U.S. FOOD & DRUG ADMINISTRATION

In-vitro to *In-vivo* Correlation of Corrosion in Nitinol Cardiovascular Stents

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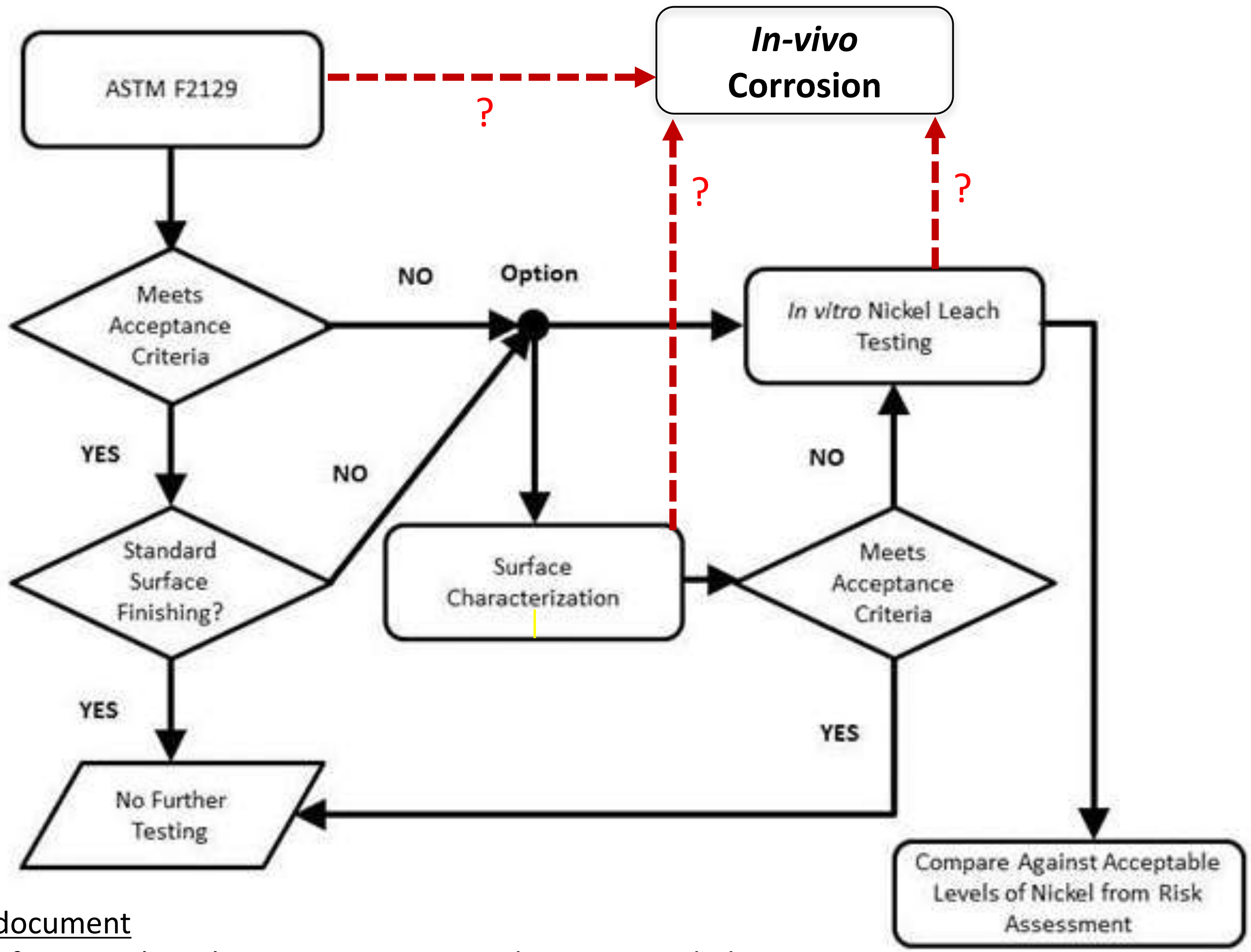
Stent Corrosion Testing Paradigm



FDA guidance document
Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

Motivation

- ASTM F2129 not intended to represent *in-vivo* conditions
- Results difficult to correlate with *in-vivo* performance
- Variability in breakdown potentials from workshop respondents

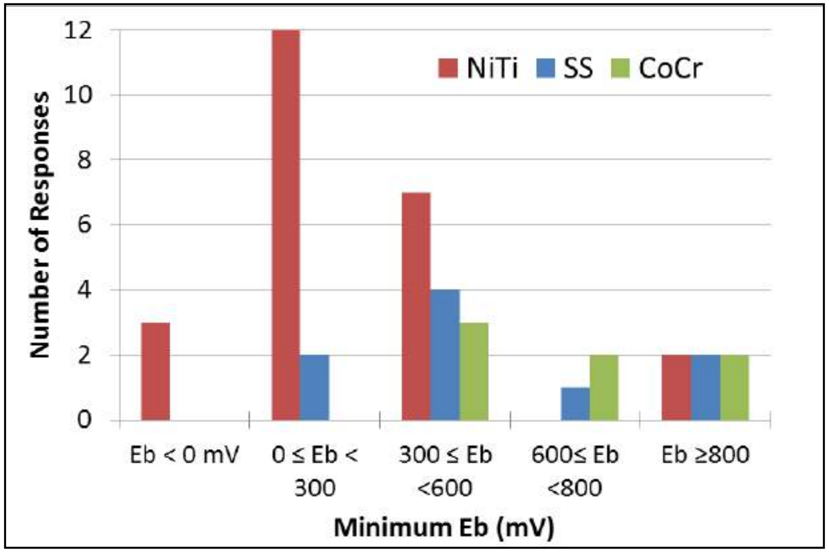
Proposed Acceptance Criteria

Eb ≥ 600 mV → Acceptable

Eb = 300-600 mV → Marginal

Eb < 300 mV → Unacceptable

Rosenbloom and Corbett, 2007



2012 FDA Corrosion Workshop
Nagaraja et al., 2016

Objectives

1. Manufacture and characterize Nitinol stents manufactured to possess low to high corrosion resistance (ASTM F2129)

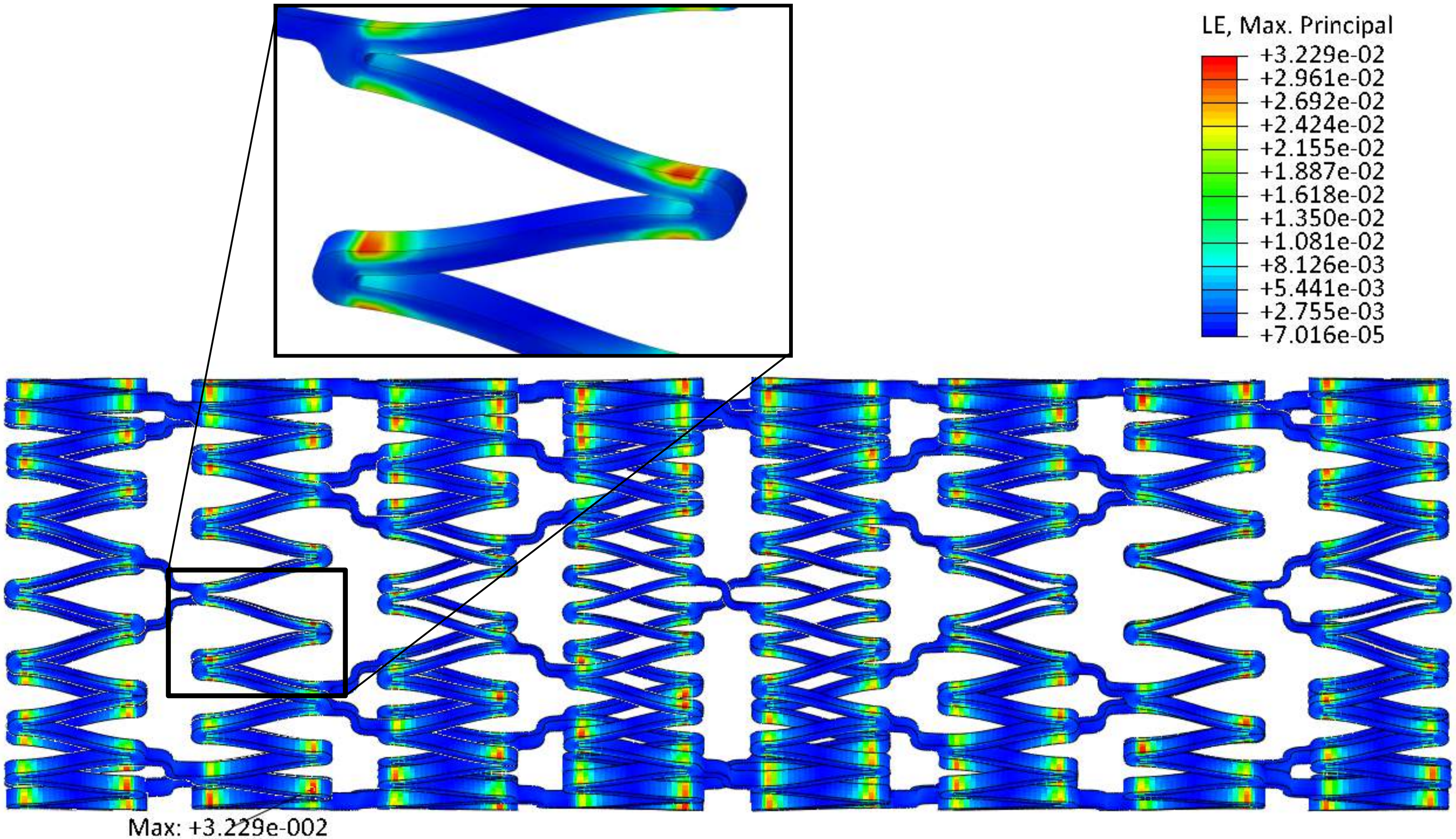
2. Investigate *in-vivo* pitting corrosion of Nitinol stents manufactured to possess low to high corrosion resistance

3. Correlate *in-vitro* nickel leaching with *in-vivo* release and biocompatibility in Nitinol stents with low to high corrosion resistance

