Perioperative Management of the Surgical Patient with a Drug-Eluting Stent

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Objectives

- Review the history of Drug Eluting Stents (DES)
- Discuss the recent controversy surrounding DES
- Outline the latest recommendations for managing surgical patients with a DES
History

- 1977-87 – Balloon Angioplasty
  - 6 month restenosis rate 32-40%
- 1986 – First Bare Metal Stent
  - Introduced into clinical practice early 1990’s
  - Initial 6 month restenosis rate 17-32%
  - Now much closer to 1.6%
Balloon vs. Stent

Drug-eluting stents designed to address the problem of restenosis

- 2003 – The Cypher Stent (sirolimus)
- 2004 – The Taxus Stent (paclitaxel)

Average costs
- BMS $800
- DES $2200
Cypher

Cypher

Cypher
Cypher

Cypher

Cypher
The Cypher Stent

Sirolimus

- Potent immunosuppressant and antiproliferative effects
- A macrolide antibiotic (rapamycin)
- Inhibits response to IL-2
- A product of a bacterium discovered on Easter Island
- Initially approved in renal tx recipients
The Cypher Stent

Why Would Anyone Take a Drug-Eluting Stent Seriously?

Analysis of 1-Year Clinical Outcomes in the SIRIUS Trial
A Randomized Trial of a Sirolimus-Eluting Stent Versus a Standard Stent in Patients at High Risk for Coronary Restenosis

David R. Holmes, Jr, MD; Martin B. Leon, MD; Jeffrey W. Moses, MD; Jeffrey J. Popma, MD; Donald Cutlip, MD; Peter J. Fitzgerald, MD, PhD; Charles Brown, MD; Tina Fischer, MD; Shing Chiu Wong, MD; Mark Molder, MD; David Sneed, PhD; Richard E. Knutr, MD, MSc
The SIRIUS Trial

- 1058 pts
- 53 North American centres
- double blind randomized to BMS or (investigational) sirolimus-eluting stent
- Primary end point: failure of target vessel


The SIRIUS Trial

- At 9 months, pts requiring revascularization was 4.1% in the sirolimus limb vs. 16.6% (p<0.001)
- At 12 months, the difference increased to 4.9% vs. 20% (p<0.001)
- No difference in death or MI rates
- 3 months of dual antiplatelet therapy

Getting Even More SIRIUS

- C-SIRIUS\(^1\)
- E-SIRIUS\(^2\)
- Pooled analysis of the 3 SIRIUS Trials (n=1510)
  - In-stent restenosis 38.5% in control group
  - Only 3.1% in sirolimus group


Taxus

- Name given to a genus of yews
- *Taxus brevifolia*
Taxus

- Taxus canadensis

The TAXUS Stent
Paclitaxel

- Chemotherapeutic agent
- Interferes with microtubule function
- Induces apoptosis
- Inhibits production of IL-2

The TAXUS-IV Trial

One-Year Clinical Results With the Slow-Release, Polymer-Based, Paclitaxel-Eluting TAXUS Stent

The TAXUS-IV Trial

Gregg W. Stone, MD; Stephen G. Ellis, MD; David A. Cox, MD; James Herrlinger, MD; Charles O. Shaughnessy, MD; James Tiff Mann, MD; Mark Turco, MD; Ronald Caputo, MD; Patrick Bergin, MD; Joel Greenberg, MD; Jeffrey J. Pepma, MD; Mary E. Russell, MD; for the TAXUS-IV Investigators*

The TAXUS-IV Trial

- 1314 patients
- 75 US hospitals
- randomized to paclitaxel-eluting stent or BMS
- aspirin and clopidogrel for 6 months


The TAXUS-IV Trial

- At 12 months, target revascularization was 4.4% in paclitaxel arm vs. 15.1% (p<0.0001)
- Composite major cardiac adverse events 10.8% in paclitaxel arm vs. 20% (p<0.0001)
- Similar rates of cardiac death

FDA Approval

- FDA-approved indications were strict and limited
  - Lesions less than 30 mm
  - Clinically stable
  - No serious medical conditions
- 5 year follow-up of original patients
- DES soon represented > 80-90% of all interventions in US, >60% Canada

Trouble in Paradise?
Aim: To determine the incidence and risk factors of stent thrombosis after DES implantation in real-world practice

Risk Factors for Stent Thrombosis

- 1545 patients
- Prospective, all pts who had DES
- Heparin +/- IIb/IIIa
- All had aspirin & clopidogrel premed
- All took aspirin indefinitely, clopidogrel to at least 6 months
- Long term follow-up (median 19.4 months)

Results

- Incidence of stent thrombosis at 19.4 months = 0.8% (95% CI 0.5-1.3%)
- Recent data for BMS = 0.5 – 2.0%
- Incidence of late thrombosis = 0.6%


