Drug-Eluting Coronary Stents

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Surgical Grand Rounds
Resident Debate
Outline

- Coronary Artery Disease
- Evolution of Percutaneous Coronary Intervention
- Drug-Eluting Stents
- CABG vs PCI
- Current/Future Trials
Coronary Artery Disease

- **Etiology**
  - Atherosclerosis
  - Internal elastic membrane rupture and regeneration
  - Endothelial proliferation with lipid deposits
  - Formation of plaque

- **Worldwide Incidence of Death**
  - 3.8 million men yearly
  - 3.4 million women yearly

...'worst episode ever'
Treatments for CAD

- **Medical**
  - Aspirin, beta blockers, statins, ACE inhibitors, Ca Channel blockers, ARBs, platelet inhibitors, heparinization, tPA

- **Surgical**
  - CABG: Reversed Saphenous Vein, Internal Thoracic Arteries, Radial Artery, off pump, robotic

- **Interventional**
  - IABP, balloon angioplasty, bare metal stents (BMS), drug-eluting stents (DES)
Percutaneous Coronary Intervention (PCI)

- Balloon dilation angioplasty successfully used in 1978 for single vessel, isolated lesions
  - Improved technology
  - Increasing experience
Stenting

- **1850s**: Dentist Charles Stent created metal scaffolding for aligning teeth\(^1\)
- **1960s**: Charles Dotter described concept of stenting after dilation angioplasty
- **1980s**: Sigwart et al introduce coronary stents\(^2\)
Stents

- Structure... Now over 40 designs
  - Flexibility
  - Trackability
  - Radiopacity
  - Scaffolding
  - Corrugated vs Slotted Tube
  - Materials
  - Covered Stents/Coated Stents
    - Gold
    - Silicon Carbide
    - Heparin
Problems with Stents

- **Thrombosis**
  - Acute, subacute, late
  - No difference between BMS and DES

- **Hypersensitivity**
  - Dyspnea, bronchospasm, urticaria, hypotension, asymptomatic bradycardia

- **Restenosis**...the ‘achilles heel’
Mechanism of Restenosis

- Elastic Recoil of Vessel
  - immediate
- Negative Remodeling
  - late constrictive process
- Vessel Injury
- Neo-Intimal Hyperplasia
  - stress induced protein kinases
  - growth factors and cytokines
  - smooth muscle cell proliferation and migration to intima
  - thrombus/platelet activation
  - Formation of **Matrix**
Restenosis Risk Factors

- Diabetes
- Lesion Length
- Use of Multiple Stents
- Inadequate Stent Expansion
- Gaps Between Stents
- Luminal Cross-section Area after Stenting
Restenosis Rates

- **Balloon Angioplasty:**
  - 40% rate of angiographic restenosis 6 months after PTCA, with majority having recurrent symptoms\(^6\)
  - 20-30% required clinically driven repeat target lesion revascularization

- **Bare Metal Stents:**
  - Prevent Recoil and Negative Remodeling, but not Intimal Hyperplasia
  - 20-30% angiographic restenosis at one year
  - 10-15% target lesion revascularization
Preventing Restenosis

- **Brachytherapy**
  - Catheter based delivery of radiation to vessel
  - Reduced rate of intimal hyperplasia/restenosis
  - Too many late effects such as thrombosis

- **Addition of Abciximab**
  - Stone et al, NEJM 2002
    - N = 2082
    - PTCA with/without Stent, abciximab
    - Death, CVA, MI, revascularization occurred least in group with stent and abciximab
Preventing Restenosis

- Is there any other way to reduce restenosis?
Drug-Eluting Stents

- **Delivery Mechanism**-
  - Biostable or bioerodible polymer with controlled release of drug, usually over 14–30 days
  - Non-thrombogenic
  - Inert

- **Delivered Goods**
  - Lipophilic Medications
    - Locally absorbed
    - Less variable concentration
  - Various Classes of Drugs
    - Anti-inflammatory, antiproliferative, immunomodulators...
Stents Eluting Drugs

- Sirolimus
- Everolimus
- Paclitaxel
- Beta-Estradiol
- Dexamethasone
Sirolimus

- **Rapamycin**
  - Produced by *Streptomyces hygroscopicus*, a fungus discovered on Easter Island
  - Macrolide antibiotic
    - Antifungal
    - Anti-tumor
    - Immunosuppressant
Sirolimus

- Arrests smooth muscle cells in G1 phase via FK506 binding protein and p27
- Inhibits proliferation and migration of vascular smooth muscle cells
- First DES approved by FDA in 2003

