Immunology Devices Panel Advisory Committee Meeting:
*Immunological responses to metal-containing Implants*

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Gaithersburg, Maryland

*My disclosures:*
I have not been paid for this presentation.
I own no shares in any company.
I sit on the scientific advisory board of Medtronic Vascular and am a consultant to Cook
I have received funds for speaking from Lutonix (Bard), Boston Scientific, Medtronic and Cook.
I have maintained objectivity in all studies I have performed or spoken of
CVPath Institute (Non-profit organization [501 3C])

- CVPath has been in the forefront of FDA, CE Mark in Europe, and Japan PMDA approval of safety studies performed in animals.
- CVPath performed preclinical studies (~500 studies) in animals following metal implants in the coronary and peripheral arteries, and percutaneous valve implants.
- Cardiovascular field:
  - Coronary stents – BMS, DES, and Peripheral stents:
  - Balloon expandable and self expanding stents
- CVPath has the largest registry of stented human arteries in the world (BMS, DES, peripheral) with large number of publications (>250 papers on stents alone).
- Widely published in the area of human autopsy studies: classification of atherosclerotic coronary disease, carotid and peripheral artery disease.
- I have examined > 750 autopsies (from 1999 until 2019) with > 1500 stents implanted in coronary and/or peripheral arteries in humans.
CVPath/AFIP Stent Registry

740 Patients with 1278 lesions

Coronary stenting
- 713 pts/1245 lesions
  - 1st-G DES: 529 lesions
    - SES: 249
    - PES: 258
    - E-ZES: 22
  - Newer -G DES: 285 lesions
    - CoCr-EES: 152
    - PtCr-EES: 42
    - R-ZES: 59
    - BP/PtCr-EES: 10

Peripheral stenting
- Femoro-popliteal: 11 Pts/13 lesions
- Iliac: 10 Pts/12 lesions
- Carotid: 6 Pts/6 lesions
- Renal: 1 Pts/2 lesions
- 28 pts/33 lesions
- BMS: 477 lesions
  - Stainless-Steel: 304
  - Cobalt-Chromium: 158
Type of Bare Metal Stents (BMS)

Number of lesions

Stent Material

135
81
63
42
30
19
15
12
12
9
7
7
18
15

N=477 lesions

N=304

N=158
# Type and percentage of Stent metal composition

<table>
<thead>
<tr>
<th>Metal Platform</th>
<th>Ni (%)</th>
<th>Co (%)</th>
<th>Cr (%)</th>
<th>Mb (%)</th>
<th>Fe (%)</th>
<th>Tn (%)</th>
<th>Ti (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>316L stainless Steel</td>
<td>14</td>
<td>-</td>
<td>18</td>
<td>2.7</td>
<td>64</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L606 Cobalt Chromium</td>
<td>10</td>
<td>50</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>MP35N Cobalt Chromium</td>
<td>35</td>
<td>34</td>
<td>20</td>
<td>9.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nitinol (Nickel titanium)</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>45</td>
</tr>
</tbody>
</table>

Is Metal Allergy a problem in stents?

- Metals that May Result in Contact Allergy and Allergic Contact Dermatitis

<table>
<thead>
<tr>
<th>Metal</th>
<th>Magnitude of clinical problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td></td>
</tr>
<tr>
<td>Cobalt</td>
<td>+</td>
</tr>
<tr>
<td>Chromium</td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td>?</td>
</tr>
<tr>
<td>Palladium</td>
<td>?</td>
</tr>
<tr>
<td>Aluminum</td>
<td></td>
</tr>
</tbody>
</table>

Modified Table 1 from Thyssen JP, Menne T. Chem Res Toxicol 2010.23.309-318
Injury is an important cause of restenosis

Medial Injury with RESTENOSIS

No medial Injury without restenosis

Restenosis = $>50\%$ diameter stenosis on angiography

No Restenosis = $<50\%$ diameter stenosis on angiography
In stent Restenosis: Mechanisms

- **Vessel Injury** – results in endothelial denudation and medial wall injury that leads to inflammation
- **Thrombus** formation
- **Inflammation** – Local induction of cytokines (IL1, IL6, TNF-α), activated macrophages, increased macrophage infiltration correlates with the extent of neointimal formation.
- **VSMC** (conversion of contractile to synthetic SMC) proliferation and migration, along with extracellular matrix production
Relationship between Inflammation and Restenosis

% Area occupied by Macrophage in neointima

Nickel and molybdenum contact allergies is associated with coronary in-stent restenosis following BMS

131 patients (mean age 62 years [SD 9]) with 171 stents (316L stainless steel)

Epicutaneous patch tests for nickel, chromate, molybdenum, manganese, and small 316L stainless-steel plates was accessed by independent dermatologists

89 patients with in-stent restenosis (>50 diameter stenosis)/All 10 patients with positive patch test had restenosis. (4 patients positive for Molybdenum, 7 had reaction to nickel). None of the patients without restenosis had positive patch test

Percentage diameter stenosis measured by QCA at 6 months
Single case of metal Allergy in a patient with x3, CoCr BMS implanted for 4 years

Mori H et al. JACC Cardiovasc Interv. 2017 Jun

1.1% (eosinophils) (macrophages) (T cells)

Prevalence of Hypersensitivity

9/814

1.1%

0.2%

1/477
Stent Fracture Does Not Lead to Hypersensitivity

Case of Grade V Cypher Fracture With Subacute Thrombosis

No Association of Fracture with Hypersensitivity

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Fracture+</th>
<th>No fracture</th>
<th>Total stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS-SES/ SS-PES (DES)</td>
<td>51</td>
<td>127</td>
<td>178</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (2.0%)</td>
<td>3 (2.4%)</td>
<td>4 (2.2%)</td>
</tr>
</tbody>
</table>

Outcome after Percutaneous Stent Implantation in Patients with Metal Allergy

• A comparison was made on outcome of pts with metal allergy vs. without metal allergy at Mayo Clinic. (N=29 with allergy vs. 250 no allergy).

• A clinical history of hypersensitivity to nickel was reported in 26 of 29, and to chromium in 9/19. Patch test was performed in 11 of 29 and was positive in all.

• Pts with h/o of metal allergy had similar adverse early (30-days) or late outcomes (4-years) (death, restenosis, and MI) as pts without h/o allergy.

No Documented case of Hypersensitivity in Peripheral Stent CVPath Registry

Total = 33 lesions from Lower Extremity, Iliac, Carotid and Renal Arteries

Balloon or Self Expandable
Balloon Expandable Stent: 9 Lesion
Self-Expandable Stent: 20 Lesions
Unknown: 4 Lesions

No case with Hypersensitivity

Type of Materials
Cobalt-Chromium: 2 Lesions
Stainless-Steel: 7 Lesion
Nitinol: 20 Lesions
Unknown: 4 Lesions
Although metal allergy was thought to be related to cardiac adverse events after stenting, no relationship documented in recent studies (Mayo Clinic 2012).

Prevalence of hypersensitivity reaction to BMS (Stainless steel and CoCr) stents <1% (CVPath Registry)

Hypersensitivity reaction in DES is higher than in BMS but still only 1.1%. (CVPath Registry) and is related to polymer or drug (sirolimus)

In Peripheral stents no hypersensitivity reaction documented, irrespective of balloon- or self-expandable stents (cobalt-chromium or nitinol), with or without fracture (CVPath Registry).

These results suggest that metals are safe in the vasculature.