Results

- Mortality from late thrombosis = 40%

Independent Predictors of Stent Thrombosis

1. Premature Interruption of Antiplatelet Therapy
2. Primary Stent in Acute MI
3. Total Stent Length


Independent Predictors of Stent Thrombosis

1. Premature Interruption of Antiplatelet Therapy (19.21, p<0.001)
2. Primary Stent in Acute MI (12.24, 0.01)
3. Total Stent Length (1.04, 0.037)

Independent Predictors of Stent Thrombosis

1. Premature Interruption of Antiplatelet Therapy (24.79, <0.001)
2. Primary Stent in Acute MI (74.22, 0.001)
3. Total Stent Length (1.04, 0.048)

Study Drawbacks

- Nonrandomized
- Observational
- Underpowered to show any differences between sirolimus vs. paclitaxel stents

BASKET-LATE

- Aim: To determine incidence of late thrombosis in DES vs. BMS after discontinuation of clopidogrel

BASKET = Basel Stent Kosten Effektivitats Trial
J Am Coll Cardiol; 2006 Dec 19;48(12):2592-5.

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BASKET-LATE

- 746 consecutive patients with 1133 stents
- Randomized 2:1 to DES:BMS
- Followed for 1 year following discontinuation of clopidogrel (18 mos)
- Primary outcomes: Death and MI

J Am Coll Cardiol; 2006 Dec 19;48(12):2592-5.
BASKET-LATE: Results

- After discontinuation of clopidogrel, composite rates of cardiac death and MI:
  - DES: 4.9%
  - BMS: 1.3%
- Rates of late thrombosis:
  - DES: 2.6%
  - BMS: 1.3%

J Am Coll Cardiol; 2006 Dec 19;48(12):2592-5.

BASKET-LATE: Comments

- Strict control of clopidogrel timing
- Compares DES vs. BMS
- Not a study that defines the optimum length of clopidogrel requirement

J Am Coll Cardiol; 2006 Dec 19;48(12):2592-5.
Other Supporting Articles


WCC 2006 – Panel Statements

- Panel of cardiologists reviewing DES data
- Each one of them stated that, if implanted with a DES, they would take aspirin and clopidogrel *forever*
- (one qualified his statement with “if I could afford it”)
Postulated Reasons for DES Thrombosis

- Delayed endothelialization
- Incomplete neointimal healing
- Hypersensitivity reactions
- Endotheliopathy

FDA Statement - Sept. 2006

- New data suggest small but significant increased risk of stent thrombosis in DES
- Not enough data to draw conclusions
- The risks and causes are unclear
- All data will be reviewed and future action may occur (such as labeling change or more studies)
The FDA Follow-up Response

- Special meeting convened Dec 7-8, 2006 to examine safety of DES
- Estimated 60% of DES are used off-label
- When used on-label, benefits outweigh risks
- Dual antiplatelet therapy should continue for 12 months for both sirolimus and paclitaxel stents (as optimal duration is unknown)

The Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society joint statement on drug-eluting stents

- Goal: to summarize available evidence relating to DES thrombosis
- Timing: increasing data supporting DES late thrombosis and questions surrounding safety and role of DES

Can J Cardiol, 2007;23(2):121-123.
CAIC and CCS Joint Statement

- Agrees with FDA Advisory Panel that the risk of DES late thrombosis is small, but higher than BMS
- Risk likely balanced by reduction in vessel narrowing

Can J Cardiol, 2007;23(2):121-123.

CAIC and CCS Joint Statement

Recommendations for DES Use

- Always consider benefits & risks when choosing DES vs. BMS
- Use extra care when using DES in off-label applications (increased risk of late thrombosis)
- Use meticulous technique
- Do not use DES in pts who cannot tolerate dual antiplatelet therapy
- Do not use DES in pts with upcoming surgery

Can J Cardiol, 2007;23(2):121-123.
CAIC and CCS Joint Statement
Recommendations for Antiplatelet Therapy

- All pts with DES should remain on aspirin 81-325 mg daily and clopidogrel 75 mg daily for at least one year
- Consider longer term dual antiplatelet therapy in pts thought to be higher risk (multiple stents, left main stent, bifurcation)

Can J Cardiol, 2007;23(2):121-123.

CAIC and CCS Joint Statement
Recommendations for Antiplatelet Therapy

- If discontinuation of both antiplatelet agents is required in a high-risk pt, consider heparin therapy
- No evidence to support restarting clopidogrel in those pts with DES who have finished their course and remain event-free on monotherapy

Can J Cardiol, 2007;23(2):121-123.
What About the Perioperative Patient Presenting with a DES?