- the **Cypher**
  Johnson and Johnson
First In Man Study\textsuperscript{9} Brazil and Netherlands

- Single de novo coronary lesions
  - \(<18\text{mm length, 3.0-3.5 mm diameter}\)
- Tested fast and slow release Sirolimus stents
- Followed at intervals with Intravascular Ultrasound (IVUS)
- Found 0\% restenosis at 24 months
More Sirolimus Trials

- **RAVEL**\(^{10}\)
  - Randomized Double Blind Study
  - 238 patients with single coronary lesions, not including left main
    - 0% in-stent restenosis (ISR) at 6 months
    - 0% revascularization at 2 years

- **SIRIUS**\(^{11}\)
  - Multicenter Randomized Double Blind Study
  - 1058 patients with de novo coronary artery lesions, including diabetes and multivessel disease
    - 3.2% ISR at 8 months versus 35.4% in BMS
    - 8.3% ISR with diabetics versus 48.5% in BMS
      - Further benefit from those on GIIb/IIIa inhibitors
Paclitaxel

- Broad Spectrum Antineoplastic Agent
  - Ovary
  - Breast
  - Lung
  - Head and Neck
  - Esophagus

- TAXUS stent, Boston Scientific

- Pacific Yew Tree *Taxus brevifolia*
  - Found in Northwestern US and Canada
Paclitaxel Mechanism

- Enhances and stabilizes microtubule assembly

- Prevents mitosis, migration, endocytosis, and secretion
  - Cell arrest at $G_0$

- Lipophilic

- Cell remains viable

- Long lasting antiproliferative effect after short dosing
Paclitaxel Trials

**ELUTES**  
*n = 304 European Evaluation of Paclitaxel Eluting Stent*  
- At 6 months, DES restenosis rate was 3% vs 21% in BMS

**ASPECT**  
*n = 117 Asian Paclitaxel Eluting Stent Clinical Trial*  
- At 6 months, DES restenosis rate was 4% vs 27% in BMS

**TAXUS II**  
*n = 1314*  
- At 9 months, angiographic restenosis rate was 8% (versus 27% for BMS) and target revascularization rate was 3% (versus 11% for BMS).  
- At one year, major adverse cardiac events were significantly less (10.8% versus 20% in BMS).
DES vs BMS

- Indolfi et al: Meta-analysis\textsuperscript{13}
  - RAVEL, TAXUS, ASPECT, SIRIUS, ELUTES, DELIVER, SMART
  - N = 3680
  - DM population ranged from 13 to 29% in studies
  - MACEs occurred less frequently with DES (RR 0.40). Major Adverse Cardiac Events: MI, Death, Revasc
  - Significant decrease in need for revascularization (RR 0.30) for DES vs BMS
DES vs BMS

- Kong et al 2005 Meta-analysis¹⁴
  - Eleven trials, N = 5140
  - Significant reduction in target lesion revascularization (4% vs 13%) and major adverse cardiac events (8% vs 16%) with DES.
How does CABG weigh in?

- CABG vs Balloon Angioplasty
- CABG vs Bare Metal Stents
- CABG vs Drug-Eluting Stents?
PTCA vs CABG

- RITA-1 (Randomized Intervention Treatment of Angina) 1993-1998
  - N = 1011
  - No difference in mortality at 6.5 yr f/u
  - Angina 3x more frequent in PTCA
  - Similar costs after 5 years
  - 26% of PTCA patients later underwent CABG
PTCA vs CABG²

- **BARI** (Bypass Angioplasty Revasc. Investigation) 1996 - 2000
  - N = 1829
  - PTCA- more frequent revascularization (52% v 6%)
  - 5 year survival better with CABG* for diabetics (94% v 80%).
    * required IMA graft
  - Survival at 7 years better for CABG (76% v 56%)

- **EAST** (Emory Angioplasty v Surgery Trial) 1995 - 2000
  - N = 392
  - Non-significant late survival benefit in CABG for those with proximal LAD stenosis or diabetes
CABG vs PTCA

- Are results any better for PTCA with stents?
Stent vs CABG

- **SoS** (Stent or Surgery)\(^{15}\) 1999-2002
  - N = 988
  - Repeat revascularization 21% (stent) vs 6% (surgery) at 2 yr
  - In hospital events no different (CVA, death, MI)