Stent Manufacturing Process

Group	SP Salt Pot	MP Mechanical Polish	AF Air Furnace	OT Oxidized Tubing
Tubing	• Ground • Honed			As –received
Laser Cut				
Heat Affected Zone	• Honed • Debur & Deslug • Chemically Polish			(no processing)
Stress Relief	505°C Salt Pot		540°C Air furnace	505°C Salt Pot
Expansion	505°C Salt Pot		505°C Air furnace	505°C Salt Pot
Af Tuning	505°C Salt Pot		550°C Air furnace	505°C Salt Pot
Finishing	Ultrasonic clean	• Ultrasonic clean • Chemical Etch • Chemical Polish • Burnish • Ultrasonic clean	Ultrasonic clean	
Visual Appearance				

OSS Stent FEA – Crimping & Deployment



→ High strain regions at the apex of V-struts

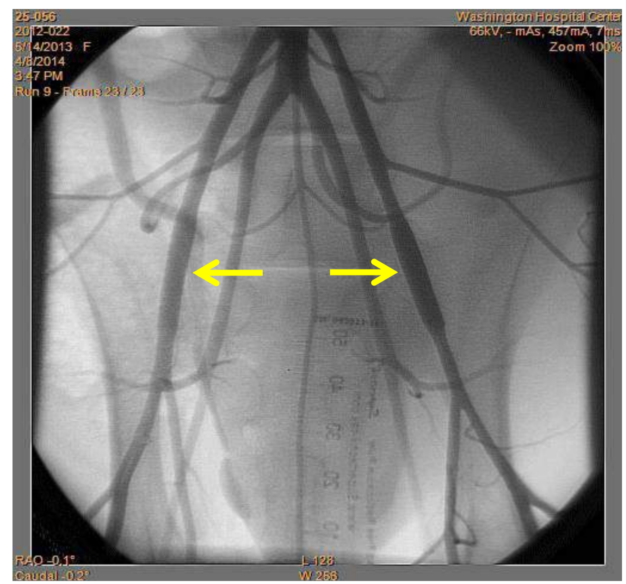
Methods

<u>*In-vitro*</u>

- Surface characterization → SEM/Auger
- Pitting corrosion → ASTM F2129
- Uniform corrosion → Nickel leach

<u>*In-vivo*</u>

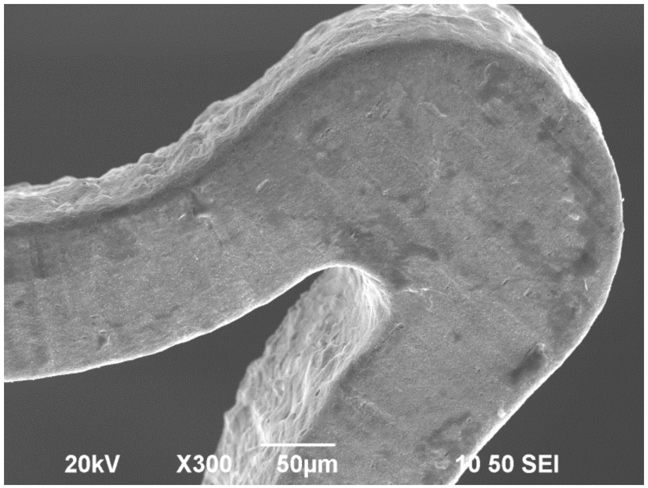
- Minipig implantation:
    - left and right iliac arteries
    - 12 animals implanted
- Single stent conditions (n=6/group)
- 6 month implantation period
- Explanted stent surface analysis
    - SEM and EDS



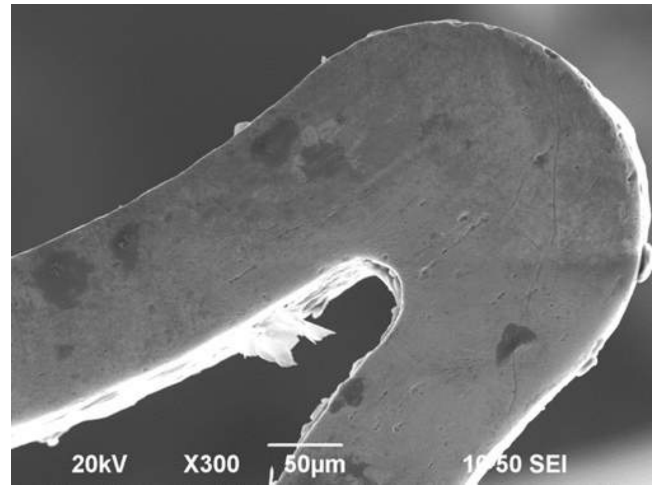
In-vitro Testing

Surface Characterization - SEM

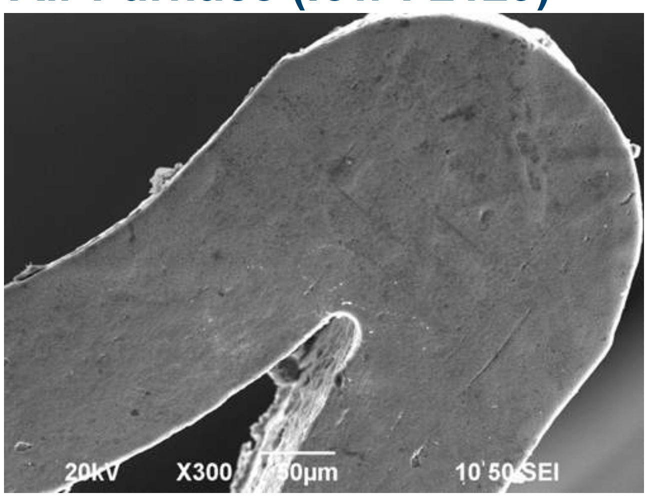
Salt Pot (high F2129)



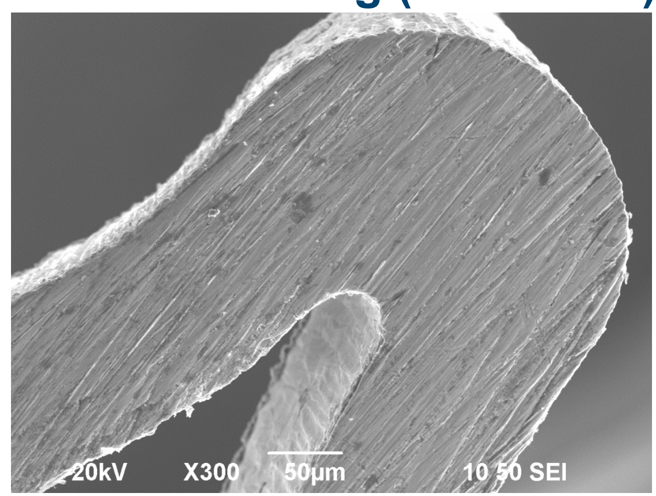
Mech. Polish (medium F2129)



Air Furnace (low F2129)

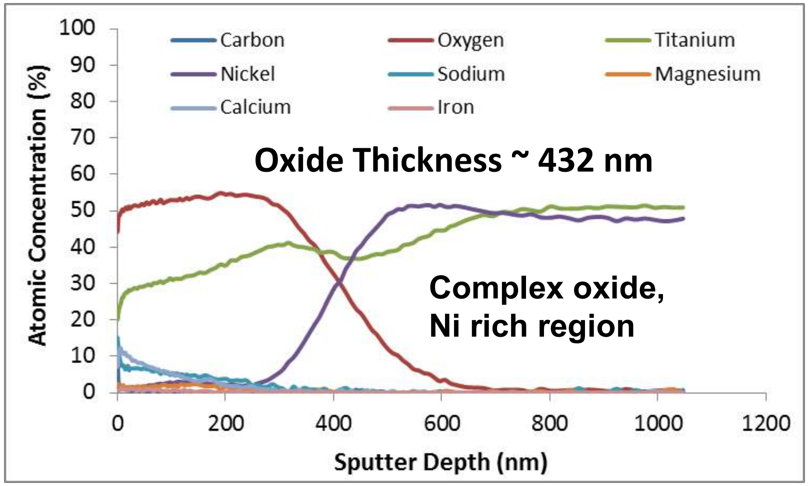


Oxidized Tubing (low F2129)