Case Report

- 56 yo male with ESRD 2° to type II DM
- Known CAD
- Had a cath 8 months prior to scheduled renal tx: 1 BMS, 3 DES
- Stopped clopidogrel and aspirin 7 days prior to surgery

Case Report

- Uneventful surgery and 45-min stay in PACU
- Transfer to ward: Chest pain
- Emergent transfer to cath lab
- 100% occlusion of DES within RCA

J Clin Anes 2007;19:386-396

Case Report #2

- Pt received 1 BMS and 2 DES for stable angina
- Rx: clopidogrel 75 mg/d, aspirin 100 mg/d
- Both stopped at 12 weeks for knee arthroscopy

J Am Coll Cardiol, 2004 Feb 18;43(4):713
Case Report #2

- 2 hours post-op, chest pain
- MI diagnosed by EKG and enzymes
- Angiography: total occlusion of both paclitaxel-eluting stents, BMS was clean.

J Am Coll Cardiol, 2004 Feb 18;43(4):713

The Perioperative Period

- Most hospitals do not have a protocol
- Stent thrombosis is still a rare event
- Over 8 Million people with DES
- Last year alone, 35000 implanted in Canada
Risk of Surgery After Stent Implantation

- High risk first described in 2000 with BMS
- 8 out of 25 pts undergoing noncardiac surgery within 2 weeks of stenting died
- 7 of the 25 had an acute MI (6 of these died)

J Am Coll Cardiol 2000;35:1288-94

What is the Problem in the Perioperative Period?

- Surgery induces hypercoagulable state
- Pts often asked to stop aspirin and/or clopidogrel without consulting cardiology/anesthesia
- Mortality from DES thrombosis is 40%
- (Mortality from BMS thrombosis is 7-9%)
Wake Forest University Health Sciences Protocol

- Stop clopidogrel 5 days pre-op
- Continue aspirin throughout
- Admit pt 2 days pre-op for bridging therapy
- Start IV heparin and eptifibatide
- Stop infusions 6 hours pre-op
- Load with clopidogrel post-op, 600 mg

APSF Newsletter, Winter 2006-2007

Successful management of pts with DES presenting for elective, non-cardiac surgery

- 5 days pre-op
  - Stop clopidogrel
- 3 days pre-op
  - Admit to CCU
  - Start tirofiban infusion
  - Start heparin infusion

Successful management of pts with DES presenting for elective, non-cardiac surgery

- 6 hours pre-op
  - Stop both infusions

- POD 1
  - Clopidogrel 300 mg PO
  - Heparin 5000 mg SC BID

- Continue aspirin throughout

Is Bridge Therapy Necessary?

- Lack of guidelines
- Lack of resources
- Heparin – is it enough?
- Is bridging the safest alternative?
**Recommendations: Science Advisory from AHA, ACC, SCAI, ACS, ADA**

- Discuss with pt prior to implantation
- If pt will require surgery, consider BMS
- Educate pt
- Contact cardiologist
- Postpone elective procedures
- Continue aspirin, restart clopidogrel ASAP

*Circulation 2007;115:813-818.*

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**The Important Stuff**

- Delay elective surgery for 12 months post-implantation of DES
- Every effort should be made to continue dual antiplatelet therapy
- Even if clopidogrel must be stopped, aspirin should continue throughout the perioperative period
Managing the Antiplatelet Agents

What You Need to Consider

- Date of Stent Implantation
- Type of Stent
- Type of Surgery (Risk of Bleeding)
- Pt factors that suggest higher risk of thrombosis (renal failure, diabetes, low EF)
- Technical details of stent placement (length, diameter, location)
Front of Patient Card

Name: ________________________

You have ____ bare metal stent(s) inserted on ________
____ drug coated stent(s)

Stopping Aspirin and Clopidogrel early can CAUSE A HEART ATTACK!

Interventional Cardiologist ________________________

Back of Patient Card

ASA (Aspirin®) and Clopidogrel (Plavix®) prevent clots in blood vessels, reduce risk of heart attacks and prevent clots in newly placed stents.

Take ASA 325mg daily for _____ months, then 81mg daily for life.

Take Plavix everyday for at least __________

DO NOT STOP these medications early without asking your cardiologist.
Stopping Clopidogrel: Perception vs. Reality

- Risk is low (0.6% per year)
- Mechanical valve: ~3% per year without anticoagulation (vs. 1% per year with)
- Off-therapy window only ~10 days

Take Home Messages

- Premature discontinuation of antiplatelet therapy is the most important predictor of DES thrombosis
- Risk of late stent thrombosis in DES is 0.6% per year
- Mortality from DES thrombosis is 40%
Thank You

Boston Scientific (BSX-N)
World’s Top Selling Drugs in 2005

1. Lipitor ($12.9 Billion)
2. Plavix ($5.9 Billion)
3. Nexium
4. Advair
5. Zocor
6. Norvasc
7. Zyprexa (olanzapine)
8. Risperdal
9. Prevacid
10. Effexor

Source: Forbes 2006