DES or maybe BMS?

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Conflict of Interest Statement

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Astra Zeneca  Abbott
Bayer            Biotronik
Boehringer Ingelheim  Bristol Myers-Squibb
Correvio          Daiichi-Sankyo
Lilly             Novartis
The 1996 Grünzig Lecture

Stents: a mechanical solution for a biological problem?

U. Sigwart
Royal Brompton Hospital, London, U.K.

"Heavier-than-air flying machines are impossible" (Lord Kelvin, President, Royal Society, 1895)

The question mark in the title of this paper may look outdated and even artificial in view of the recent exponential increase in the use of stents. This almost frightening upswing occurred after a little less than one decade following their introduction into clinical medicine. It was, however, only a few years ago that the role of stents in cardiology was in serious doubt. In what follows, I shall try to review the story of stenting in the light of my personal experience against the background of diverse currents in the catheter treatment of human vascular disease.

History
The concept of placing a scaffold into injured blood vessels, or other conduits, is so simple that it comes as no surprise to find traces of such thinking long ago. It is generally believed that Alexis Carrel (Fig. 1), who first tried to place glass tubes into the arteries of dogs in the hope of treating traumatic injury to blood vessels, also performed surgical anastomoses. Carrel was a Nobel laureate and brilliant mind.
Rationale for Stents
Which Problems Did We Want to Solve With Stents?

• mechanically scaffold the artery
• (re)create a larger circular lumen
• prevent abrupt vessel closure
• prevent late restenosis
Abrupt Vessel Closure

Early Data with POBA:

- **frequency**: 5-10%
- **consequences**: MI ~35%, mortality ~8-20%, emergency CABG ~30%

- stents for abrupt closure as bridge to bypass surgery
- stents as definite treatment for abrupt vessel closure
- routine surgical back-up became obsolete

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Quantitative Coronary Analysis of Stents versus POBA

**STRESS** \( n = 410 \)

- **Acute lumen gain**: 1.72 \( P < .001 \)
- **Late lumen loss**: 0.98 \( P < .001 \)
- **Net gain**: 0.74 \( p = 0.01 \)

**BENESTENT** \( n = 520 \)

- **Acute lumen gain**: 1.40 \( P < .001 \)
- **Late lumen loss**: 0.97 \( P < .001 \)
- **Net gain**: 0.65 \( p = 0.09 \)


_Prof. Dr. Helmut Schühlen, FESC, FACC_
Clinical Results & Longterm Outcome Stents versus POBA

**STRESS**  
- MACE at 12 mo. 19.5% (p=0.16) vs 23.8% (p=0.06)  
- TLR 10.2% vs 15.2%  
- Restenosis 42.1% (p=0.046)  

**BENESTENT**  
- MACE at 7 mo. 20.1% (p=0.02) vs 29.6% (p=0.001)  
- TLR 13.5% vs 23.3%  
- Restenosis 32% (p=0.02)  


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Randomized Trials Stent versus POBA

