M VAVURANAKIS
Professor of Cardiology
Director of 3d Department of Cardiology
National and Kapodistrian University of Athens

TAVI

Γ' Πανεπιστημιακή Καρδιολογική Κλινική, ΓΝΘ "Η ΣΩΤΗΡΙΑ", Ιατρική Σχολή, Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών
CONFLICT OF INTEREST

• PROCTOR MEDTRONIC CORE VALVE
Aortic Stenosis in the Elderly: Understanding the New Therapeutic Options

Valentina Boasi¹*, Maria Carla Casale¹*, Milena Aste¹, Giuseppe Tarantini², Sabina Gallina³, Manrico Balbi¹, Claudio Brunelli¹, Gian Paolo Bezante¹#

![Graph showing the onset of severe symptoms](image)
1/3 of the elderly remain untreated!!!
HOW DID EVERYTHING BEGIN?
Special Report

Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis
First Human Case Description

Alain Cribier, MD; Helene Eichmanoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; Francois Laborde, MD; Martin B. Leon, MD

Figure 1. The percutaneous valve crimped over the 30-mm-long balloon before implantation.

Alain Cribier: First Transcatheter Aortic Valve Implantation (TAVI) April 16, 2002

April 16, 2002 8 days post implantation

Circulation. 2002;106:3006-3008
1985
F.I.M. Balloon Aortic Valvuloplasty

1993-1994
Post-mortem studies of intra-valvular stenting

1999
Animal implantations (sheep)

2000
Feasibility Studies (antegrade)

2002-03
International TF and TA Feasibility Studies

2004
Edwards Lifesciences

2005-07
CE mark commercialization

2007
Post market registries

2008-09
PARTNER US Pivotal

Since 2007
FDA Approval (non-surgical and high risk surgical)

Nov 2011
Oct 2012
TAVI as an alternative therapy for AS in elderly patients

(Mean Age 83.1 years, Logistic EuroSCORE: 26.4% TAVI vs. 30.4% standard therapy)
TAVI should be determined NOT by Age per se Clinical Characteristics

- Very high STS score
TAVR is Equivalent to Surgery

PARTNER Cohort A (TAVR vs. SAVR)

HR [95% CI] = 1.03 [0.85, 1.24]
p (log rank) = 0.76

All-Cause Mortality

<table>
<thead>
<tr>
<th>Months post Randomization</th>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>348</td>
<td>351</td>
</tr>
<tr>
<td>12</td>
<td>262</td>
<td>236</td>
</tr>
<tr>
<td>24</td>
<td>228</td>
<td>210</td>
</tr>
<tr>
<td>36</td>
<td>191</td>
<td>174</td>
</tr>
<tr>
<td>48</td>
<td>154</td>
<td>131</td>
</tr>
<tr>
<td>60</td>
<td>61</td>
<td>64</td>
</tr>
</tbody>
</table>

69.8% vs. 69.3%
Is TAVR Superior to Surgery?

CoreValve US Pivotal High Risk Cohort

mean age of 83.2 years
CoreValve: 3-y Results

Log-rank $P = .0058$

![Bar chart showing all-cause mortality or stroke percentage over time postprocedure for SAVR and TAVR procedures.](chart)

$\Delta = 9.4$

The PARTNER 2A Trial

**Design**

Symptomatic severe aortic stenosis

Assessment by heart valve team:
Operable (STS ≥ 4%)

Randomized patients (n = 2032)

Yes

Assessment:
transfemoral (TF) access

No

TF

1:1 randomization (n = 1550)

TF TAVR (n = 775) vs Surgical AVR (n = 775)

Transapical (TA)/transaortic (TAo)

1:1 randomization (n = 482)

TA/TAo TAVR (n = 236) vs Surgical AVR (n = 246)

