

Impact of Stent Thrombosis on Outcomes of Death and MI after Drug-Eluting Stenting

Importance of Standard Definitions and Analytical Methods

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Patient Oriented Outcomes

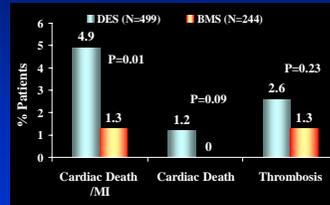
Net Clinical Benefit

- The outcome of **all cause mortality or myocardial infarction** is the optimal measure of overall risk and benefit of a device or drug treatment for coronary artery disease.
 - Over long-term follow-up cardiac specific mortality may be a better measure but requires careful adjudication
 - Are mechanistic outcomes related to treatment specific events such as stent thrombosis important, even in the absence of a measurable effect on net clinical benefit

Death and MI Outcomes

Role of Late Stent Thrombosis Mechanism

BASKET-LATE Trial – 743 pts from BASKET cost-effectiveness trial followed for 12 months after clopidogrel completion

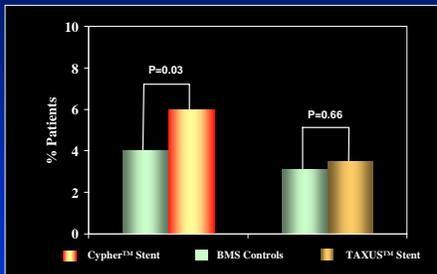


Thrombosis Events
• Angiographic confirmation
• Cardiac death/TV MI

Pfisterer M. Presented at ACC 2006

DES 'Meta Analysis' - 3 Year Results

Death and Q wave MI

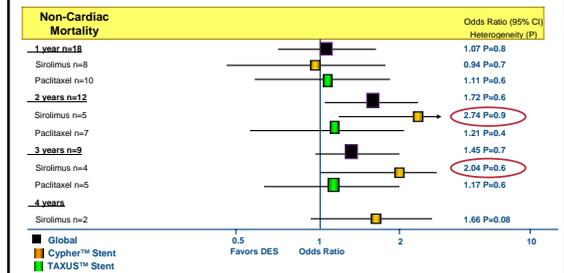


Camenzind et al. ESC/WCC 2006

Non-Cardiac Mortality

Nordmann Meta-Analysis

SES showed an increase in non-cardiac death after 1 year compared to BMS



DES = drug-eluting stent; BMS = bare metal stent; CI = confidence interval.

Based on presentation by Nordmann, ESC/WCC 2006

Death or MI after Stenting

Not a Single Mechanism

- Non-cardiac causes
- Progression of disease outside of the stented segment
- Procedure complications
- Restenosis – “malignant”, occlusive, adverse outcome from restenosis treatment
- Stent thrombosis

Stent Thrombosis

Impact on Overall Death and MI Rate

- Are there differences in thrombosis risk between stent types that outweigh efficacy benefits?
- Are there differences that should impact overall treatment decisions (DES vs BMS; Medical Rx vs Revascularization; Stent vs. CABG)?

The failure to detect a statistically significant difference in death or MI between groups with different rates of stent thrombosis does not exclude the importance of a stent thrombosis mechanism on death or MI outcome.

Defining Stent Thrombosis

ARC Definitions and Method of Analysis

- **Timing**
 - Early (0-30 days)
 - Late (31 days – one year)
 - Very Late (> one year)
- **Level of Certainty**
 - Definite
 - Probable
 - Possible

Stent Thrombosis Proposed Standard Definitions

- **Definite/Confirmed**
 - Acute coronary syndrome AND
 - [Angiographic confirmation of thrombus or occlusion OR
 - Pathologic confirmation of acute thrombosis]
- **Probable**
 - Unexplained death within 30 days
 - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
- **Possible**
 - Unexplained death after 30 days

Proposed Standard Definitions

Other Considerations

- What is the impact of intervening TLR?
 - Excluding or censoring these events introduces bias and does not assess initial strategy
 - Inclusion of the events by intention-to-treat may not reflect the index device risk, but rather the restenosis Rx (brachytherapy, subsequent DES)
 - Long-term outcomes of death and MI may be different for events associated with prior restenosis versus primary events (slower progression, preconditioning)

Analysis of ST by ARC Definitions

- **Timing** – To evaluate mechanistic differences it will be important to assess overall rates as well as within early, late, and very late classifications.
- **Level of Certainty**
 - Possible ST may include unexplained deaths not due to ST
 - Unlikely to be the only signal of an increased risk for ST
 - May dilute differences that are based on higher level of certainty.
 - ST assessment should include overall rates as well as definite or probable separately.

Analysis of ST by ARC Definitions

- **Primary ST**
 - Prior TLR is a major factor that may modify rates and outcomes
 - Analyses must include overall as well as primary rates in order to assess for possible mechanistic differences in stent thrombosis

Conclusions

- The major safety outcome of drug-eluting stenting relative to different devices or other treatment strategies is assessed best by measures of overall mortality, cardiac mortality, or composites of mortality and MI.
- Stent thrombosis as a mechanism impacting overall safety remains critical even if no measurable effect on mortality or MI outcomes.
 - Definitions and analytical methods are critical
 - Small or immeasurable effects may become significant with larger numbers and increasing complexity of lesions/patients being treated