

Stent Thrombosis: The Implications of Broader DES Use

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Broader Use of DES and its Implications

- Earlier discussions focused on the risk of DES thrombosis associated with CYPHER® and TAXUS™ *when used in accordance with their approved indications.*
- However, since their approval in 2003 and 2004 (respectively) they have been implanted in an expanding number of patient and lesion subsets for which they are **not** currently indicated.

Broader Use of DES and its Implications

- Current data (i.e., post market studies) suggest that the majority of DES are implanted in patients and lesion subsets that are not indicated in their label
- This use-pattern can be typical of promising and rapidly adopted medical interventions
- Can be difficult to determine whether an observed problem is inherent to the **device** or whether it resulted from **inappropriate use**

Broader Use of DES and its Implications

- FDA does not regulate the practice of medicine
- While physicians can decide to use a device “off-label” for a particular patient, manufacturers may not promote such use
- If a manufacturer wants a new indication added to the device’s label, they must provide FDA with data to support that expanded use

Ongoing Trials

Several important studies with broad public health implications are currently underway:

- **SYNTAX** (Boston Scientific)
 - Randomized trial comparing PCI with TAXUS stents to CABG for patients with complex coronary disease (Left main and 3-vessel disease)
- **FREEDOM** (NIH)
 - Randomized trial comparing Cypher/Taxus vs. CABG in diabetics
- **HORIZONS AMI** (Cardiovascular Research Foundation)
 - Randomized trial comparing TAXUS to BMS and two different anticoagulation regimens in patients having a heart attack (STEMI).

*** Additional randomized, controlled studies are needed to better understand the risks and benefits of broader DES use, as well as to support additional indications for use.**

Broader Use of DES and its Implications

Specific *patient* subsets that may influence the risk of stent thrombosis:

- Diabetes (insulin and non-insulin dependent)
- Renal dysfunction
- Multi-vessel disease

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Specific *lesion* subsets that may influence the risk of stent thrombosis:

- Left Main disease
- Bypass Grafts
- Chronic Total Occlusions
- In-Stent Restenosis
- Bifurcation lesions
- Long Lesions and Overlapping DES
- Small Vessels (<2.5mm diameter)
- Acute Myocardial Infarction (thrombus containing)
- Multiple Stents per Vessel

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Risk of stent thrombosis may be modified in these subsets

- Time-points at which patients are most at risk may vary (consider early *and* late)
- Uncertainty regarding the optimal duration and effectiveness of dual antiplatelet therapy in these subsets
- Long term follow-up data is needed

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- FDA has asked both Boston Scientific and Cordis to perform specific analyses on these patient and lesion specific subsets
- A standardized definition for stent thrombosis, developed by the Academic Research Consortium, were used for their analyses and presentations at the request of FDA.

Broader Use of DES and its Implications

- Data for these patient and lesions specific subsets are available from a variety of potential sources:
 - Randomized controlled trials
 - Pivotal studies
 - Label expansion studies
 - Other: cost-effectiveness, delivery of care, head-to-head stent comparison studies, etc.
 - Registry studies
 - Condition of approval studies ($n \geq 2000$)
 - Other single-arm, consecutive, “all-comer” registries
 - *Meta-analyses*

Challenges in Data Interpretation

1. Frequent overlap between subsets and their definitions
 - Multiple vessel disease ↔ multiple stents ↔ overlapping stents
 - Diabetes ↔ renal dysfunction
2. Variable and/or evolving clinical practice patterns
 - Anti-platelet therapy, procedural techniques, adjunctive treatments, etc.
3. Lack of adequate control arms
 - Comparative risk/benefit difficult to assess
 - Accepted standard of care may not exist (e.g., bifurcations)
 - Generally limited data on bare metal stents in complex lesions
4. Data may not capture adherence to anti-platelet therapy

Challenges in Data Interpretation (cont'd)

5. Studies may be under-powered for patient- and lesion-specific subset analyses
6. Meta-analyses may fail to capture patient-level data
7. Definition of stent thrombosis is variable
 - Need for standardization
8. Length of follow-up varies across studies
9. Few long term data are available

Conclusions

- Data on the risk of stent thrombosis come from a variety of studies, each having its own strengths and weaknesses, and each contributing its own unique piece to the larger picture.
- We need to understand what these studies are telling us about the risk of stent thrombosis in the broader population of patients who receive DES.