Primary endpoint: all-cause mortality or disabling stroke at 2 years

ClinicalTrials.gov. NCT01314313.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR (N=1011)</th>
<th>Surgery (N=1021)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>81.5±6.7</td>
<td>81.7±6.7</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>548 (54.2)</td>
<td>560 (54.8)</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td>28.6±6.2</td>
<td>28.3±6.2</td>
</tr>
<tr>
<td>STS risk score‡</td>
<td>5.8±2.1</td>
<td>5.8±1.9</td>
</tr>
<tr>
<td>NYHA class III or IV — no./total no. (%)</td>
<td>782/1011 (77.3)</td>
<td>776/1020 (76.1)</td>
</tr>
<tr>
<td>Coronary artery disease — no. (%)</td>
<td>700 (69.2)</td>
<td>679 (66.5)</td>
</tr>
<tr>
<td>Previous myocardial infarction — no. (%)</td>
<td>185 (18.3)</td>
<td>179 (17.5)</td>
</tr>
<tr>
<td>Previous CABG — no. (%)</td>
<td>239 (23.6)</td>
<td>261 (25.6)</td>
</tr>
<tr>
<td>Previous PCI — no. (%)</td>
<td>274 (27.1)</td>
<td>282 (27.6)</td>
</tr>
<tr>
<td>Previous balloon aortic valvuloplasty — no. (%)</td>
<td>51 (5.0)</td>
<td>50 (4.9)</td>
</tr>
<tr>
<td>Cerebral vascular disease — no. (%)</td>
<td>325 (32.1)</td>
<td>317 (31.0)</td>
</tr>
<tr>
<td>Peripheral vascular disease — no. (%)</td>
<td>282 (27.9)</td>
<td>336 (32.9)</td>
</tr>
<tr>
<td>Diabetes mellitus — no. (%)</td>
<td>381 (37.7)</td>
<td>349 (34.2)</td>
</tr>
<tr>
<td>COPD — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>321 (31.8)</td>
<td>306 (30.0)</td>
</tr>
<tr>
<td>Oxygen-dependent</td>
<td>34 (3.4)</td>
<td>32 (3.1)</td>
</tr>
<tr>
<td>Creatinine &gt;2 mg/dl — no. (%)‡</td>
<td>51 (5.0)</td>
<td>53 (5.2)</td>
</tr>
<tr>
<td>Atrial fibrillation — no. (%)</td>
<td>313 (31.0)</td>
<td>359 (35.2)</td>
</tr>
<tr>
<td>Permanent pacemaker — no. (%)</td>
<td>118 (11.7)</td>
<td>123 (12.0)</td>
</tr>
<tr>
<td>Frail condition — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Meter walk-test time&gt;7 sec</td>
<td>416/936 (44.4)</td>
<td>418/901 (46.4)</td>
</tr>
<tr>
<td>Serum albumin &lt;3.5 g/dl</td>
<td>150/988 (15.2)</td>
<td>140/951 (14.7)</td>
</tr>
<tr>
<td>Liver disease — no. (%)</td>
<td>19 (1.9)</td>
<td>26 (2.5)</td>
</tr>
<tr>
<td>Aortic-valve area — cm²</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Mean gradient — mm Hg</td>
<td>44.9±13.4</td>
<td>44.6±12.5</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %</td>
<td>56.2±10.8</td>
<td>55.3±11.9</td>
</tr>
<tr>
<td>Left ventricular mass index — g/m²</td>
<td>119.8±31.5</td>
<td>120.6±32.6</td>
</tr>
<tr>
<td>Moderate or severe mitral regurgitation — no./total no. (%)</td>
<td>151/899 (16.8)</td>
<td>171/894 (19.1)</td>
</tr>
</tbody>
</table>
Figure 1. Time-to-Event Curves for the Primary Composite End Point.
The insets show the same data on an enlarged y axis. TAVR denotes transcatheter aortic-valve replacement.
### Table 2. Clinical End Points at 30 Days, 1 Year, and 2 Years.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>At 30 Days</th>
<th></th>
<th>At 1 Year</th>
<th></th>
<th>At 2 Years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVR (N=1011)</td>
<td>Surgery (N=1021)</td>
<td>P Value</td>
<td>TAVR (N=1011)</td>
<td>Surgery (N=1021)</td>
<td>P Value</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>62 (6.1%)</td>
<td>80 (8.0%)</td>
<td>0.11</td>
<td>145 (14.5%)</td>
<td>160 (16.4%)</td>
<td>0.24</td>
</tr>
<tr>
<td>From cardiac causes</td>
<td>39 (3.9%)</td>
<td>41 (4.1%)</td>
<td>0.78</td>
<td>123 (12.3%)</td>
<td>124 (12.9%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Not from cardiac causes</td>
<td>6 (0.6%)</td>
<td>9 (0.9%)</td>
<td>0.41</td>
<td>53 (5.6%)</td>
<td>47 (5.2%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Neurologic event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>64 (6.4%)</td>
<td>65 (6.5%)</td>
<td>0.94</td>
<td>99 (10.1%)</td>
<td>93 (9.7%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>9 (0.9%)</td>
<td>4 (0.4%)</td>
<td>0.17</td>
<td>23 (2.4%)</td>
<td>16 (1.8%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Any stroke</td>
<td>55 (5.5%)</td>
<td>61 (6.1%)</td>
<td>0.57</td>
<td>78 (8.0%)</td>
<td>79 (8.1%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>32 (3.2%)</td>
<td>43 (4.3%)</td>
<td>0.20</td>
<td>49 (5.0%)</td>
<td>56 (5.8%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Nondisabling stroke</td>
<td>23 (2.3%)</td>
<td>18 (1.8%)</td>
<td>0.43</td>
<td>30 (3.0%)</td>
<td>24 (2.5%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>64 (6.5%)</td>
<td>62 (6.5%)</td>
<td>0.99</td>
<td>142 (14.8%)</td>
<td>135 (14.7%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Death from any cause or rehospitalization</td>
<td>99 (9.8%)</td>
<td>101 (10.2%)</td>
<td>0.78</td>
<td>234 (23.4%)</td>
<td>225 (23.3%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Death from any cause, any stroke, or rehospitalization</td>
<td>140 (13.9%)</td>
<td>153 (15.3%)</td>
<td>0.37</td>
<td>274 (27.4%)</td>
<td>276 (28.3%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (1.2%)</td>
<td>19 (1.9%)</td>
<td>0.22</td>
<td>24 (2.5%)</td>
<td>29 (3.0%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>80 (7.9%)</td>
<td>51 (5.0%)</td>
<td>0.008</td>
<td>84 (8.4%)</td>
<td>54 (5.3%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Life-threatening or disabling bleeding</td>
<td>105 (10.4%)</td>
<td>442 (43.4%)</td>
<td>&lt;0.001</td>
<td>151 (15.2%)</td>
<td>460 (45.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>13 (1.3%)</td>
<td>31 (3.1%)</td>
<td>0.006</td>
<td>32 (3.4%)</td>
<td>48 (5.0%)</td>
<td>0.07</td>
</tr>
<tr>
<td>New atrial fibrillation</td>
<td>91 (9.1%)</td>
<td>265 (26.4%)</td>
<td>&lt;0.001</td>
<td>100 (10.1%)</td>
<td>272 (27.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New permanent pacemaker</td>
<td>85 (8.5%)</td>
<td>68 (6.9%)</td>
<td>0.17</td>
<td>98 (9.9%)</td>
<td>85 (8.9%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>7 (0.8%)</td>
<td>6 (0.7%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Aortic-valve reintervention</td>
<td>4 (0.4%)</td>
<td>0</td>
<td>0.05</td>
<td>11 (1.2%)</td>
<td>4 (0.5%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Coronary obstruction</td>
<td>4 (0.4%)</td>
<td>6 (0.6%)</td>
<td>0.53</td>
<td>4 (0.4%)</td>
<td>6 (0.6%)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number of patients in the treatment group. P values are for point-in-time comparisons.
Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials

