

# The PAD Patient and the Impact of Paclitaxel Device Therapy

## Pan-Industry Presentation

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# Primary concern is the safety of our patients and the enhancement of their lives



Industry has come together to collect additional data and provide additional analyses.



Collaboration and data transparency are paramount to inform the Healthcare Community and, importantly, the patients.

# PAD: Patient Experience

Afflicts over 8 million Americans and 200 million people worldwide.<sup>1,2</sup>

Third-leading cause of cardiovascular morbidity behind coronary heart disease and stroke.<sup>2</sup>

## Association with Other Diseases



Cerebrovascular disease



Coronary heart disease



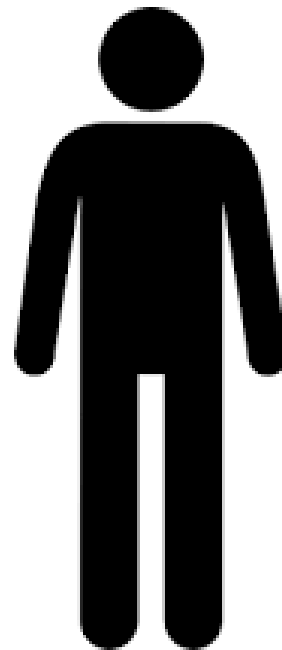
Renal disease



Hypertension



Hyperlipidemia



## Quality of Life Impact



Reduction in mobility



Pain + discomfort



Reduction in self-care



Anxiety + depression



Inability to “break the cycle”

1. Selvin E and Erlinger TP. Circ 2004;110:738-40.  
2. Fowkes FGR, et al. Lancet 2013;382:1329-40.

# PAD: Patient Experience

Treating claudicants includes both Quality of Life and Cardiovascular Risk Factors.

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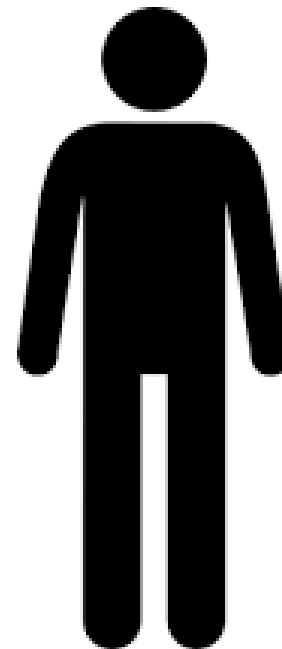
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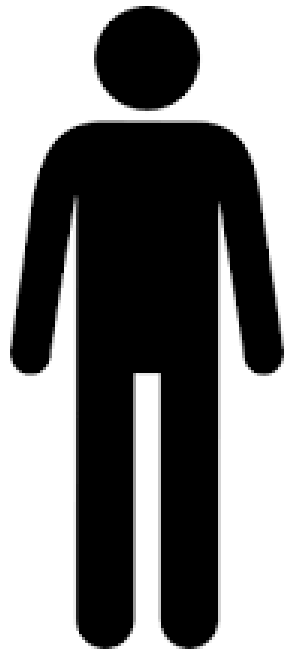


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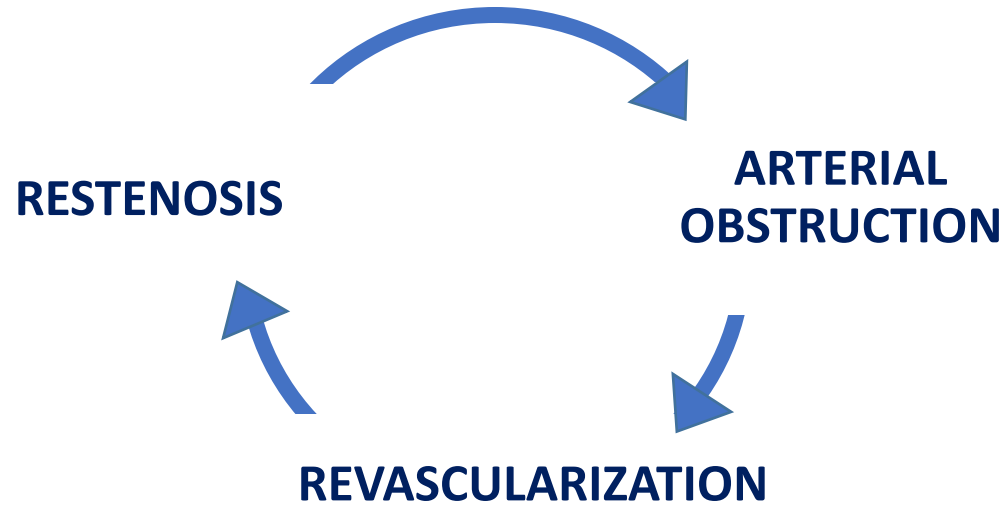
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## Cardiovascular Events



Association with higher risk of major cardiovascular events (stroke and myocardial infarction)<sup>3</sup>