- **ERACI II** (Argentina) 2001
  - N = 450
  - Repeat revascularization 14.8% (stent) vs 4.8% (surgery) at 1 yr

- **ARTS** (Arterial Revascularization Therapies Study) 2002
  - N = 205
  - No difference in death, CVAs, MIs for multivessel disease
  - Repeat revascularization 29.2% (stent) vs 7.3% (surgery) at 3 yr
Stent vs CABG

- Serruys et al 2001 NEJM\textsuperscript{16}
  - N = 1205
  - Studied multivessel disease
  - Rates of death, stroke, myocardial infarction were no different
  - Revascularization occurred in 16.8% of stented patients vs 3.5% in CABG group
Stent vs. CABG

- **New York Cardiac Registry, NEJM 2005**
  - N = 37,212
  - Observational Study
  - 3 yr survival rate favored Stenting
  - 3 yr ‘risk-adjusted survival rate’ favored CABG
  - Revascularization rate BMS > CABG
    - 7.8% vs 0.3% underwent subsequent CABG
    - 27.3% vs 4.6% underwent subsequent PCI
  - In hospital mortality rate CABG > BMS (650 vs 150 deaths)
Stent vs CABG

- Hoffman et al 2003 JACC
  - Meta-analysis
    - RITA, EAST, ERACI, CABRI
    - BARI, SIMA, ARTS, SoS
  - 13 randomized trials
    - N = 7964

- Revascularization
  - Stents: 15% more at 1,3 yrs

- Survival
  - Same at 1,3 yrs
  - 5 and 8 year data includes PTCA without Stents

- A. All Trials in Investigation
- B. Multivessel Disease Only
Stent vs CABG

- How about stents vs CABG in special scenarios?
Stent vs CABG in High Risk

- **AWESOME** trial\(^{19}\)
  - Angina With Extremely Serious Operative Mortality Evaluation
  - VA Multicenter, Randomized Trial
  - N = 2431
  - At least one risk factor
    - IABP
    - MI within 7 days
    - LVEF < 35%
    - Age > 70
    - Prior heart surgery
Stent vs CABG in High Risk

- **AWESOME** trial
  - 36 month survival rate
    - CABG: 79%
    - PCI: 80%
Stent vs CABG in Diabetes\textsuperscript{20}

- BARI, EAST, CABRI- survival at 8 years
  - CABG 76%
  - PCI 60%*
    - * before stent usage

- ARTS one year results in diabetics
  - Similar death rates (3.1% vs 6.3%, \( p = 0.40 \))
  - Similar MI rates (3.1% vs 6.3%, \( p = 0.40 \))
  - Revascularization Rates
    - CABG 3.1%
    - Stent 22%
CABG vs Stent in Diabetics
2006

- **New Developments**
  - **Drugs**
    - Clopidogrel: ADP-induced aggregation inhibitor
    - Ticlodipine: ADP-induced aggregation inhibitor
    - Abciximab: IIb/IIla Platelet Inhibitor
      - EPISTENT (12% reduction of TVR in diabetics)\(^\text{21}\)
  
- **DES in Diabetics**
  - RAVEL (12.2% revascularization with CYPHER vs 27.1% with BMS)
CABG vs DES??

- CARDia Trial UK\textsuperscript{22}
  - 600 Diabetics with multivessel disease
  - Surgeon and Cardiologist in agreement about ability to be randomized
  - Will include sirolimus stents, bare metal stents, and abciximab
- End Points Include
  - Death/nonfatal MI/nonfatal stroke
  - Revascularization
  - Major Bleeding Complications
CABG vs DES??

- **FREEDOM Trial** North America
  - Enrolling 2600 diabetics with multivessel disease
  - Sirolimus Stents with abciximab vs CABG
  - Primary End-Point: 5 year mortality
Summary

- Drug-Eluting Stents are yet another advancement in non-surgical technology for the treatment of CAD
  - Mode of controlled, tissue-directed drug release
  - Significant reduction in restenosis and revascularization
  - Experience and technology advance faster than research that can support it
Summary

- Major limitation of PTCA with stenting is the need for target vessel revascularization...

- DES reduce need for revascularization...
References

7. Stone et al. Comparison of Angioplasty with Stenting, with or without Abciximab, in Acute Myocardial Infarction. NEJM 2002; 346: 957-66
10. Serruys et al. Intravascular Ultrasound Findings in the Multicenter, Randomized, Double-Blind RAVEL (Randomized study with the sirolimus-eluting Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery Lesions) trial. Circulation 2002; 106: 798
References

References