George C.M. Siontis1, Fabien Praz1, Thomas Pilgrim1, Dimitris Mavridis2, Subodh Verma3, Georgia Salanti2,4,5, Lars Søndergaard6, Peter Jüni7, and Stephan Windecker1*

<table>
<thead>
<tr>
<th>Trial</th>
<th>TAVI</th>
<th>SAVR</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER 1A</td>
<td>116/348</td>
<td>114/351</td>
<td>0.90 (0.71, 1.15)</td>
<td></td>
</tr>
<tr>
<td>US CoreValve</td>
<td>85/391</td>
<td>99/359</td>
<td>0.79 (0.61, 1.01)</td>
<td></td>
</tr>
<tr>
<td>NOTION</td>
<td>11/145</td>
<td>14/135</td>
<td>0.72 (0.33, 1.59)</td>
<td></td>
</tr>
<tr>
<td>PARTNER 2A</td>
<td>165/1011</td>
<td>170/1021</td>
<td>0.92 (0.74, 1.13)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.87 (0.76, 0.99)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Figure 2. Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the primary outcome of death from any cause. Forest plots showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the primary outcome of death from any cause at 2 years of follow-up. Hazard ratio estimates according to intention-to-treat principle were retrieved from three trials (PARTNER 1A, NOTION, and PARTNER 2A); whereas one trial (US CoreValve High Risk) contributed with the estimated risk ratio by using the events provided in as-treated populations. The provided number of events and total trial population in each arm correspond to intention-to-treat or as-treated populations, according to the available information in each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of overall hazard ratio. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centred on pooled hazard ratios. Heterogeneity estimate of $\tau^2$ accompanies the summary estimate. Values of $\tau^2$ around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval.

