Current Status of Drug Eluting Stents

Dr Bernard Prendergast DM MRCP
Wythenshawe Hospital Manchester UK

Advanced Angioplasty
London January 2005
- Real world vs. clinical trial data
- Stent thrombosis
- Head-to-head studies
- Cost effectiveness
Drug Eluting Stents: Hot Topic

PubMed search results for "drug eluting stents" showing Items 1 - 20 of 450.
A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents

Mohan N Babapulle, Lawrence Joseph, Patrick Bélsile, James M Brophy, Mark J Eisenberg

**Mortality**

<table>
<thead>
<tr>
<th>Trial</th>
<th>DES n/N</th>
<th>BMS n/N</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemens</td>
<td>27/20</td>
<td>31/18</td>
<td>0.98 (0.84 to 1.15)</td>
</tr>
<tr>
<td>Abiomed</td>
<td>50/33</td>
<td>34/35</td>
<td>1.00 (0.85 to 1.18)</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>34/37</td>
<td>28/25</td>
<td>0.94 (0.77 to 1.15)</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>56/40</td>
<td>42/33</td>
<td>1.21 (0.96 to 1.52)</td>
</tr>
<tr>
<td>Pivotal</td>
<td>52/36</td>
<td>40/34</td>
<td>1.13 (0.88 to 1.44)</td>
</tr>
<tr>
<td>Total</td>
<td>252/184</td>
<td>212/149</td>
<td>1.11 (0.95 to 1.29)</td>
</tr>
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</table>

**MACE**

<table>
<thead>
<tr>
<th>Trial</th>
<th>DES n/N</th>
<th>BMS n/N</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Siemens</td>
<td>53/40</td>
<td>59/44</td>
<td>0.92 (0.70 to 1.21)</td>
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<tr>
<td>Abiomed</td>
<td>10/9</td>
<td>15/9</td>
<td>1.23 (0.59 to 2.55)</td>
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<tr>
<td>C-SIRIUS</td>
<td>35/30</td>
<td>25/26</td>
<td>1.36 (0.47 to 4.02)</td>
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<tr>
<td>E-SIRIUS</td>
<td>71/54</td>
<td>56/46</td>
<td>1.25 (0.87 to 1.79)</td>
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<tr>
<td>Pivotal</td>
<td>54/36</td>
<td>40/34</td>
<td>1.13 (0.83 to 1.55)</td>
</tr>
<tr>
<td>Total</td>
<td>207/144</td>
<td>194/149</td>
<td>1.03 (0.78 to 1.35)</td>
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</table>

**MI**

<table>
<thead>
<tr>
<th>Trial</th>
<th>DES n/N</th>
<th>BMS n/N</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Siemens</td>
<td>18/15</td>
<td>20/23</td>
<td>0.80 (0.60 to 1.07)</td>
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<tr>
<td>Abiomed</td>
<td>5/4</td>
<td>7/8</td>
<td>0.71 (0.32 to 1.57)</td>
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<tr>
<td>C-SIRIUS</td>
<td>18/21</td>
<td>15/26</td>
<td>1.14 (0.60 to 2.16)</td>
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<tr>
<td>E-SIRIUS</td>
<td>43/39</td>
<td>47/33</td>
<td>0.90 (0.59 to 1.30)</td>
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<tr>
<td>Pivotal</td>
<td>12/9</td>
<td>15/12</td>
<td>1.00 (0.42 to 2.34)</td>
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<tr>
<td>Total</td>
<td>71/51</td>
<td>77/49</td>
<td>0.83 (0.55 to 1.25)</td>
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**TLR**

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<th>Odds Ratio (95% CI)</th>
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<tr>
<td>Siemens</td>
<td>23/20</td>
<td>25/20</td>
<td>0.94 (0.82 to 1.08)</td>
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<tr>
<td>Abiomed</td>
<td>6/5</td>
<td>8/7</td>
<td>1.12 (0.49 to 2.57)</td>
</tr>
<tr>
<td>C-SIRIUS</td>
<td>29/25</td>
<td>30/26</td>
<td>0.97 (0.75 to 1.25)</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>30/25</td>
<td>35/30</td>
<td>0.85 (0.54 to 1.36)</td>
</tr>
<tr>
<td>Pivotal</td>
<td>18/14</td>
<td>20/15</td>
<td>0.90 (0.49 to 1.63)</td>
</tr>
<tr>
<td>Total</td>
<td>111/84</td>
<td>133/109</td>
<td>0.85 (0.54 to 1.36)</td>
</tr>
</tbody>
</table>