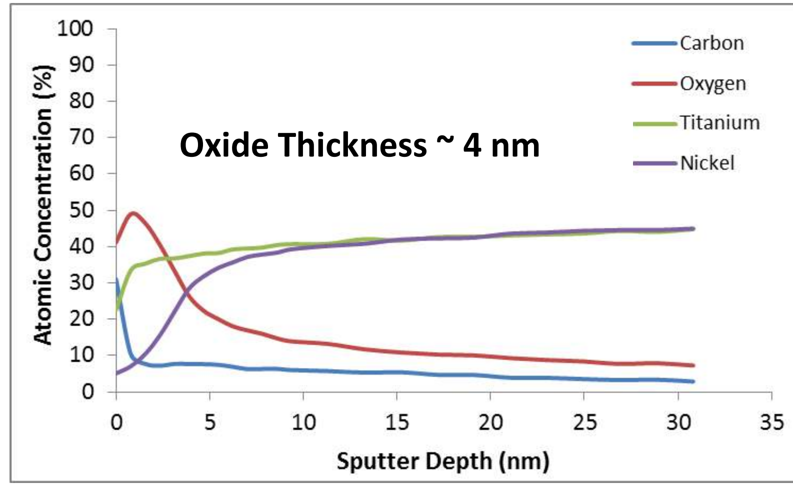


Surface Characterization - Auger

Salt Pot

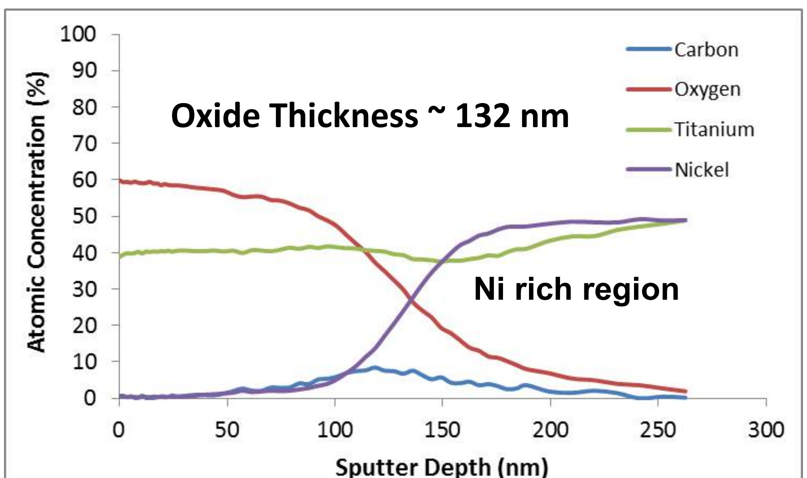


Mech. Polish

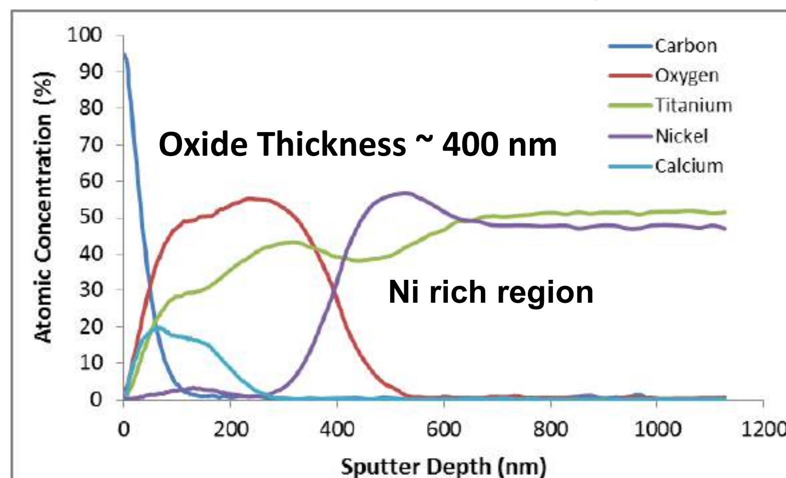


Strut

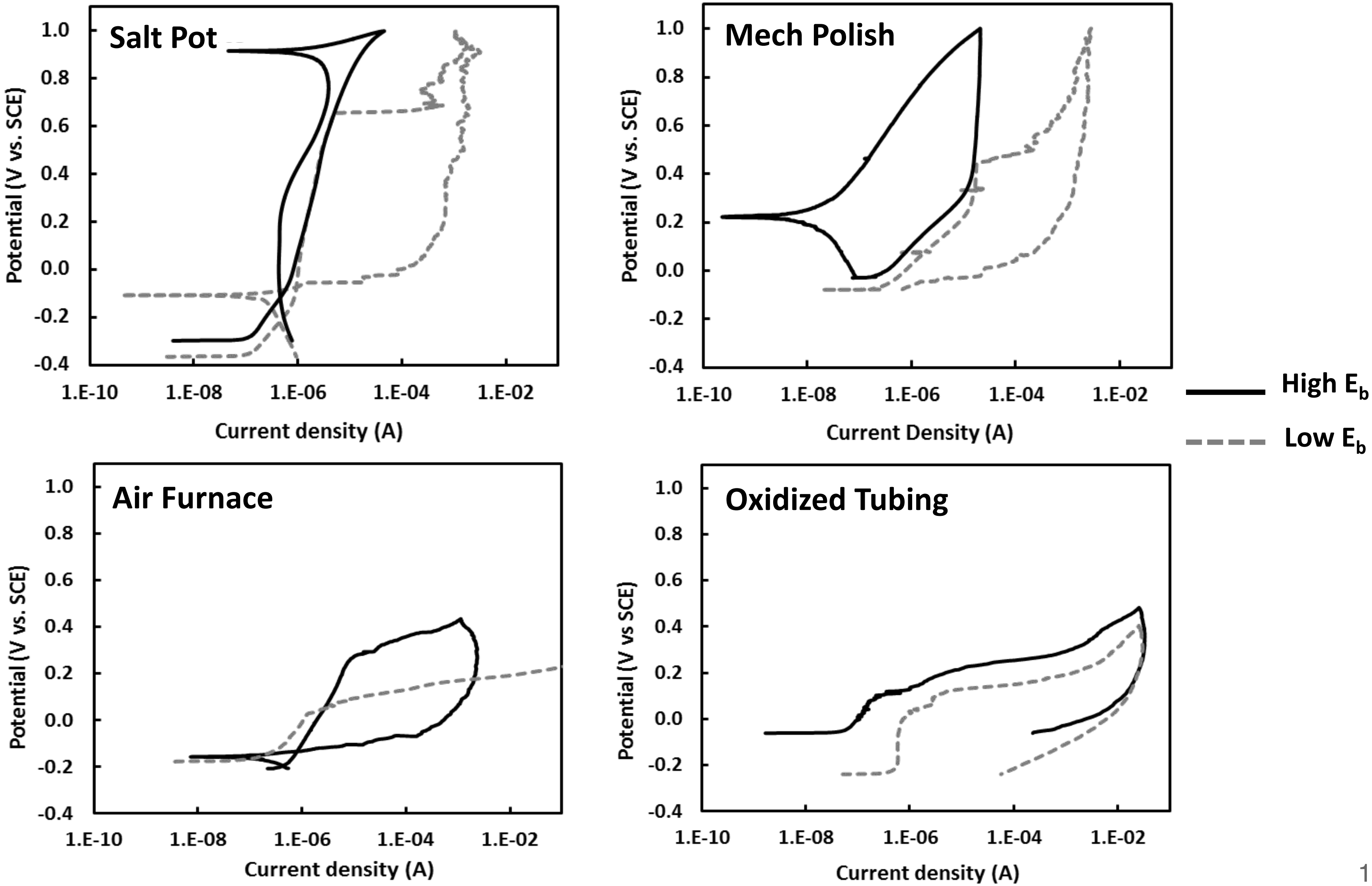
Air Furnace



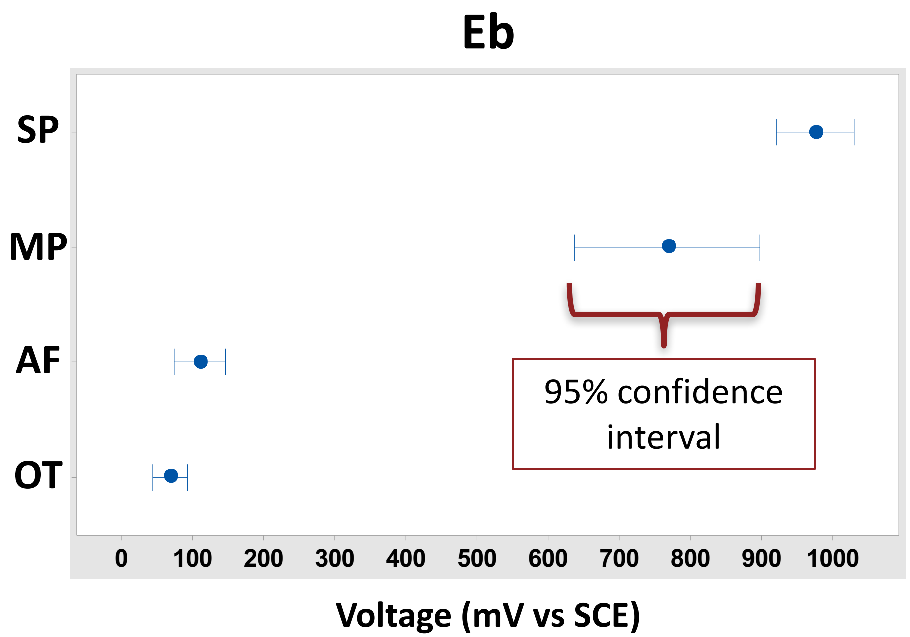
Oxidized Tubing

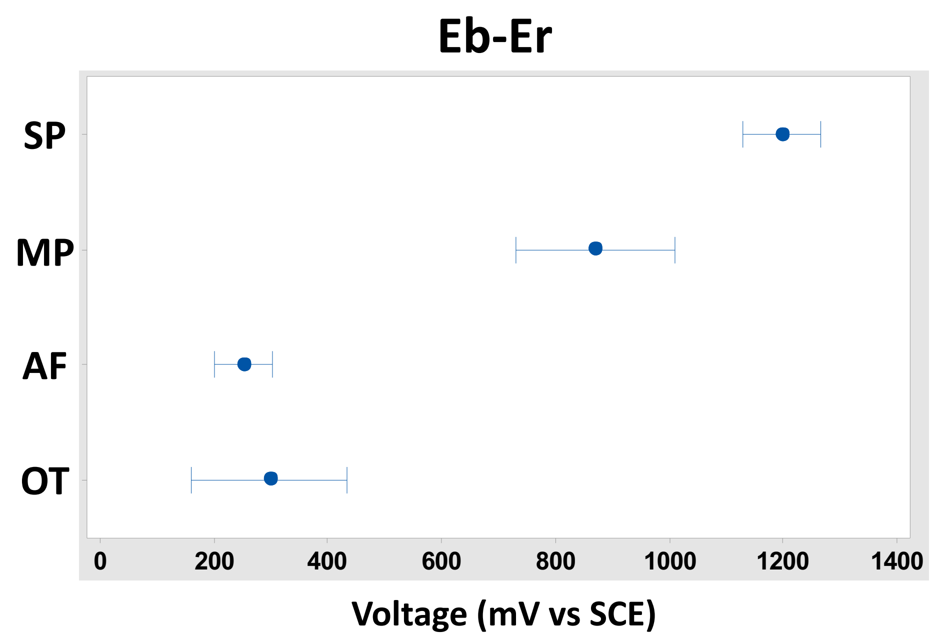


ASTM F2129 Testing



ASTM F2129 Results



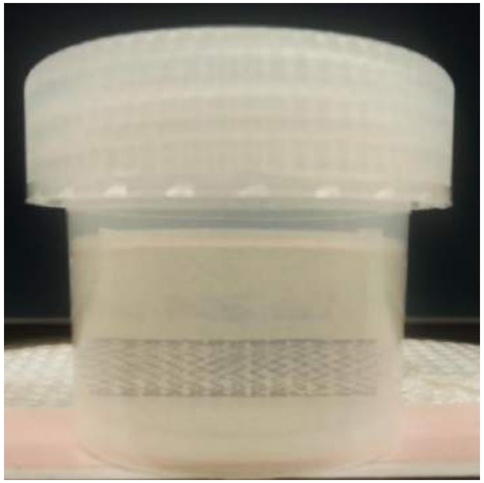


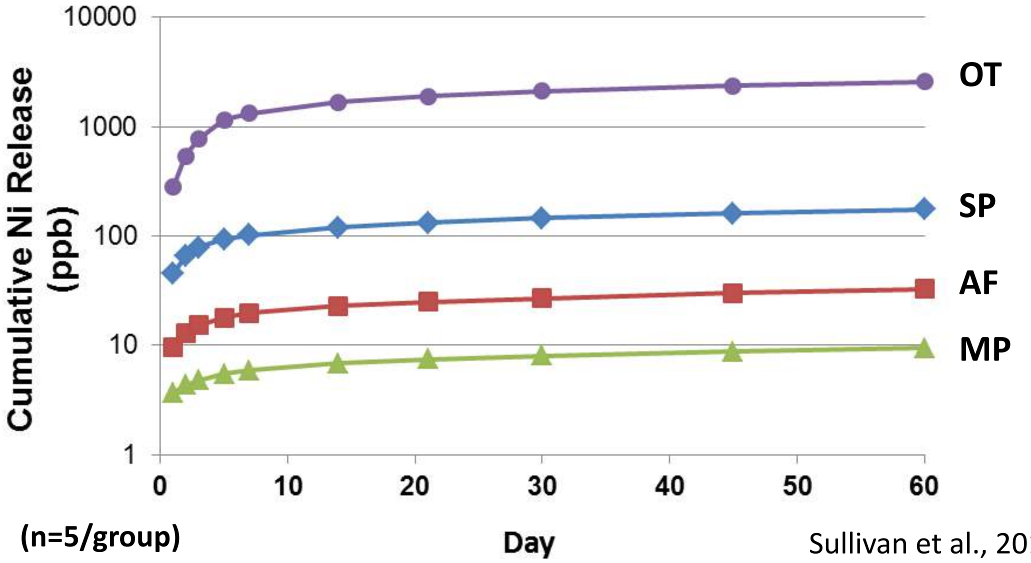
	SP	MP	AF	OT
E_r (mV)	-224 ± 112	-103 ± 65	-141 ± 44	-230 ± 178
E_b (mV)	975 ± 94	767 ± 226	111 ± 63	68 ± 29
E_b-E_r (mV)	1199 ± 118	870 ± 240	252 ± 90	297 ± 165

n=8-14/group