European Heart Journal (2016) 37, 3503–3512
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Trials</th>
<th>$\tau^2$</th>
<th>HR (95% CI)</th>
<th>$P$ inter.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>4</td>
<td>&lt;0.001</td>
<td>0.97 (0.76, 0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Access route</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfemoral</td>
<td>4</td>
<td>&lt;0.001</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.024</td>
</tr>
<tr>
<td>Transthoracic</td>
<td>2</td>
<td>&lt;0.001</td>
<td>1.17 (0.88, 1.56)</td>
<td></td>
</tr>
<tr>
<td><strong>TAVI valve system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon-expandable</td>
<td>2</td>
<td>&lt;0.001</td>
<td>0.91 (0.78, 1.07)</td>
<td>0.306</td>
</tr>
<tr>
<td>Self-expandable</td>
<td>2</td>
<td>&lt;0.001</td>
<td>0.76 (0.61, 0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>2</td>
<td>&lt;0.001</td>
<td>0.84 (0.69, 1.02)</td>
<td>0.810</td>
</tr>
<tr>
<td>Non high-risk</td>
<td>2</td>
<td>&lt;0.001</td>
<td>0.90 (0.74, 1.11)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>0.002</td>
<td>0.99 (0.77, 1.28)</td>
<td>0.050</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>&lt;0.001</td>
<td>0.68 (0.50, 0.91)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3** Subgroup analyses for the primary outcome of death from any cause. Hazard ratios and corresponding confidence intervals for patient subgroups from individual trials were pooled and interactions were evaluated by random-effects meta-analyses. Risk ratios were calculated whenever the respective hazard ratios were not reported. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of the overall hazard ratio. Heterogeneity estimates of $\tau^2$ accompany each estimate. Values of $\tau^2$ around 0.04 are considered to indicate low heterogeneity. Transthoracic corresponds to transapical or transaortic approach. TAVI, transcatheter aortic valve implantation; SAIV, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval; $P$ inter, $P$ for interaction.
<table>
<thead>
<tr>
<th>Trial</th>
<th>TAVI</th>
<th>SAVR</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrovascular event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 5/9/348</td>
<td>13/251</td>
<td>18/351</td>
<td>1.01 (0.93, 1.09)</td>
<td>0.301</td>
</tr>
<tr>
<td>US CoreValve 4/2/380</td>
<td>57/357</td>
<td>57/357</td>
<td>0.79 (0.65, 1.11)</td>
<td>0.402</td>
</tr>
<tr>
<td>NOTION 12/8/35</td>
<td>19/357</td>
<td>19/357</td>
<td>1.19 (0.94, 2.04)</td>
<td>0.717</td>
</tr>
<tr>
<td>PARTNER 2A 12/10/11</td>
<td>103/1021</td>
<td>103/1021</td>
<td>1.19 (0.93, 1.52)</td>
<td>0.151</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.070$, $P = 0.055$)</strong></td>
<td></td>
<td></td>
<td>1.15 (0.86, 1.56)</td>
<td>0.442</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 29/3/48</td>
<td>14/351</td>
<td>14/351</td>
<td>1.22 (0.67, 2.23)</td>
<td>0.508</td>
</tr>
<tr>
<td>US CoreValve 4/3/350</td>
<td>59/357</td>
<td>59/357</td>
<td>0.70 (0.48, 1.04)</td>
<td>0.044</td>
</tr>
<tr>
<td>NOTION 8/14/11</td>
<td>77/357</td>
<td>77/357</td>
<td>0.65 (0.42, 1.04)</td>
<td>0.065</td>
</tr>
<tr>
<td>PARTNER 2A 6/10/11</td>
<td>88/1021</td>
<td>88/1021</td>
<td>0.80 (0.56, 1.13)</td>
<td>0.213</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.001$, $P = 0.433$)</strong></td>
<td></td>
<td></td>
<td>0.89 (0.67, 1.08)</td>
<td>0.295</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 9/3/348</td>
<td>5/351</td>
<td></td>
<td>0.11 (0.01, 2.07)</td>
<td>1.000</td>
</tr>
<tr>
<td>US CoreValve 2/3/350</td>
<td>7/357</td>
<td></td>