Unrestricted Utilization of Sirolimus-Eluting Stents Compared With Conventional Bare Stent Implantation in the “Real World”

The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry

Consecutive patients with de novo lesions (n=508) treated with SES compared with historical controls (n=450) treated with bare metal stents

One year TVR (clinically driven)

Lesions Treated

n = 17,249 lesions (1.2 + 0.5 lesions/patient)

- de novo: 87.9%
- restenosis: 12.1%
- SVG: 1.56%
- >30 mm: 11.7%
- LM: 2.2%
- total occl: 8.8%
- ostial: 8.2%
- Bifurcation: 10.4%

n = 15,160  2,089  295  2,017  372*  1,512**  1,410  1,795

* 158 unprotected LM
** 427 older than 3 months

August 2004
6 months follow-up: Total Patient Population (n= 10,962)

ERC-adjudicated events

All cases with reported death, AMI, TLR or stent thrombosis were reviewed and adjudicated by the Independent Endpoints Review Committee (ERC)

August 2004
Subsets with insufficient or variable data

Gregg Stone
Advanced Angioplasty January 2005

- Ultra-long lesions
  - TAXUS VI, Korean registry, DES LONG
- Unprotected LM
  - RESEARCH registry, SYNTAX
- ISR after failed BMS or failed brachytherapy
  - ISAR DESIRE, TROPICAL
- CTO
  - SICTO
- Bifurcations
- SVG
- AMI

Registry data only
“All that glisters is not gold,-
Often have you heard that told”
Prince of Morocco, The Merchant of Venice Act II, Scene VI.
April 03: CYPHER DES approved for use
July 03: Physician notification of SAT clusters
October 03: 300 SAT cases (60 deaths)
  - voluntary reporting, denominator unknown
  - advisory letter re: pt selection, sizing and anti-platelet Rx
November 03: Website update and concerns withdrawn
March 04: TAXUS DES approved for use
April 04: 40 cases of failed balloon deflation
May 04: Manufacturing modification approved
July 04: 88,000 stents recalled, investigation ongoing
September 04: Problems with balloon withdrawal identified
<50% power to exclude a two-fold higher risk of stent thrombosis with DES

- Male, 58 yrs, smoker, hyperlipidaemia
- Cx Cypher stents (3/18, 2.5/18) for unstable angina
- 3/52: pruritic rash - ticlopidine switched to clopidogrel for 2/12
- 8/12: angiogram and 1 year isotope scan normal
- 18/12: NSTEMI 2° to Cx occlusion. EMD cardiac arrest during PCI.

Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugene P McFadden, Eugenio Steabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys

- **63 yrs, male**
  - LAD 3/16 Taxus stent
  - Day 338: Aspirin withdrawal for bladder polyp excision
  - Day 343: Anterior MI
  - Successful PCI, CK 6500IU/L

- **73 yrs, male**
  - LAD 3.5/16 Taxus stent
  - Day 435: Aspirin withdrawal for colonic surgery
  - Day 442: Anterior MI
  - Successful PCI, CK 3500IU/L

- **42 yrs, male**
  - LAD 3/18, 3/18 Vision stents, Cx 3/33 Cypher
  - Day 180: Clopidogrel withdrawn
  - Day 361: Aspirin withdrawn
  - Day 375: Cypher occlusion, Vision patent
  - Successful PCI

- **62 yrs, male**
  - LAD 3/18 Cypher, Cx 3/18 Vision
  - Day 331: Aspirin/clopidogrel withdrawn for colonoscopy
  - Day 335: Anterior MI
  - Cypher occluded, Vision patent
  - Successful PCI

Aspirin/clopidogrel resistance

DEFINITION
✓ Failure of an agent to achieve its intended pharmacological effect
✗ Failure of an agent to prevent unwanted recurrent clinical events

EVIDENCE
● Effects 10-20% in vitro
● Correlates with recurrent clinical events in patients with:
  ➢ Aspirin: CVA and PVD\(^1,2\)
  ➢ Clopidogrel: AMI undergoing primary PCI\(^3\)
● Causes:
  ➢ Extrinsic: smoking, drug interaction, inadequate dosing
  ➢ Intrinsic: Aspirin - COX-1, COX-2 metabolism, non-platelet thromboxane
  Clopidogrel - P450 metabolism, P2Y receptor variability