Nickel Leach Testing and Results

- OT, AF, SP, and MP stents (8 X 30mm) immersed in PBS at 37C
- Stents crimped prior to testing
- 10 time points: Day 1, 2, 3, 5, 7, 14, 21, 30, 45, 60
- Ni release: OT > SP > AF > MP for all time points (*p≤0.001)
- ASTM F2129 breakdown potentials not correlated to Ni release



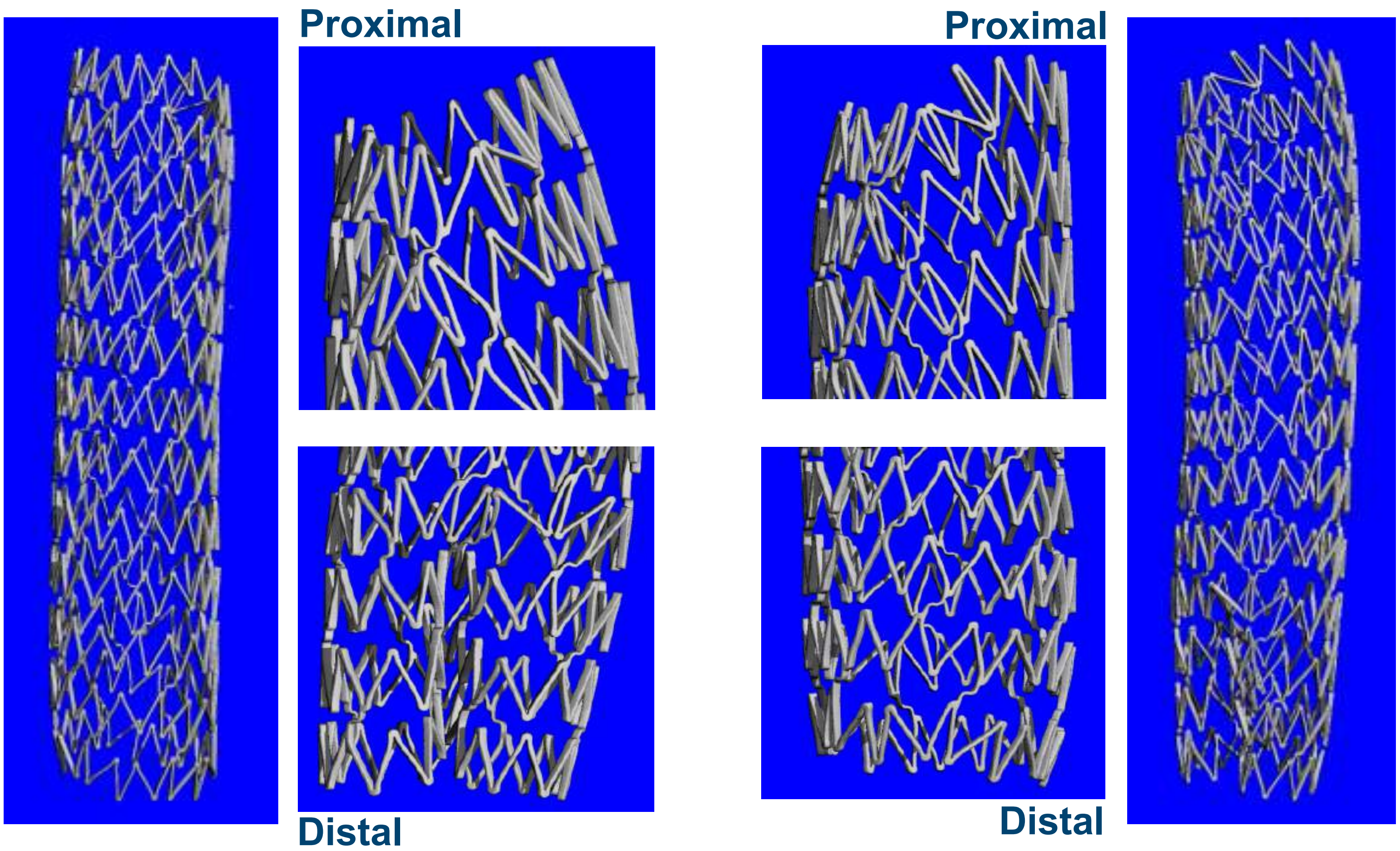


(n=5/group)

Sullivan et al., 2015

Explant Analysis

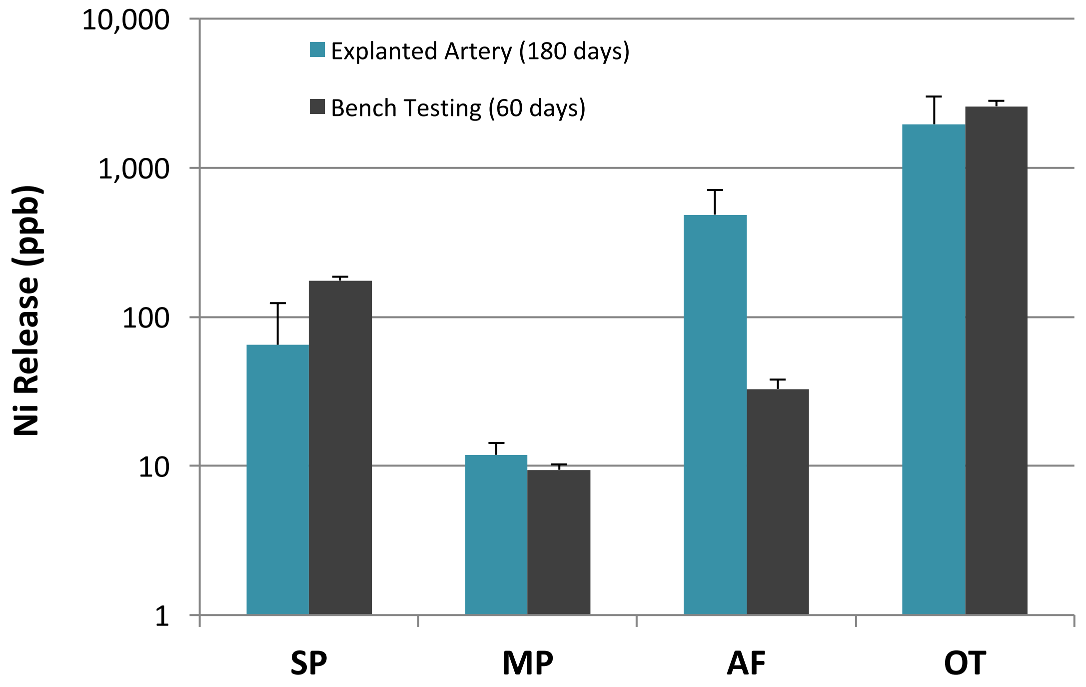
In-Situ Imaging



→Deformation, but no fractures observed in explants

Explanted Artery Nickel

Arterial tissue surrounding stent digested using papain



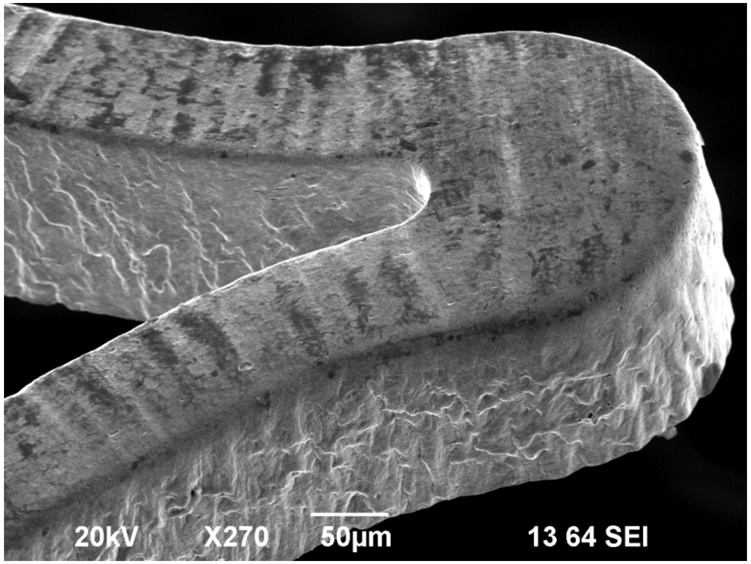
(n=3-5/group)