<td>0.92 (0.32, 2.68)</td>
<td>1.000</td>
</tr>
<tr>
<td>NOTION 8/14/11</td>
<td>77/357</td>
<td></td>
<td>1.06 (0.38, 2.94)</td>
<td>1.000</td>
</tr>
<tr>
<td>PARTNER 2A 3/10/11</td>
<td>37/1021</td>
<td></td>
<td>0.90 (0.57, 1.33)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.001$, $P = 0.561$)</strong></td>
<td></td>
<td></td>
<td>0.89 (0.61, 1.21)</td>
<td>0.558</td>
</tr>
<tr>
<td><strong>Kidney injury</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 20/3/48</td>
<td>21/351</td>
<td></td>
<td>0.98 (0.53, 1.74)</td>
<td>1.000</td>
</tr>
<tr>
<td>US CoreValve 4/2/350</td>
<td>54/357</td>
<td></td>
<td>0.61 (0.28, 0.55)</td>
<td>1.000</td>
</tr>
<tr>
<td>NOTION 8/14/11</td>
<td>27/357</td>
<td></td>
<td>0.61 (0.35, 1.18)</td>
<td>1.000</td>
</tr>
<tr>
<td>PARTNER 2A 6/10/11</td>
<td>57/1021</td>
<td></td>
<td>0.64 (0.42, 0.69)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.004$, $P = 0.155$)</strong></td>
<td></td>
<td></td>
<td>0.61 (0.41, 0.95)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>New-onset AF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 4/3/48</td>
<td>60/351</td>
<td>60/351</td>
<td>0.71 (0.49, 1.02)</td>
<td>0.045</td>
</tr>
<tr>
<td>US CoreValve 7/13/350</td>
<td>82/357</td>
<td>82/357</td>
<td>0.64 (0.42, 0.69)</td>
<td>0.001</td>
</tr>
<tr>
<td>NOTION 8/14/11</td>
<td>80/357</td>
<td>80/357</td>
<td>0.68 (0.51, 0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>PARTNER 2A 11/10/11</td>
<td>273/1021</td>
<td>273/1021</td>
<td>0.41 (0.33, 0.50)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.076$, $P = 0.004$)</strong></td>
<td></td>
<td></td>
<td>0.46 (0.34, 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 6/3/348</td>
<td>98/351</td>
<td>98/351</td>
<td>0.64 (0.48, 0.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>US CoreValve 2/2/350</td>
<td>132/357</td>
<td>132/357</td>
<td>0.83 (0.69, 1.02)</td>
<td>0.001</td>
</tr>
<tr>
<td>NOTION 8/14/11</td>
<td>29/357</td>
<td>29/357</td>
<td>0.54 (0.31, 0.90)</td>
<td>0.001</td>
</tr>
<tr>
<td>PARTNER 2A 11/10/11</td>
<td>47/1021</td>
<td>47/1021</td>
<td>0.26 (0.12, 0.55)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.212$, $P = 0.001$)</strong></td>
<td></td>
<td></td>
<td>0.57 (0.35, 0.95)</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>Major vascular complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 3/3/348</td>
<td>13/351</td>
<td>13/351</td>
<td>3.10 (1.69, 5.70)</td>
<td>0.001</td>
</tr>
<tr>
<td>US CoreValve 2/3/350</td>
<td>7/357</td>
<td>7/357</td>
<td>3.63 (1.99, 6.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>NOTION 8/14/11</td>
<td>2/357</td>
<td>2/357</td>
<td>3.77 (0.82, 17.48)</td>
<td>0.134</td>
</tr>
<tr>
<td>PARTNER 2A 6/10/11</td>
<td>55/1021</td>
<td>55/1021</td>
<td>1.58 (1.14, 2.19)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.151$, $P = 0.004$)</strong></td>
<td></td>
<td></td>
<td>2.46 (1.49, 4.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Valve endocarditis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A 3/5/48</td>
<td>3/351</td>
<td>3/351</td>
<td>1.34 (0.30, 6.08)</td>
<td>0.702</td>
</tr>
<tr>
<td>US CoreValve 3/3/350</td>
<td>5/357</td>
<td>5/357</td>
<td>0.55 (0.13, 2.48)</td>
<td>0.001</td>
</tr>
<tr>
<td>NOTION 8/14/11</td>
<td>2/357</td>
<td>2/357</td>
<td>4.21 (0.04, 14.48)</td>
<td>0.001</td>
</tr>
<tr>
<td>PARTNER 2A 11/10/11</td>
<td>6/1021</td>
<td>6/1021</td>
<td>1.05 (0.69, 1.59)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Overall (Heterogeneity $I^2 = 0.128$, $P = 0.004$)</strong></td>
<td></td>
<td></td>
<td>1.56 (0.74, 3.36)</td>
<td>0.244</td>
</tr>
</tbody>
</table>