# PAD: Treatment Paradigm

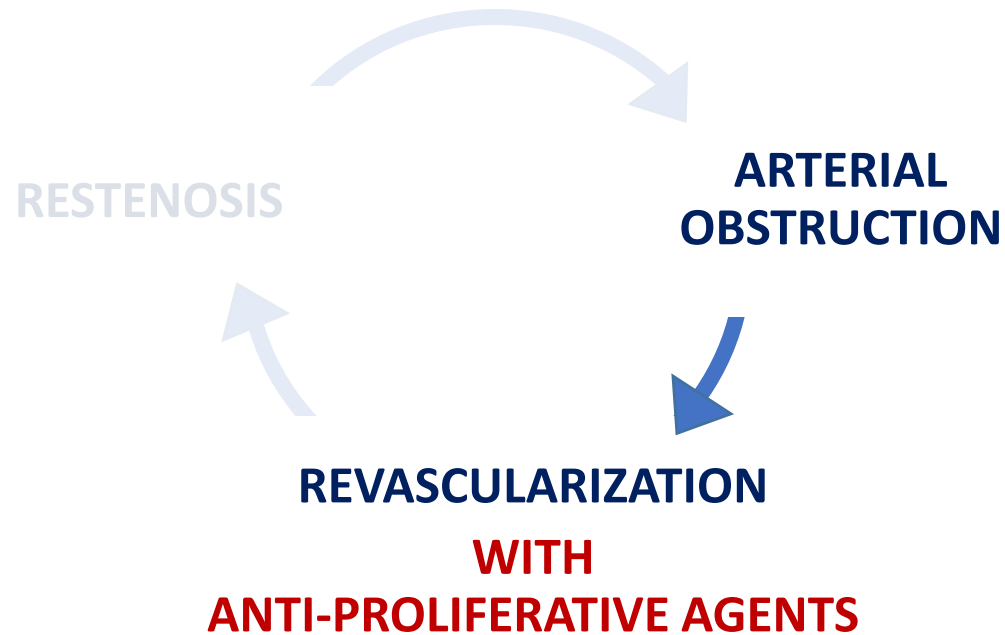


Revascularization is an important treatment option for claudicants...

...but it is not benign, and risks include mortality, morbidity, infection, wound complications, as well as additional revascularization procedures.<sup>1</sup>

1. Klein AJ, et al. Catheter Cardiovasc Interv 217;90:E90-E110.

# PAD: Treatment Paradigm



- Paclitaxel devices have consistently reduced restenosis over non-drug devices
- –limus-based devices failed to show increased effectiveness over conventional controls<sup>1,2</sup>
- The benefits are reducing restenosis AND lowering rates of revascularization and its associated risks

1. Duda SH, et al. J Endovasc Ther 2006;13:701-10.

2. Lammer J, et al. J Vasc Surg 2011;54:394-401.

# Current Status

“For most patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents should generally be used until additional analysis of the safety signal has been performed.”

- Food and Drug Administration Update March 15, 2019

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Decline and stagnation of paclitaxel device use



Patients relegated to inferior treatment or deferring treatment altogether



Consequences may be patients returning for revascularization

- Increased risks related to revascularization procedures
- Increased costs to healthcare systems
- Loss of quality of life
- Higher cardiovascular risks



# Limitations of Existing Analyses

- Individual randomized trials not designed for mortality analyses
- Heterogeneity of trials (patient, lesion, and previous treatment characteristics, study design, etc.)
- Paclitaxel exposure before and after randomization was not always recorded
  - Patients who require target lesion revascularization frequently receive paclitaxel during reintervention
- Confounding effect of revascularization procedures
  - Control patients exhibited more revascularization procedures
  - These patients are treated differently
- Patients lost to follow-up affect completeness of vital status

# Industry's Call to Action

- FDA prompted working collaboration across industry
- Additional vital status data were collected by industry sponsors
  - Vital status data collection of patients lost-to-follow-up within completed studies
  - Additional vital status data collection of ongoing studies
- Additional patient-level analyses were performed by industry sponsors
  - Inclusion of additional vital status data
  - Inclusion of “as-treated” and “modified as-treated” analyses
  - Analysis of independent predictors of mortality
- Data transparency for analyses by independent parties

# Findings From Industry Analyses

- Higher relative risk of mortality is not demonstrated in all studies
- For studies with 5-year data, modified as-treated analysis of additional vital status data shows no mortality signal
- No clustering of adverse events or causes of mortality
- No paclitaxel dose-mortality relationship
- No plausible biologic association of paclitaxel to mortality
  
- Predictors of mortality are those expected from a PAD patient population
  - Age, renal failure, diabetes, cardiovascular disorders
  - Paclitaxel is NOT a predictor of mortality

# Industry Presentations Placeholder

# Response to FDA Questions 1 – 6

FDA Question	Response
1. Presence of Signal	<ul style="list-style-type: none"><li>• No significant mortality difference between paclitaxel and non-paclitaxel devices</li></ul>
2. Class Effect	<ul style="list-style-type: none"><li>• Cannot conclude a common class effect for late mortality<ul style="list-style-type: none"><li>• Inconsistent observations across studies and sponsors</li><li>• Differences in device platforms</li></ul></li></ul>
3. Impact of Missing Data	<ul style="list-style-type: none"><li>• Previously missing vital status data introduced uncertainty</li><li>• Updated vital status information reduces observed mortality difference</li></ul>
4. Subgroup Analysis	<ul style="list-style-type: none"><li>• Predictors of mortality are those expected from PAD patient population, not paclitaxel</li><li>• No clear treatment interactions by subgroups</li></ul>
5. Cause of Death	<ul style="list-style-type: none"><li>• No clustering of adverse events or mortality patterns to support a causal mechanism</li></ul>
6. Paclitaxel Dose/Mortality Relationship	<ul style="list-style-type: none"><li>• No paclitaxel dose-mortality relationship observed</li></ul>