60 pts: 1° PCI for AMI
- 100% stent rate
- Aspirin 300mg, 200mg od, Clopidogrel 300mg post-op, 75 mg od for 3/12
- Heparin/eptifibitide for all
- Platelet aggregometry under basal and flow conditions
- 3 & 6 month follow up

Practical Recommendations

- **Stent selection**
  - Is DES desirable/essential
  - Forthcoming non-cardiac surgery
  - Compliance with combined anti-platelet therapy

- **Non cardiac surgery in DES patients**
  - Continue anti-platelet therapy at increased bleeding risk
  - Withhold anti-platelet therapy for maximum 48hrs
  - Defer elective surgery for at least 1 year

- **Research**
  - Factors predisposing to thrombosis
  - Optimum duration of anti-platelet therapy

- **Education**
  - Patients and their physicians
“Any new study in which the control arm is constituted by a non-DES is untenable. Even for simple lesions, any new study evaluating the performance of a new DES will have another DES in the control group.”

REGISTRY/SINGLE CENTRE DATA

**Historical cohort comparisons**

- Hong MK *et al*, Seoul
  - TCT 2004
- Iakovou I *et al*, Milan
  - ESC 2004
- Goy JJ *et al*, Lausanne
  - ESC 2004
- Kumar S *et al*, Manchester
  - TCT 2003

**Randomised controlled trial**

- TAXI trial
  - 1000 pts: 1:1 Cypher:Taxus
  - Fast-track publication
  - J Am Coll Cardiol January 2005
REALITY Trial

Overview

- Randomized, prospective, multi-centre trial - 89 sites in Europe, Latin America and Asia
- 1-2 lesions/pt, each 2.25-3.0 mm RVD, at least one >15 mm long
- Angiography @8 mo and clinical f/u @ 1, 8, 12, 18 and 24 months
- PI - Marie-Claude Morice; Sponsor - Cordis

Primary Endpoint

- 8-month angiographic binary restenosis (in-segment)

Secondary Endpoints

- TLR, TVR, MACE @ 1, 8, 12, 18, and 24 months

Status

- Enrollment completed: 1,386 pts, 1,941 lesions, 32% diabetics
ENDEAVOR III
Randomized Multicenter Trial

Single De Novo Native Coronary Artery Lesions (Type A/B)
Stent Diameters: 2.5-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: >14 mm and ≤ 27 mm
Pre-dilatation required

436 Patients
3:1 Randomization
30 sites
United States

Endeavor Stent
n=327

Control Cypher Stent
n=109

Clinical/MACE
Angio/IVUS

30d  6mo  8mo  9mo  12mo  2yr  3yr  4 yr  5 yr

Primary Endpoint: In-segment Late lumen loss by QCA at 8 months
Secondary Endpoints: TSR, TVR, TVF at 9 months & ABR at 8 months
Antiplatelet therapy for > 3 months
10 µg ABT-578 per mm stent length
The XIENCE™ V Clinical Program

<table>
<thead>
<tr>
<th>SPIRIT II</th>
<th>SPIRIT III</th>
<th>SPIRIT IV</th>
</tr>
</thead>
</table>
| - International Trial  
- 300 patients, Europe, Asia and New Zealand  
- Randomization 3:1, XIENCE™ V EECSS vs TAXUS® EXPRESS²™ PECSS  
- Beginning Ethics approval now | - US Trial, 1390 patients  
- Safety and efficacy of the XIENCE™ V EECSS in comparison to the TAXUS® EXPRESS²™ PECSS  
- Enrollment to begin Q1 | - 700 patients, 70 sites OUS  
- Timing and study design to be confirmed |
Cost effectiveness

● DES programmes have major financial implications
  – CABG very well reimbursed, DES currently underfunded
  – eg. Duke USA (1425 PCI/year) projected annual losses of $3.8-6 million over first 5 years  

    Am Heart J 2004;147:449-456

● Economic analyses suggest breakeven at 1.43 DES/patient

● Projected clinical and financial benefits may be negated in the real world: multivessel disease, complex lesions (LMS, bifurcation, ostial disease, calcification)  

    Eur J CT Surg 2004;26:528-534
209 patients with multivessel disease undergoing CABG 2002
Mean age 65 years, Diabetes 26%
CABG: LIMA 100%, 3.0+/0.8 grafts, discharge mean 9 days
Clinical/angiographic review by two senior interventional cardiologists
Multivessel PCI feasible 76%: 3.6+/1.4 DES, 72+/37mm
Costs: CABG £19,821, PCI £17266
- no difference after correction for 16% ISR
“Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong”