Figure 4 Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the secondary outcomes of interest. Forest plots showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the secondary outcomes of interest at up to 2 years of follow-up. In the NOTION trial, for the outcomes of major bleeding and major vascular complications, 30-day follow-up data were included. The provided number of events and total trial population in each arm correspond to intention-to Treat as-treat populations, according to the available information for each outcome and each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centred on pooled hazard ratios. Heterogeneity estimates of $I^2$ accompany each summary estimate. Values of $I^2$ around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation.
## Permanent pacemaker implantation

<table>
<thead>
<tr>
<th>Trial</th>
<th>TAVI</th>
<th>SAVR</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Balloon-expandable TAHV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTNER 1A</td>
<td>23/48</td>
<td>19/351</td>
<td>1.22 (0.68, 2.20)</td>
<td></td>
</tr>
<tr>
<td>PARTNER 2A</td>
<td>114/1011</td>
<td>98/1021</td>
<td>1.20 (0.93, 1.55)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (Heterogeneity $\tau^2 &lt; 0.001$, $P = 0.960$)</td>
<td></td>
<td></td>
<td>1.20 (0.95, 1.52)</td>
<td>0.122</td>
</tr>
<tr>
<td><strong>Self-expandable TAHV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US CoreValve</td>
<td>96/390</td>
<td>42/357</td>
<td>2.09 (1.50, 2.92)</td>
<td></td>
</tr>
<tr>
<td>NOTION</td>
<td>55/142</td>
<td>5/134</td>
<td>10.36 (4.29, 25.14)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (Heterogeneity $\tau^2 = 1.168$, $P = 0.001$)</td>
<td></td>
<td></td>
<td>4.41 (0.92, 21.14)</td>
<td>0.063</td>
</tr>
<tr>
<td><strong>Overall</strong> (Heterogeneity $\tau^2 = 0.341$, $P &lt; 0.001$)</td>
<td></td>
<td></td>
<td>2.12 (1.13, 3.99)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

**Figure 5**  Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the outcome of permanent pacemaker implantation stratified according to transcatheter heart valve system. Forest plot showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the outcome of permanent pacemaker implantation at 2 years of follow-up. The provided number of events and total trial population in each arm correspond to as-treated populations, according to the available information for each outcome and each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of the overall hazard ratio. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centred on pooled hazard ratios. Heterogeneity estimates of $\tau^2$ accompany each summary estimate. Values of $\tau^2$ around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval; TAHV, transcatheter heart valve system.
### Figure 6