Analysis of 12 randomized trials with 6300 patients

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Follow-up, mo</th>
<th>No., Stent/Angioplasty</th>
<th>Angiographic Restenosis, %</th>
<th>Stent</th>
<th>Angioplasty</th>
<th>P Value</th>
<th>Target Vessel Revascularization (TVR), %</th>
<th>Stent</th>
<th>Angioplasty</th>
<th>P Value</th>
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<tbody>
<tr>
<td>STRESS,2 1994</td>
<td>6</td>
<td>205/202</td>
<td>31.6</td>
<td>10.2</td>
<td>15.4</td>
<td>.06</td>
<td></td>
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<tr>
<td>Benestent,5,14 1994</td>
<td>7/60†</td>
<td>259/257</td>
<td>22</td>
<td>13.5/17.3‡</td>
<td>23.3/27.6 &lt;.05/.006</td>
<td>.‡</td>
<td></td>
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<tr>
<td>TASC I,10 1995§</td>
<td>6</td>
<td>270 (Overall)</td>
<td></td>
<td></td>
<td>31</td>
<td>46</td>
<td>.01</td>
<td>...</td>
<td>...</td>
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<td>Versaci et al,15 1997</td>
<td>12</td>
<td>60/60</td>
<td>19</td>
<td>6.6</td>
<td>22</td>
<td>...</td>
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<td>STRESS II,12 1998</td>
<td>12</td>
<td>100/89</td>
<td>...</td>
<td>10</td>
<td>20</td>
<td>...</td>
<td></td>
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<tr>
<td>Benestent II,13 1998</td>
<td>6</td>
<td>413/410</td>
<td>16</td>
<td>8‡</td>
<td>13.7</td>
<td>.02</td>
<td></td>
<td></td>
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<tr>
<td>OCBAS,16 1998</td>
<td>7</td>
<td>57/59</td>
<td>18.8</td>
<td>17.5</td>
<td>9.2</td>
<td>...</td>
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<td>WIN,17 1998§</td>
<td>6</td>
<td>299/287</td>
<td></td>
<td></td>
<td>38</td>
<td>37</td>
<td>...</td>
<td>39</td>
<td>39</td>
<td>...</td>
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<td>BOSS,18 1998§</td>
<td>8</td>
<td>40/40</td>
<td>...</td>
<td>21.4</td>
<td>23.5</td>
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<td>EPISTENT,19,20 1998¶</td>
<td>6</td>
<td>1603/796</td>
<td>...</td>
<td>8.7</td>
<td>15.4</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OPUS,21 1999§</td>
<td>6</td>
<td>480 (Overall)</td>
<td></td>
<td></td>
<td>...</td>
<td>...</td>
<td>4.0</td>
<td>10.7</td>
<td>≤.05</td>
<td></td>
</tr>
</tbody>
</table>

J Al Suwaidi et al., JAMA 2000

Prof. Dr. Helmut Schühlen, FESC, FACC
Metaanalysis of Stent versus POBA Trials

19 randomized trials with 8004 patients
- Analysis of lives saved per 1000 patients at 12 mo. -

AJ Nordmann et al.,
Eur Heart J 2004

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Initial Experience with DES

The real target is not BMS vs. DES, it’s surgery.

Interview at ACC 2003, www.theheart.org

JE Sousa et al.,
Early Data for DES & BMS in Subgroups

**SIRIUS**

- Diabetes subgroup
- Velocity Cypher
- Angiographic restenosis at 6 mo.
- 50.5% for SIRIUS
- 17.6% for Velocity Cypher
- J Moses, ACC 2003

**ISAR-STEROEO-2**

- Diabetes subgroup
- Velocity Multi-Link
- Angiographic restenosis at 6 mo.
- 44.7% for ISAR-STERYEO-2
- 20.5% for Velocity Multi-Link
- J Pache et al., J Am Coll Cardiol 2003
# Metaanalysis of Trials with DES versus BMS