→ Artery nickel: OT > AF > SP > MP

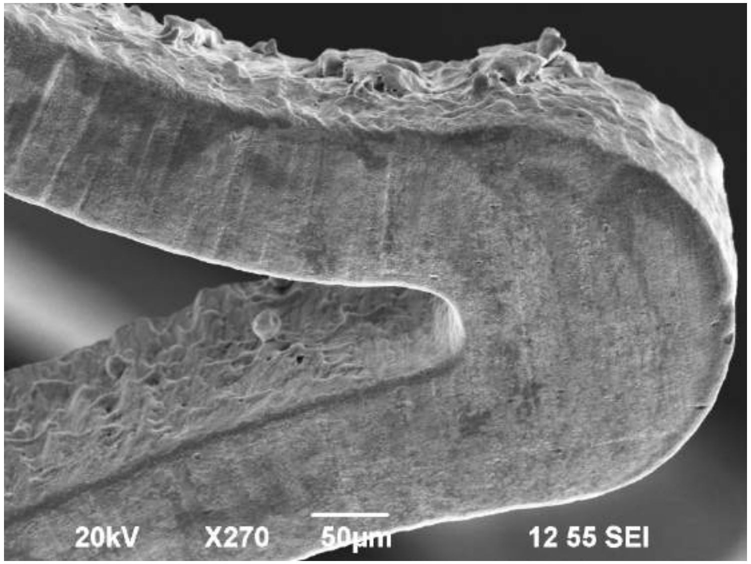
→ Explanted artery Ni values variable compared to in-vitro results

SEM Imaging – Salt Pot (high F2129)

Non-implanted



Explant

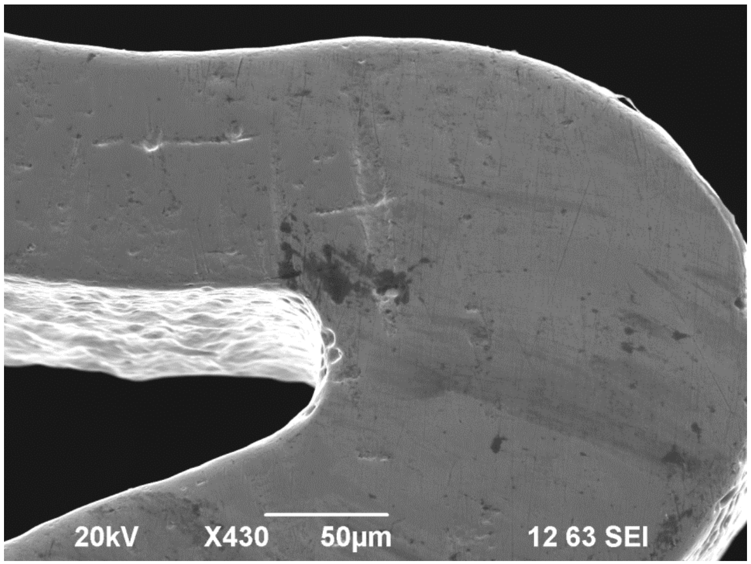


	Ni/Ti	n
SP Non-implanted	1.12 +/- 0.06	13
SP Explants	1.13 +/- 0.04	36

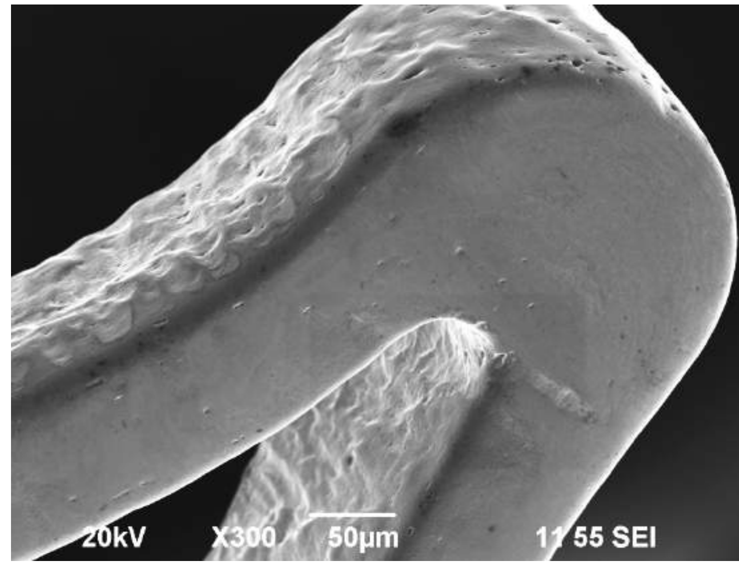
→ No corrosion observed in explanted SP stents

SEM Imaging – Mech. Polish (medium F2129)

Non-implanted



Explant

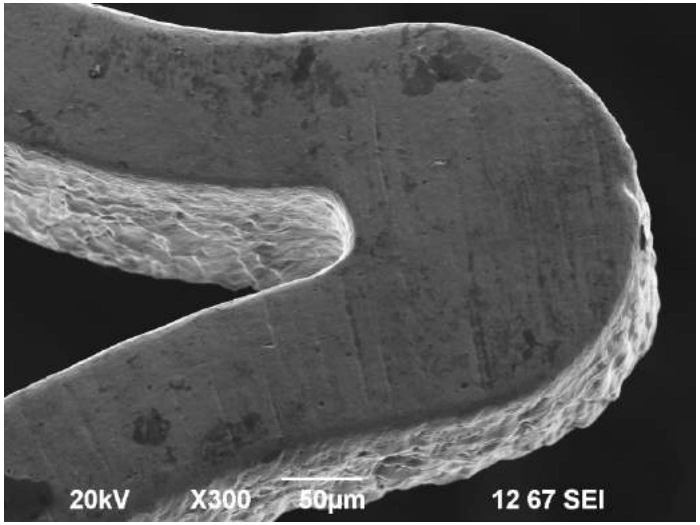


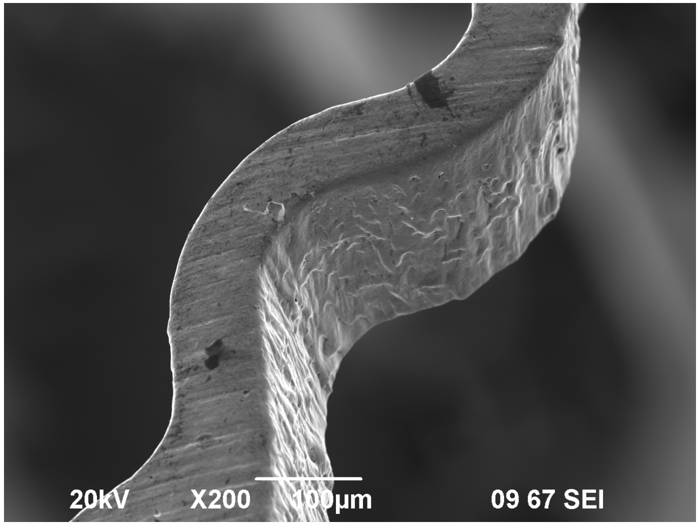
	Ni/Ti	n
MP Non-implanted	1.11 +/- 0.01	14
MP Explants	1.11 +/- 0.03	47

→ No corrosion observed in explanted MP stents

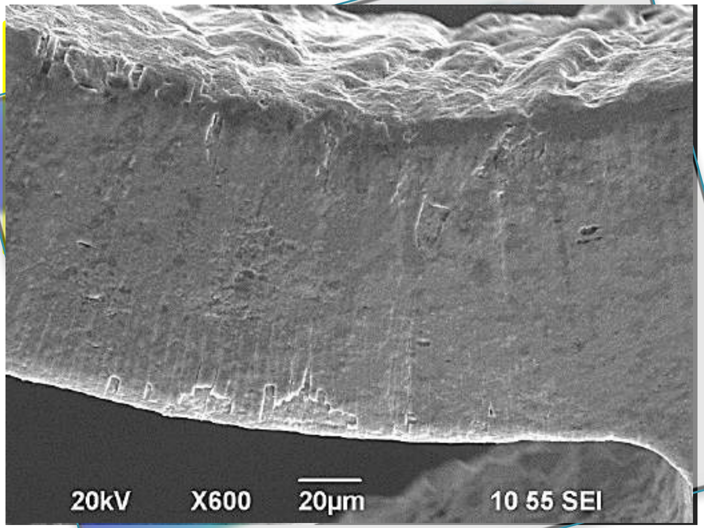
SEM Imaging – Air Furnace (low F2129)