Random-effects meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the echocardiographic outcome of paravalvular regurgitation (moderate or severe). Forest plot showing the results of meta-analysis of transcatheter aortic valve implantation vs. surgical aortic valve replacement for the echocardiographic outcome of paravalvular regurgitation (moderate or severe) at 2 years of follow-up. The provided number of events and total trial population in each arm correspond to as-treated populations, according to the available information for each outcome and each trial. Boxes and horizontal lines represent the respective hazard ratio and 95% confidence interval for each trial. The vertical solid line on the plot represents the point estimate of hazard ratio = 1. The vertical dashed line on plot represents the point estimate of the overall hazard ratio. The size of each box is proportional to weight of that trial result. Diamonds represent the 95% confidence interval for pooled estimates of the effect and are centered on pooled hazard ratios. Heterogeneity estimates of \( \tau^2 \) accompany each summary estimate. Values of \( \tau^2 \) around 0.04 are considered to indicate low heterogeneity. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; CI, confidence interval.
FDA News Release

FDA approves expanded indication for two transcatheter heart valves for patients at intermediate risk for death or complications associated with open-heart surgery
Medtronic CoreValve Evolut becomes first TAVI to receive CE mark for intermediate risk aortic stenosis patients

1st August 2016    397
Διακαθετηριακή αντικατάσταση αορτικής βαλβίδας στην κλινική πράξη. Έφτασε στην κορυφή ή είμαστε έτοιμοι για το επόμενο βήμα?

Σε Χαμηλού κινδύνου ασθενείς STS < 4
Rationale for TAVI in Low-Risk Patients

Bonow et al. Lancet 2016;387:1312-23

All-cause Mortality at 30 Days

- Inoperable
- High risk
- Combined inoperable and high risk
- Intermediate risk

All-cause mortality (%)

- P1B (TF): 6.3%
- P1A (All): 5.2%
- P1A (TF): 3.7%
- P2B (TF): 4.5%
- P2B (TF): 3.5%
- S3HR (All): 2.2%
- S3HR (TF): 1.6%
- S3i (All): 1.1%
- S3i (TF): 1.1%

Patients: 175 344 240 271 282 583 491 1072 947
After 14 years since its introduction, with over 200,000 TAVI performed worldwide

- Major reductions in TAVI-related complications and
- Reliable evidence for good medium-term valve durability
- There is less justification for the imposition of strict limitations on the use of TAVI based on surgical risk stratification.
Clinical experience has revealed a number of barriers which, if overcome, would pave the way for expansion of TAVR into more patients.

Technological advancement can touch all aspects of TAVR.
IT HAS BEEN SUGGESTED THAT AN OPTIMAL TAVI CENTRE SHOULD BE ABLE TO ACHIEVE THE FOLLOWING OUTCOMES IN HIGH-RISK PATIENTS WITH SEVERE AS IN THE FUTURE:

- **1) All-cause mortality of approximately 2–3% at 30 days and <10% at 1 year;**
- **2) Significant strokes at 30 days in <2%;**
- **3) Major vascular complications in <5%;**
- **4) New permanent pacemakers in <10%;**
- **5) Moderate or severe paraavalvular aortic regurgitation in <5%;**
MORE DATA IN LOWER-RISK PATIENTS ARE ACCUMULATED

• TAVI WILL NOT BE CURTAILED BY RISK STRATIFICATION
  BUT RATHER WILL BE INFLUENCED MORE

• BY ANATOMIC

• CLINICAL FACTORS

• AND PROBABLY PATIENT PREFERENCE

• FINANCIAL ISSUES
**Future TAVI indication**

Low surgical risk: active trials randomizing TAVI vs SAVR

- **Medtronic Low Risk**
  - N = ~1200
  - Up to 80 centers
  - Evolut R, all routes
  - Industry-sponsored 10-year follow-up

- **PARTNER 3**
  - N = 1228
  - Up to 64 centers
  - SAPIEN 3, transfemoral
  - Industry-sponsored 10-year follow-up