11 trials with 5103 patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>DES n/N</th>
<th>BMS n/N</th>
<th>Odds ratio (95% Crl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>0/120</td>
<td>27/118</td>
<td>0.01 (0.00 to 0.08)</td>
</tr>
<tr>
<td>RAEL V35</td>
<td>22/533</td>
<td>87/525</td>
<td>0.22 (0.13 to 0.35)</td>
</tr>
<tr>
<td>SIRIUS 36</td>
<td>2/50</td>
<td>9/50</td>
<td>0.23 (0.03 to 0.80)</td>
</tr>
<tr>
<td>C-SIRIUS 12</td>
<td>7/175</td>
<td>37/177</td>
<td>0.17 (0.06 to 0.35)</td>
</tr>
<tr>
<td>E-SIRIUS 18</td>
<td>33/878</td>
<td>160/870</td>
<td>0.15 (0.02 to 0.46)</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel, polymeric</td>
<td>0/31</td>
<td>3/30</td>
<td>0.12 (0.00 to 1.06)</td>
</tr>
<tr>
<td>TAXUS I 19</td>
<td>11/260</td>
<td>38/263</td>
<td>0.27 (0.13 to 0.51)</td>
</tr>
<tr>
<td>TAXUS II 20</td>
<td>20/662</td>
<td>74/652</td>
<td>0.25 (0.14 to 0.40)</td>
</tr>
<tr>
<td>TAXUS IV 21</td>
<td>31/953</td>
<td>115/945</td>
<td>0.23 (0.10 to 0.42)</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel, non-polymeric</td>
<td>8/117</td>
<td>2/58</td>
<td>1.75 (0.49 to 11.6)</td>
</tr>
<tr>
<td>ASPECT 22</td>
<td>11/152</td>
<td>6/38</td>
<td>0.41 (0.15 to 1.24)</td>
</tr>
<tr>
<td>ELUTES 23</td>
<td>27/517</td>
<td>35/512</td>
<td>0.75 (0.45 to 1.25)</td>
</tr>
<tr>
<td>DELIVER 24-25</td>
<td>3/24</td>
<td>5/26</td>
<td>0.64 (0.12 to 2.74)</td>
</tr>
<tr>
<td>PATENCY 26</td>
<td>49/810</td>
<td>48/634</td>
<td>0.64 (0.39 to 1.05)</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>111/2641</td>
<td>323/2449</td>
<td>0.26 (0.14 to 0.45)</td>
</tr>
</tbody>
</table>

MN Babapulle et al., *Lancet* 2004
The Debate at ESC 2006

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf, "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

obtained this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality - PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the
Mechanistic Insights into the Excess Risk of Late Stent Thrombosis After 1G DES

Incomplete Endothelialization and Chronic Inflammation

Aquired Malapposition

Guagliumi et al., JACC Interv 2012

Guagliumi et al, Circulation 2003

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www.escardio.org
Continuous Risk for Stent Thrombosis with 1st Gen. DES

Registry of 18,334 pts with BMS or DES
246 definite SAT

T Tada et al., JACC Intv 2013
Longterm Outcome with 1st-gen. DES vs. BMS

Incidence of death or MI

SCAAR Registry
47967 pts.

BMS n=18659
DES n=10294

ACS ~80%
STEMI ~30%

SK James et al.,

Relative risk, 1.00 (95% CI, 0.95–1.05)
### DAPT Duration in Pivotal Trials of 1G-DES

<table>
<thead>
<tr>
<th>Device</th>
<th>Trial</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypher®</td>
<td>RAVEL</td>
<td>8 wks.</td>
</tr>
<tr>
<td></td>
<td>SIRIUS</td>
<td>3 mo.</td>
</tr>
<tr>
<td></td>
<td>E- &amp; C-SIRIUS</td>
<td>2 mo.</td>
</tr>
<tr>
<td>Taxus®</td>
<td>TAXUS I, II, IV-VI</td>
<td>6 mo.</td>
</tr>
</tbody>
</table>

**ESC Guidelines on DAPT after PCI in stable CAD 2005 - 2014**

- **DAPT is indicated for at least 1 month after BMS implantation.**
  - **I A**
- **DAPT is indicated for 6 months after DES implantation.**
  - **I B**
More Favorable Results with 2nd-Gen. DES

COMPARE Trial: 1800 patients, 60% with ACS

TVR for restenosis

Stent thrombosis

E Kedhi et al., Lancet 2010

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Is Late Stent Thrombosis Still a Relevant Issue After 2nd-Gen. DES?