Guide to the Methods of Technology Appraisal. NICE, April 2004

- ‘Metal on metal’ hip £13,100
- GP inhibitors (PCI) £25,811
- Lap hernia repair £50,000
- DES: £15,000/QALY
- £31K

ICER (£ per QALY Gained)
Benefits of a competitive economy
MEDITRONIC

ENDEAVOUR programme
Agent: ABT 578
Platform: Driver

SORIN

JUPITER programme
Agent: Tacrolimus
Platform: Carbostent

GUIDANT

SPIRIT programme
Agent: Everolimus
Platform: Multilink Vision

CONOR

COSTAR/EUROSTAR programme
Agent: Paclitaxel combinations
Platform: Cobalt chromium
Evolution of Medical Procedures

Scott's parabola: the rise and fall of a surgical technique

PROMISING IDEA

Strong media pressure for universal acceptance

Encouraging reports

Widespread enthusiasm

Doubts creep in

Damaging survey reported

Condemned by several authorities

Operating theatre staff ponder possible uses for large quantities of expensive, obsolete equipment

Falls into disuse

Very old surgeons amaze their juniors with rollicking stories of the old days

Standard treatment

J W Scott consultant gynaecologist, Poole Hospital NHS Trust, Poole, Dorset BH15 2JB.
Conclusions

- Progressive adoption of DES programmes is intuitively correct for physicians, patients and healthcare systems
- Changing referral patterns in favour of PCI/DES present a significant challenge to current and future resources
- Future developments seem unlikely to halt this advance
  - Stent platforms – increased deliverability and decreased vascular injury
  - Biodegradable polymers – no consequences of retained drug or polymer
  - Pharmacokinetics – sustained drug release
  - Combination therapy – directed luminal and abluminal release of vasculoprotective agents and cell cycle inhibitors
UK Stent procedures
BCIS 2003 data from 53 of 73 centres

% of Procedures

Year

'92 '93 '94 '95 '96 '97 '98 '99 '00 '01 '02 '03

0 10 20 30 40 50 60 70 80 90 100

All DES
UK Stent procedures
BCIS 2003 data from 53 of 73 centres

*30% reduction in CABG in last 2 years in USA
## Stent Thrombosis: Cypher & Taxus

<table>
<thead>
<tr>
<th>Study</th>
<th>Cypher</th>
<th>Control</th>
<th>TAXUS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAVEL 3 years</strong>¹</td>
<td>0.0% (0/120)</td>
<td>0.0% (0/118)</td>
<td>0.0% (0/31)</td>
<td>0.0% (0/30)</td>
</tr>
<tr>
<td><strong>SIRIUS 2 years</strong>²</td>
<td>0.6% (3/533)</td>
<td>0.8% (4/525)</td>
<td>1.5% (3/131)</td>
<td>0.0% (0/136)</td>
</tr>
<tr>
<td><strong>E-SIRIUS 2 years</strong>³</td>
<td>1.7% (3/175)</td>
<td>0.0% (0/177)</td>
<td>0.7% (3/135)</td>
<td>0.0% (0/136)</td>
</tr>
<tr>
<td><strong>C-SIRIUS 1 year</strong>⁴</td>
<td>2.0% (1/50)</td>
<td>2.0% (1/50)</td>
<td>0.6% (4/662)</td>
<td>0.8% (5/652)</td>
</tr>
<tr>
<td><strong>SES-SMART 8m</strong></td>
<td>0.8% (1/129)</td>
<td>3.1% (4/128)</td>
<td>0.5% (1/219)</td>
<td>0.9% (2/227)</td>
</tr>
<tr>
<td>eCypher 6m⁵</td>
<td>0.5% (56/10962)</td>
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<tr>
<td><strong>TROPICAL 6m</strong>⁶</td>
<td>0.6% (1/162)</td>
<td></td>
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<tr>
<td><strong>Research 30d</strong>⁷</td>
<td>0.9% (9/1000)</td>
<td></td>
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<tr>
<td>ARTS II Cypher 6m⁸</td>
<td>0.8% (5/607)</td>
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¹ Reference: [1]
² Reference: [2]
³ Reference: [3]
⁴ Reference: [4]
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¹⁰ Reference: [10]
¹¹ Reference: [11]
¹² Reference: [12]
¹³ Reference: [13]
¹⁴ Reference: [14]
¹⁵ Reference: [15]
DES: Equivalent to CABG?
ARTS II – 6m outcome

Patrick Serruys TCT 2004
Stent Thrombosis After Successful Sirolimus-Eluting Stent Implantation

Allen Jeremias, MD; Brett Sylvia, BS; Jonathan Bridges, MD; Ajay J. Kirtane, MD; Brian Bigelow, MD; Duane S. Pinto, MD; Kalon K.L. Ho, MD, MSc; David J. Cohen, MD, MSc; Lawrence A. Garcia, MD; Donald E. Cutlip, MD; Joseph P. Carrozza, Jr, MD

Background—Stent thrombosis (ST) is a rare but devastating complication of coronary stent implantation, occurring in 0.5% to 1.9% of patients with bare metal stents. The incidence of ST with drug-eluting stents is less well studied, particularly among patients outside of clinical trials.