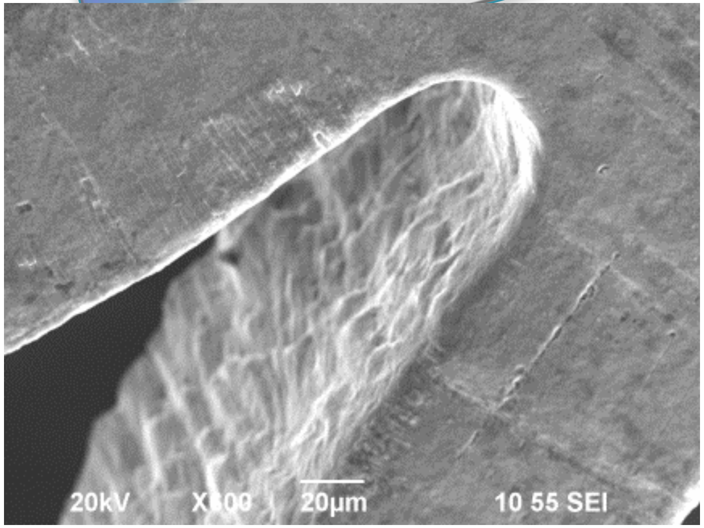
Non-implanted



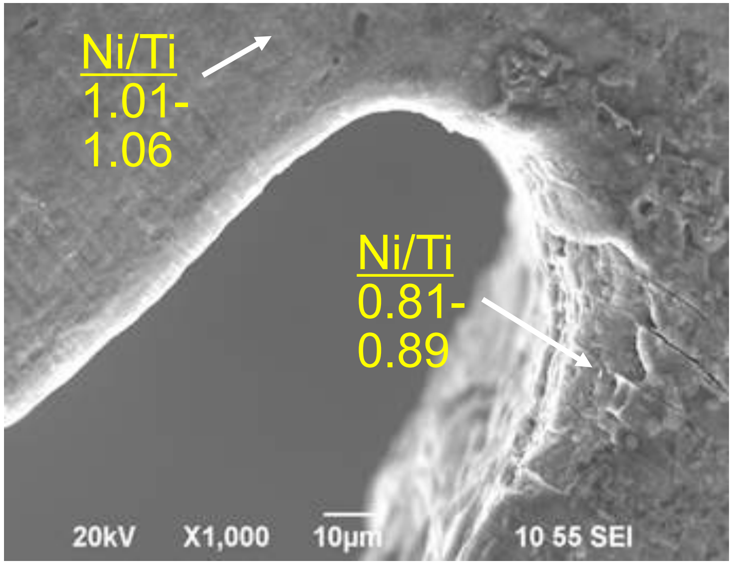


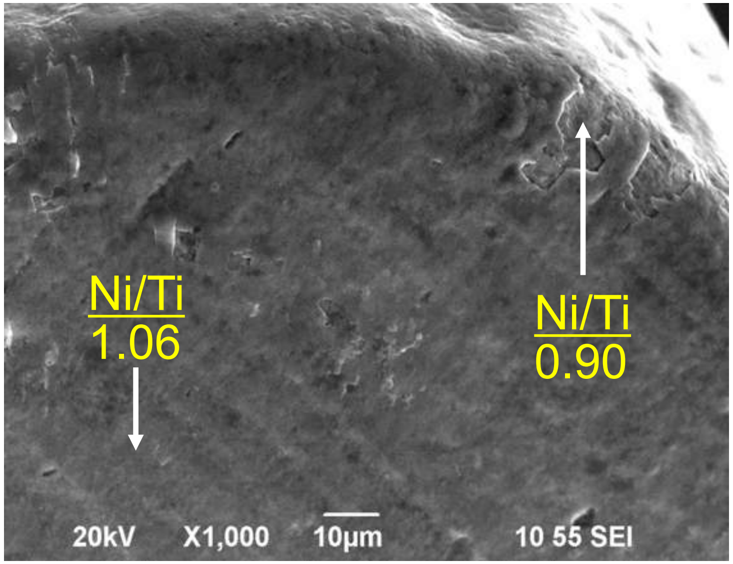
Explant





SEM Imaging – Air Furnace (low F2129)



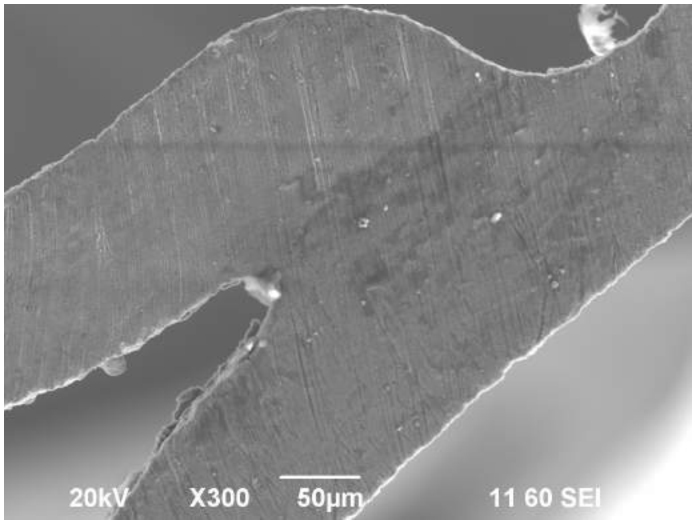


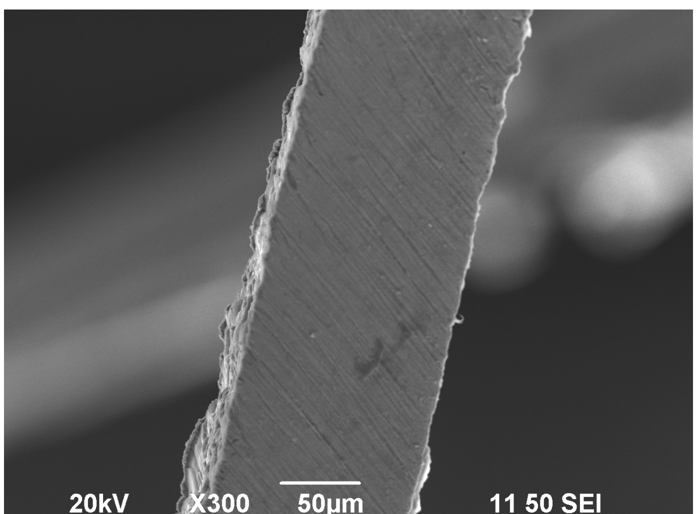
	Ni/Ti	n
AF Non-implanted	1.11 +/- 0.02	13
AF Explants - Native Surface	1.08 +/- 0.05	22
AF Explants – Corrosion	0.89 +/- 0.15	24

→ Micro-cracks & corrosion observed in explanted AF stents

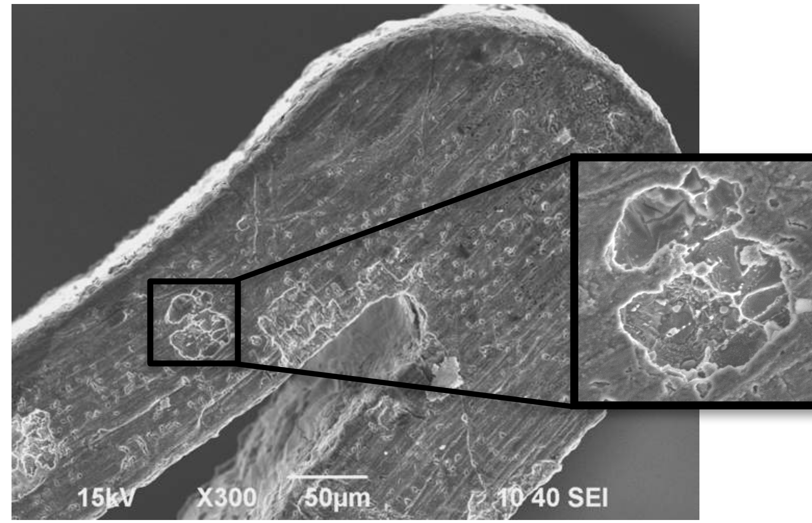
SEM Imaging – Oxidized Tubing (low F2129)

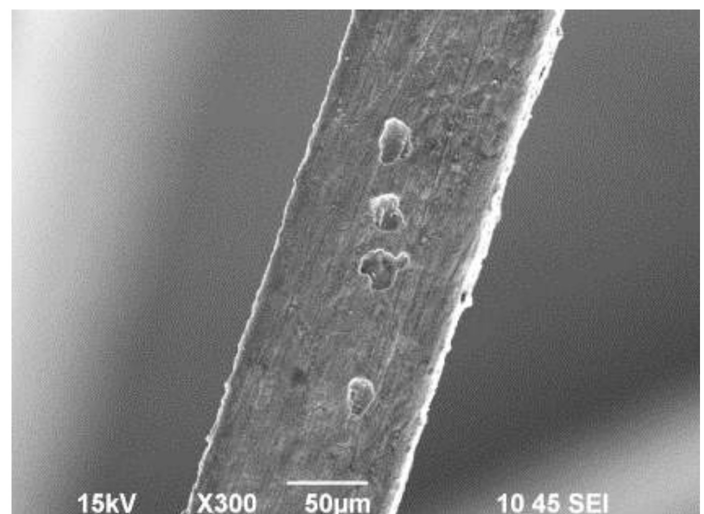
Non-implanted



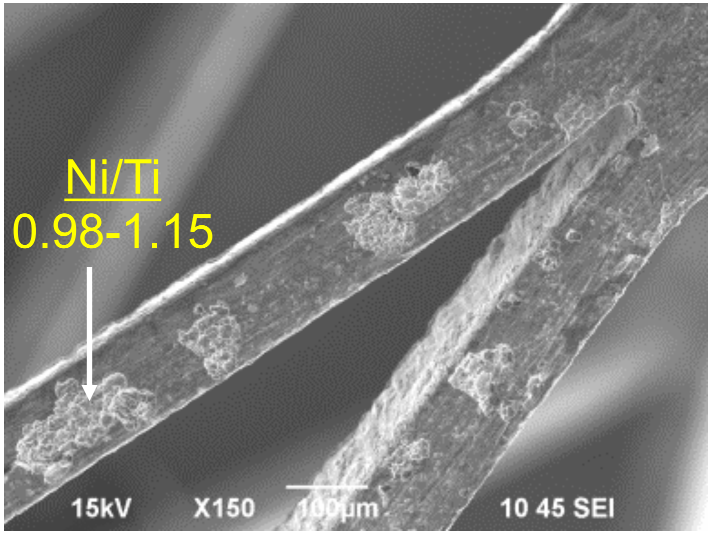


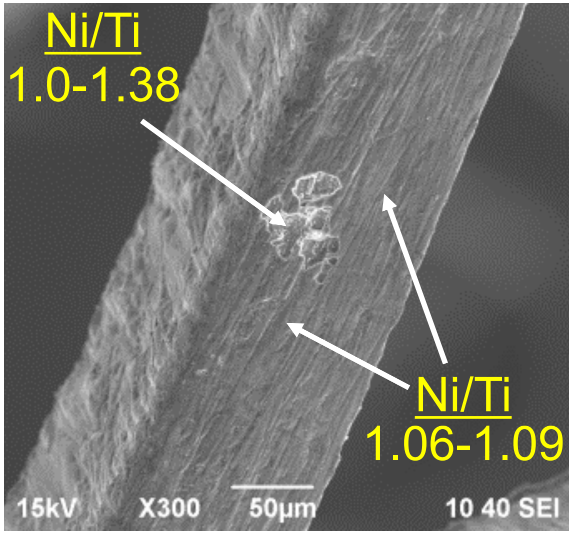
Explant

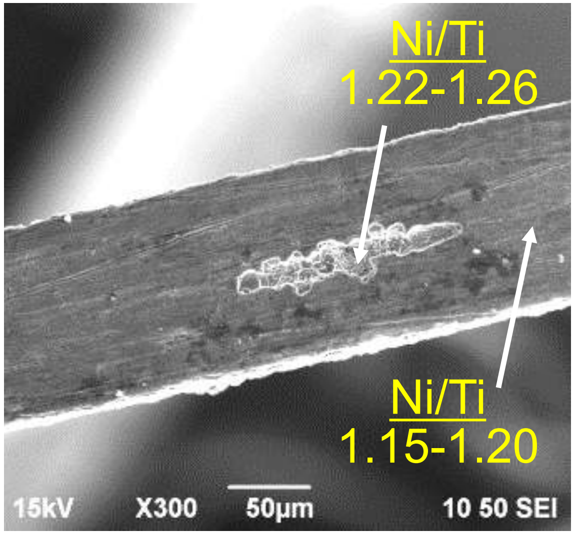




SEM Imaging – Oxidized Tubing (low F2129)