Metaanalysis of ISAR-TEST 3 + 4 & LEADERS
4062 pts. randomized to Yukon, Biomatrix or Cypher

PROTECT trial
8709 pts. randomized to Cypher or Endeavor

Definite stent thrombosis

Cumulative incidence (%)

Years after randomization

Gg Stefanini et al., Eur Heart J 2012

Log-rank p=0.015

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www.escardio.org
Late Stent Thrombosis with BMS, 1\textsuperscript{st}-Gen. & 2\textsuperscript{nd}-Gen. DES

Registry of 18,334 pts with BMS or DES

246 definite SAT

T Tada et al., JACC Intv 2013
2nd-Gen. DES vs. BMS - The NORSTENT Trial

9013 patients randomized to BMS or DES; both >9 mo. DAPT; ~60% ACS

(DES group: Promus/Xience 82.3%, Endeavor 11.9%, Cypher/Taxus 5.1%)

All-Cause Mortality

- Hazard ratio, 1.10 (95% CI, 0.94–1.29)
- P=0.22

Revascularization (PCI or CABG)

- Hazard ratio, 0.76 (95% CI, 0.69–0.85)
- P<0.001

Stent Thrombosis (definite)

- Hazard ratio, 0.64 (95% CI, 0.41–1.00)
- P=0.0498


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www.escardio.org
DES vs. BMS in Patients with DAPT for 1 Mo.

828 patients randomized to BMS or Endeavor

Death, MI or TVR

- BMS: 29.0%
- DES (Endeavor): 22.6%

HR 0.745; p=0.033

Stent Thrombosis
definite or probable

- BMS: 6.2%
- DES (Endeavor): 2.6%

HR 0.419; p=0.016

S Ariotti et al., JACC Intv 2016

Prof. Dr. Helmut Schühlen, FESC, FACC
**DES vs. BMS in Patients with DAPT for 1 Mo.**

2466 patients randomized to BMS or BioFreedom

**Cardiac Death, MI or Stent Thrombosis**

![Graph comparing Cardiac Death, MI or Stent Thrombosis between Bare-metal stent and Drug-coated stent.](chart1)

- **P<0.001 for noninferiority**
- **P=0.005 for superiority**

**TLR**

![Graph comparing TLR between Bare-metal stent and Drug-coated stent.](chart2)

- **P<0.001**

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www.escardio.org
Metaanalysis 2nd-gen. DES vs. BMS in STEMI

EXAMINATION & COMFORTABLE-AMI with 2665 pts. (Xience or Biomatrix versus BMS)

All-Cause Death

Meta-analyses HR, 0.90 (95% CI, 0.60-1.35)
P=0.92

Revascularization

Meta-analyses HR, 0.57 (95% CI, 0.51-0.88)
P=0.005

Stent Thrombosis (definite)

Meta-analyses HR, 0.35 (95% CI, 0.16-0.75)
P=0.007

M Sabaté et al., JACC Intv 2014

Prof. Dr. Helmut Schühlen, FESC, FACC
Network Metaanalysis DES vs. BMS in STEMI

22 trials with 12453 patients

Cardiac Death or MI
per 100 patient-yrs.

Stent Thrombosis
per 100 patient-yrs. (definite)

TVR
per 100 patient-yrs.

T Palmerini et al., JACC 2013
Summary

- Mortality is better perceived as the target for the mandatory & well-established longterm medical therapy.
- Stents have revolutionized & simplified PCI.
- Stents (BMS) increase the proliferative response to PTCA.
- 1\textsuperscript{st}-gen. DES diminished this proliferative response at the cost of deficient healing & a continuous thrombotic risk.
- "3\textsuperscript{rd}"gen. DES are safer than BMS, even with 1 mo. DAPT.
Is it time to take bare metal stents off the catheter laboratory shelf?

George Kassimis\textsuperscript{1*} and Adrian P. Banning\textsuperscript{2}

\textsuperscript{1}Cardiology Department, NHS Gloucestershire Hospitals, Cheltenham General Hospital, Cheltenham GL53 7AN, UK; and \textsuperscript{2}Oxford Heart Centre, Churchill Hospital, Oxford, UK

Our opinion of these data is that there is a clear benefit from DES... and that this benefit is independent of the clinical indication. ...

In 2016 implantation of BMS is no longer justified. We suggest that BMS should be honourably retired and added to the history books that document the evolution of interventional therapies.
Thank you!