Methods and Results—The aim of this study was to evaluate the incidence and potential risk factors for ST in patients receiving sirolimus-eluting stents (SES) in the “real world” after commercial release in the United States in April 2003. All 652 patients who underwent SES implantation (776 lesions treated) at our institution between April and October 2003 were followed up prospectively after the procedure (median follow-up 100 days). During that period, 7 patients (1.1%, 95% CI 0.4% to 2.2%) developed ST within a range of 2 to 13 days, and 1 patient had an ST-elevation myocardial infarction on day 39 with evidence of thrombus within the SES at angiography. Patients with an ST had significantly smaller final nominal balloon diameters (2.75 versus 3.00 mm, P=0.04), and in 4 (57%) of the 7 patients with ST versus 1.7% of patients without ST (P<0.001), antiplatelet therapy had been discontinued after the procedure. Among the ST patients, 1 died and 5 had myocardial infarctions.

Conclusions—In this single-center experience, the incidence of ST after SES implantation was ≈1%, which is within the expected range of bare metal stents. The discontinuation of antiplatelet therapy was strongly associated with the development of ST in this patient population. (Circulation. 2004;109:1930-1932.)

Key Words: revascularization □ thrombosis □ stents
Overall stent thrombosis rate = 0.51% at 6 months

 ERC-adjudicated events

Overall stent thrombosis rate = 0.51% at 6 months

All cases with reported death, AMI, TLR or stent thrombosis were reviewed and adjudicated by the Independent Endpoints Review Committee (ERC)

August 2004
This patient underwent intracoronary stent implantation at South Manchester University Hospital Trust on the __ of _______ 200_. The patient should receive both Aspirin and Clopidogrel for _______ months. Do NOT withdraw this medication before discussion with:
1) Dr ___________________ Ext _____, or
2) On-call cardiology registrar (page via switchboard), or
3) Angioplasty specialist nurse Ext 5301
Baseline Characteristics

- 14,316 patients (92% of enrolled)
- Age: 61.7 ± 11.34
- Male: 77.7%
- Obese: 18.1%
- Prior MI: 30.4%
- Prior PCI: 28.6%
- Prior CABG: 10.7%
- Hypertension: 62.3%
- Hyperlipidemia: 63.1%
- Diabetes: 28.6%
  - Non-ID: 19%
  - ID: 10%

Diseased vessels

- Single: 32.7%
- Two vessels: 43.4%
- Three vessels: 23.9%

August 2004
If OR < 1, DES is better than BMS control
**Effect (QALY)**

**Cost**

Is additional expenditure good value for money?

- **Dominated**
  - Incremental cost effectiveness ratio (ICER) = additional cost/additional effect
  - 0 = current practice e.g. bare metal stent

- **Dominant**
Drug Eluting Stent cases
2003 data from 64 of 73 centres

% DES Cases

Scotland: 5.3
England: 18.3
Wales: 28.6
N. Ireland: 49.76

Country
Trials to look out for
Trials to look out for

- FREEDOM
- CARDIA
- REALITY
- ENDEAUVOUR III
- SPIRIT II, SPIRIT III
- ACC 2006 abstracts
  - Cypher 56, Non-Cypher 18, Head-to-head 9
SYNTAX
SYNergy between PCI with TAXus and cardiac surgery -
broader DES use
left main disease
3-vessel disease
bifurcation
chronic total occlusions
Patient Flow

**screening**

- Patients with de novo 3-vessel-disease and/or left main disease

**registration**

- Physician Team (surgeon and interventionalist)
- amenable for both treatments options
- amenable for \( \leq 1 \) interventional treatment

**Multi-center randomized controlled trial**

- Randomization \( n=1500 \)
- TAXUS vs CABG
- 5 year follow up

**Registries**

- define CABG only population
- define PCI only population
- define patients/physicians refusing randomization