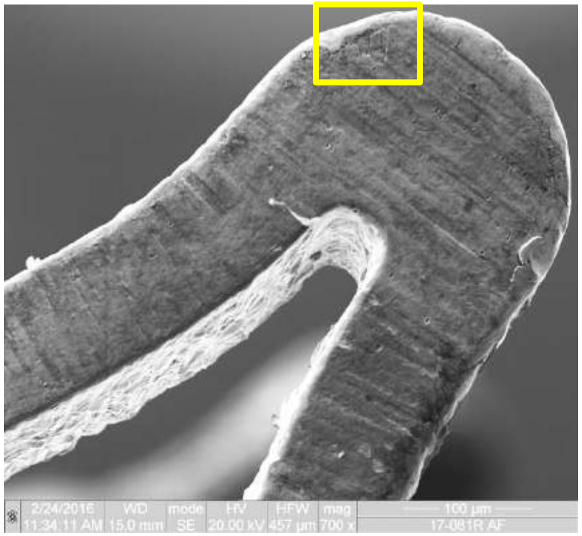


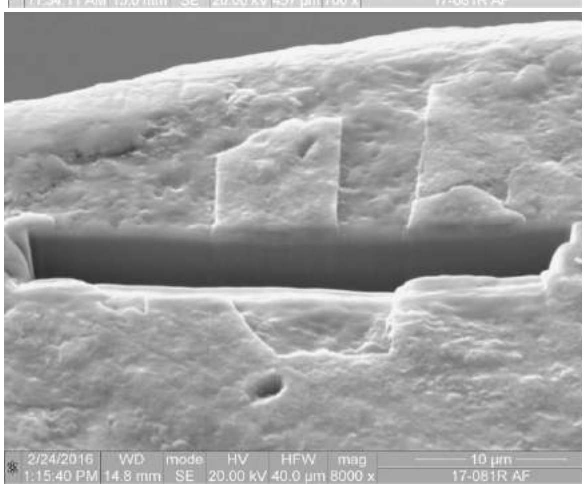
	Ni/Ti	n
OT Non-implanted	1.16 +/- 0.10	20
OT Explants - Native Surface	1.05 +/- 0.31	32
OT Explants – Corrosion	1.14 +/- 0.11	59

→ Pitting observed in explanted OT stents

Corrosion Depth (FIB milling)

