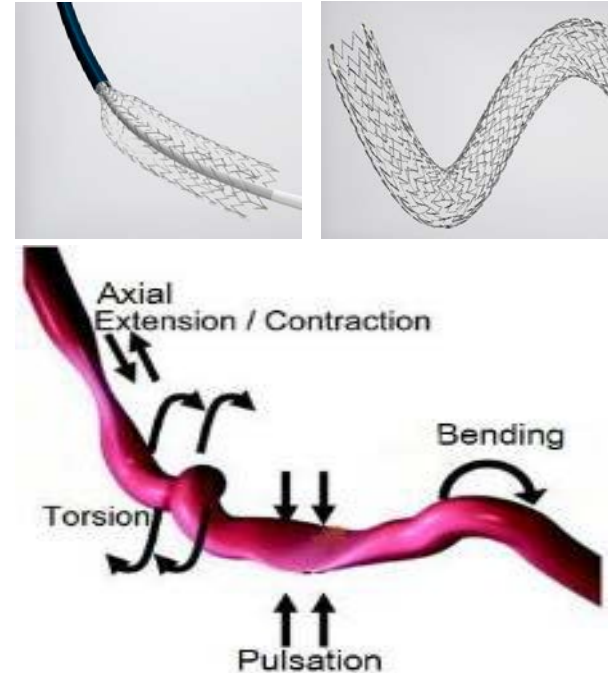
Why the low incidence of metal allergy? (continued)

Device labeling: The labeling for most metal implants includes a warning; for example, the nitinol femoral artery stent labeling states

“WARNINGS - Persons with allergic reactions to nitinol, or its components, nickel and titanium, may suffer an allergic reaction to this implant.”

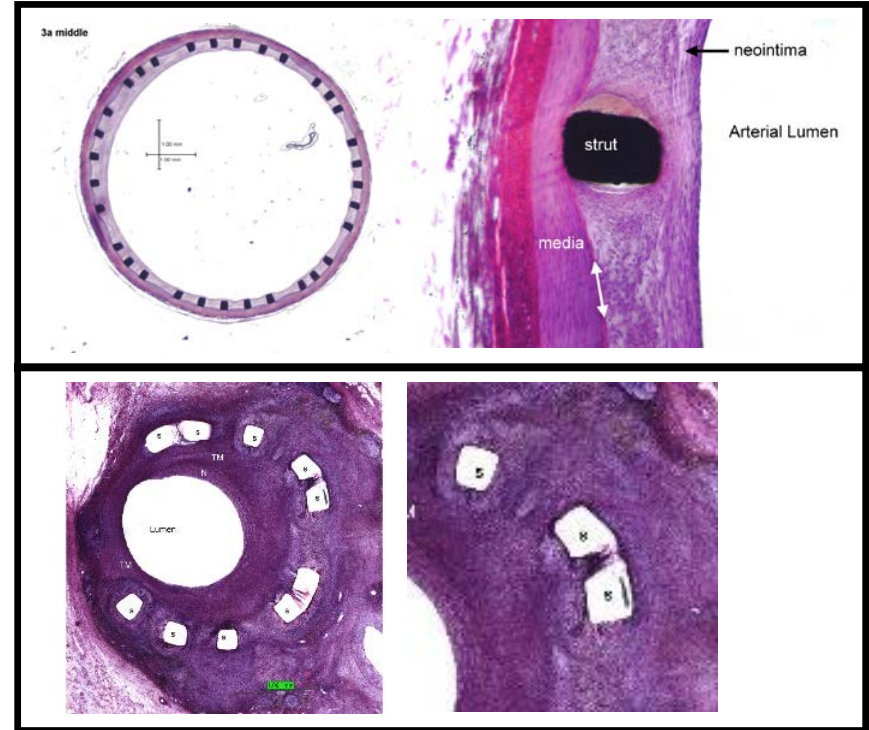
Many years, or decades, of further research may be required to find alternatives to metals that have even lower rates of adverse reactions, while maintaining the benefits of implants

- For stents, **many simultaneous requirements** ^[12] have been difficult to achieve with materials other than metals
 - Low profile and flexibility for introduction and tracking
 - Expansion and radial force for vessel support,
 - Durability for at least 10 years of fatigue motion (e.g., ≥ 400 million cardiac pulsations)
- The nickel-titanium alloy **nitinol** has **unique advantages** for locations like the femoral artery



Many years, or decades, of further research may be required to find alternatives to metals that have even lower rates of adverse reactions, while maintaining the benefits of implants (continued)

- **Current stent metals**
 - Stainless steel, nitinol, and cobalt chromium are biocompatible in blood vessels
- **Other materials**
 - Many have caused poor reactions to stents (e.g., persistent inflammation, thrombosis, occlusion, aneurysm)
 - Decades and billions invested in resorbable stents have been disappointing^[13,14]



Suggestions for the path forward

- Increased clinician and patient awareness, and discussion, regarding the potential for rare adverse reactions to metal implants
- Basic research (e.g., government, academic) to understand the biologic mechanisms, as well as potential methods to identify patients at elevated risk
- Recognition of the practical limitations of collecting clinical study data on events that occur in as few as 1/100,000 patients
- Maintaining patient access to the tremendous benefits of metal implants while this important and challenging work is ongoing

Summary

- Metal implants help save lives, save limbs, and improve the quality of life for millions of patients each year
- Allergic reactions to metal implants can be important, but are rare, not well understood, and the frequency and sequelae likely vary among different devices
- Replacing metals implants with alternatives that have lower rates of adverse reactions while maintaining the benefits, if even possible, will likely require many years, or decades, of further research
- Improved awareness, as well as results from further basic research, may help with clinician and patient decision making