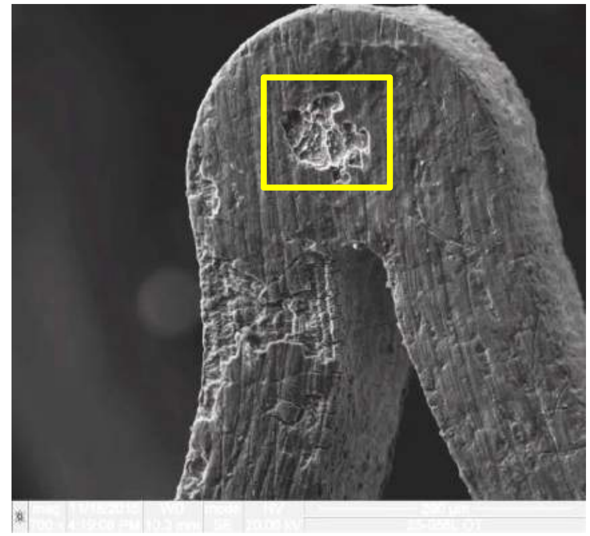
AF Stent

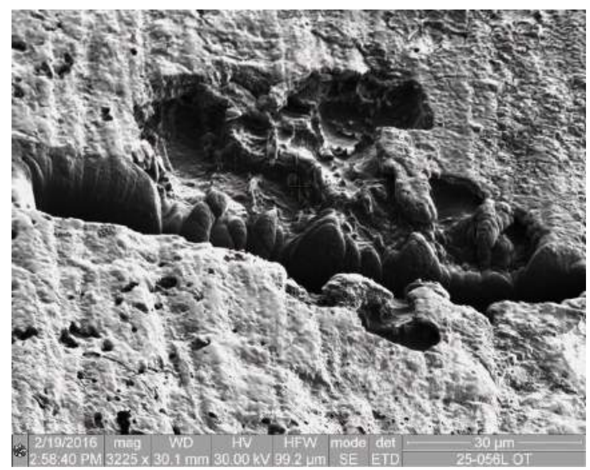




AF→ ~1 micron deep corrosion

OT Stent

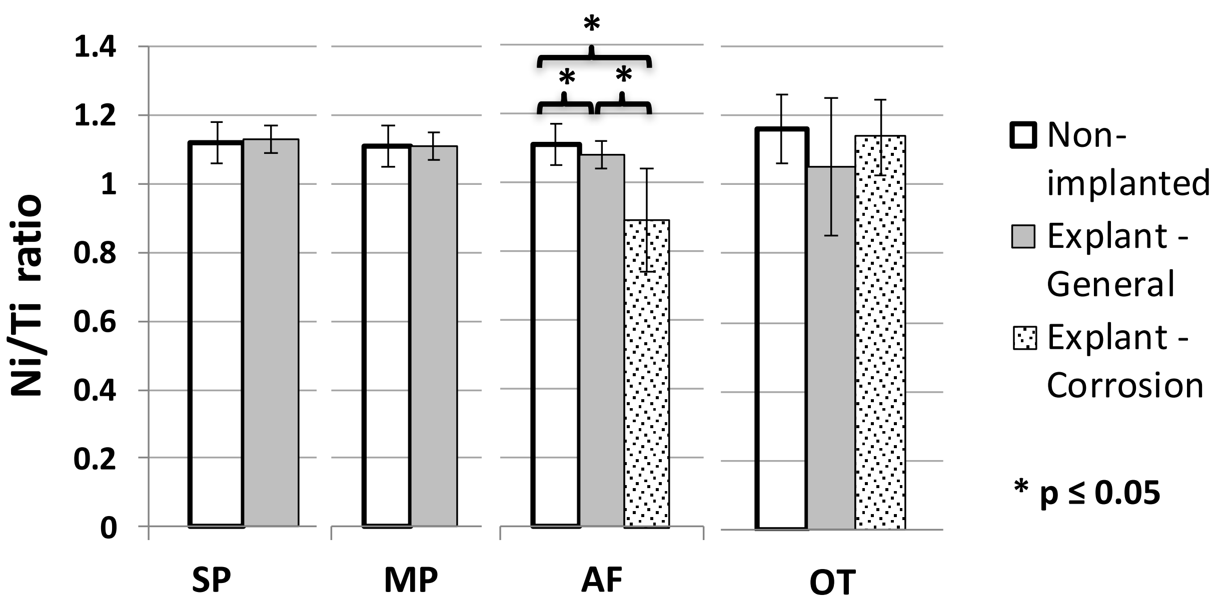




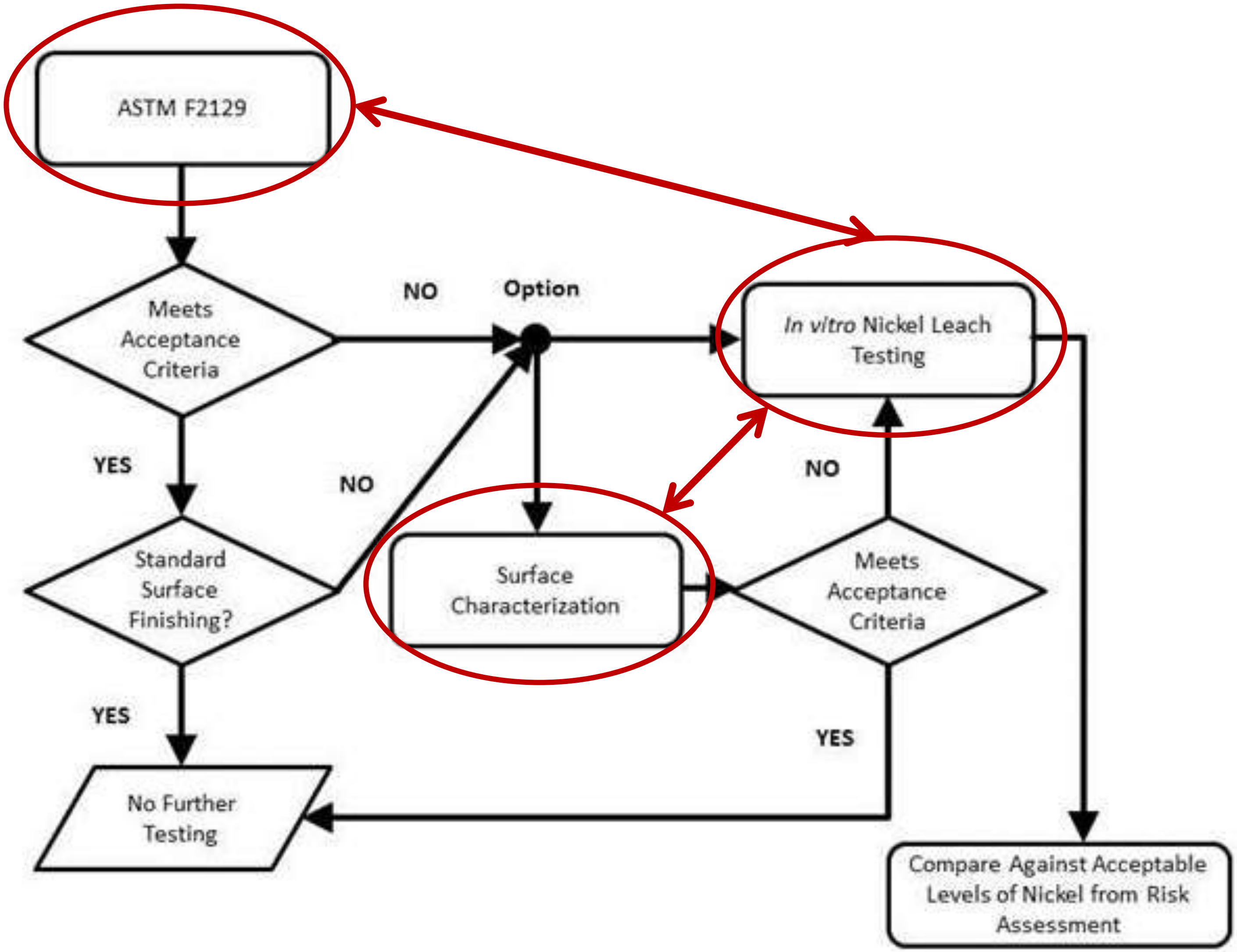
OT→ ~9 micron deep pits

Elemental Analysis Summary

- SP and MP explants: no change in Ni/Ti ratios
- AF explants: sig. lower Ni/Ti ratios in corroded regions
- OT explants: similar Ni/Ti ratios in corroded regions



Discussion



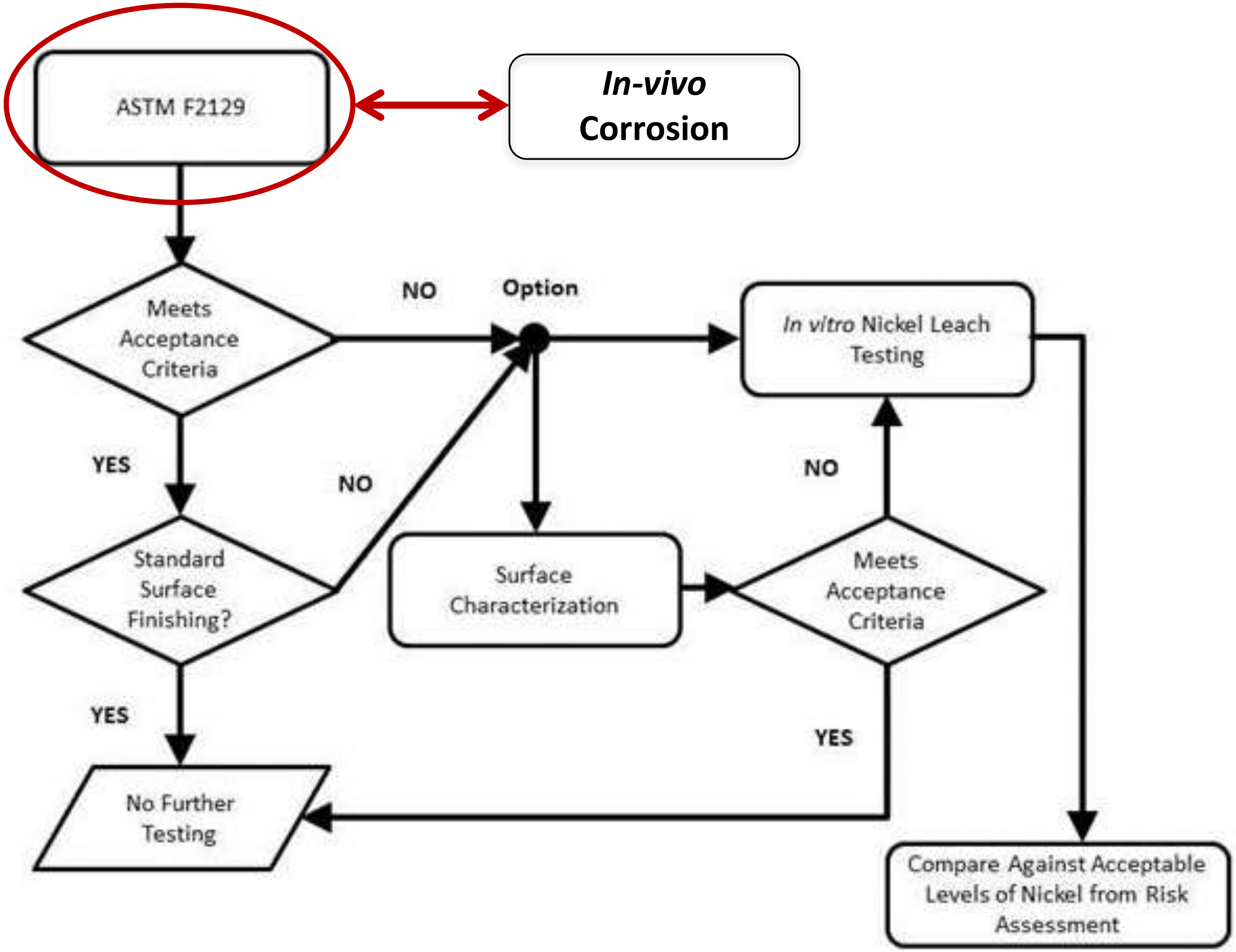
ASTM F2129
Meets Acceptance Criteria
NO
Option
In vitro Nickel Leach Testing
YES
NO
NO
Standard Surface Finishing?
Surface Characterization
Meets Acceptance Criteria
YES
YES
No Further Testing
Compare Against Acceptable Levels of Nickel from Risk Assessment

Conclusions

Bench Testing Correlations

- Ni release (uniform corrosion) is not correlated to breakdown potentials from ASTM F2129 testing
- Oxide thickness and composition provides insight into Ni release

Discussion



ASTM F2129
In-vivo Corrosion
Meets Acceptance Criteria
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In-vitro to In-vivo Correlations

- Ni release
  - *In-vitro*: OT > SP > AF > MP (uniform corrosion)
  - *In-vivo*: OT > AF > SP > MP (localized + uniform corrosion)
- Pitting Corrosion
  - E_b > ~600 mV → no localized corrosion observed
  - E_b < ~200 mV → localized corrosion observed

FDA

Acknowledgements

- Matthew Di Prima, PhD
- Phillip Stafford, PhD
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CONFLUENT

cpi Critical Path Initiative
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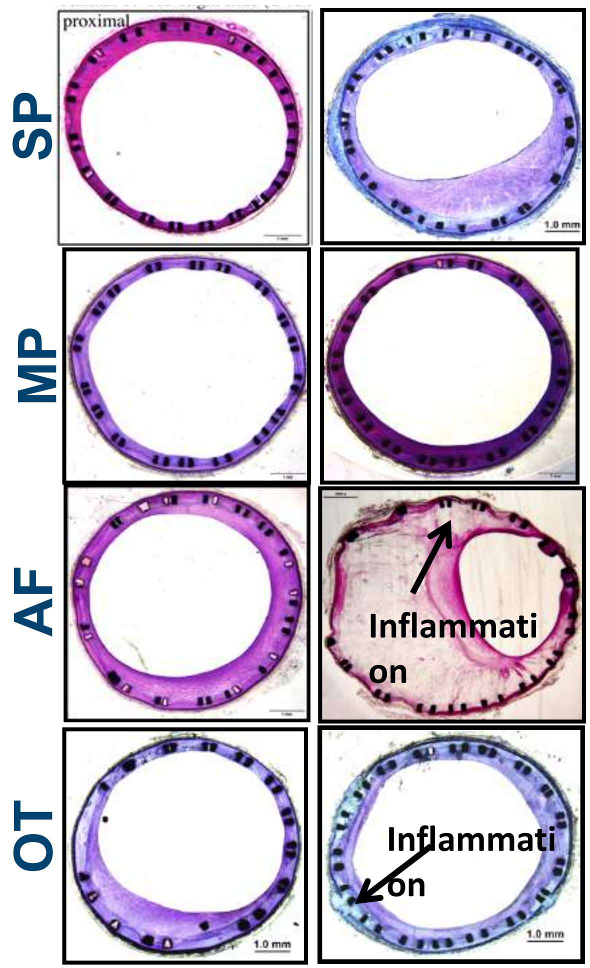
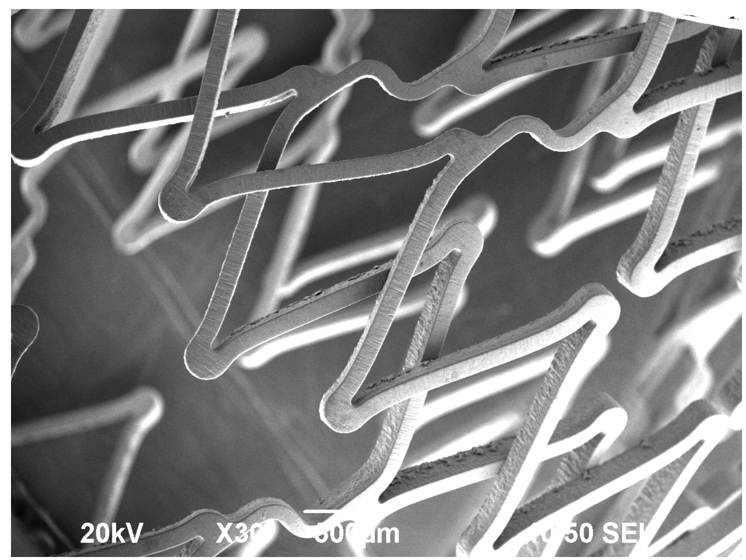
Upcoming features:

Biologics



Overlapped stents



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    - *In-vivo*: OT > AF > SP > MP (localized + uniform corrosion)
- Pitting Corrosion
    - E_b > ~600 mV → no localized corrosion observed
    - E_b < ~200 mV → localized corrosion observed