- **UK TAVI**
  - N = 808
  - All UK TAVI centers
  - All valves, all routes
  - Publicly funded 5-year follow-up

- **NOTION-2**
  - N = 992
  - All Nordic countries
  - All valves, transfemoral
  - Physician and industry-sponsored 5-year follow-up

(TAVI an example of disruptive technology)

---

Falk V, Circulation 2014; 130(25):2332-2342
The German Aortic Valve Registry: 1-year results from 13 680 patients with aortic valve disease†

Friedrich W. Mohr⁎, David Holzhey⁎, Helge Möllmann⁎, Andreas Beckmann⁎, Christof Veit⁎, Hans Reiner Figulla⁎, Jochen Cremer⁎, Karl-Heinz Kuck⁎, Rüdiger Lange⁎, Ralf Zahn⁎, Stefan Sack⁎, Gerhard Schuler⁎, Thomas Walther⁎, Friedhelm Beyersdorf⁎, Michael Böhm⁎, Gerd Heusch⁎, Anne-Kathrin Funkat⁎, Thomas Meinertz⁎, Till Neumann⁎, Konstantinos Papoutsis⁎, Steffen Schneider⁎, Armin Welz⁎ and Christian W. Hamm⁎, for the GARY Executive Board
### EuroSCORE < 10

<table>
<thead>
<tr>
<th>Treatment</th>
<th># at Risk - day</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>4731</td>
</tr>
<tr>
<td>AVR+CABG</td>
<td>2138</td>
</tr>
<tr>
<td>TV-AVR</td>
<td>409</td>
</tr>
<tr>
<td>TA-AVR</td>
<td>194</td>
</tr>
</tbody>
</table>

### EuroSCORE 20 - < 30

<table>
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<th>Treatment</th>
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<tbody>
<tr>
<td>AVR</td>
<td>312</td>
</tr>
<tr>
<td>AVR+CABG</td>
<td>235</td>
</tr>
<tr>
<td>TV-AVR</td>
<td>514</td>
</tr>
<tr>
<td>TA-AVR</td>
<td>247</td>
</tr>
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</table>

### EuroSCORE 10 - < 20

<table>
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</thead>
<tbody>
<tr>
<td>AVR</td>
<td>1060</td>
</tr>
<tr>
<td>AVR+CABG</td>
<td>809</td>
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<tr>
<td>TV-AVR</td>
<td>856</td>
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<tr>
<td>TA-AVR</td>
<td>383</td>
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### EuroSCORE ≥ 30

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<th>Treatment</th>
<th># at Risk - day</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>255</td>
</tr>
<tr>
<td>AVR+CABG</td>
<td>198</td>
</tr>
<tr>
<td>TV-AVR</td>
<td>801</td>
</tr>
<tr>
<td>TA-AVR</td>
<td>317</td>
</tr>
</tbody>
</table>
GARY: TAVR vs. SAVR in Intermediate Surgical Risk Severe AS

In-hospital and one-year death rates were significantly higher in TAVR patients than SAVR (3.8 vs. 2.6 and at one year after TAVR 16.6 percent vs. 8.9 percent

Retrospective analysis from registry data is not the method of choice to compare two treatment strategies as it should only be done by randomized controlled trials
**TAVI in Low-Risk Patients: Ongoing Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>CoreValve</th>
<th>NOTION-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARTNER 3</strong></td>
<td>NCT02675114</td>
<td>NCT02825134</td>
</tr>
<tr>
<td><strong>CoreValve</strong></td>
<td>NCT02701283</td>
<td></td>
</tr>
<tr>
<td><strong>NOTION-2</strong></td>
<td>NCT02825134</td>
<td></td>
</tr>
</tbody>
</table>

**Low surgical risk as assessed by Heart Team**

- **PARTNER 3**: STS < 4%
- **CoreValve**: STS < 3%
- **NOTION-2**: STS < 4%

**Sample Size**

- **PARTNER 3**: N=1,228
- **CoreValve**: N=1,200
- **NOTION-2**: N=992

**1:1 Randomization TAVI Vs. SAVR**

- **PARTNER 3**: SAPIEN 3
- **CoreValve**: Evolut R
- **NOTION-2**: Any CE-approved device

**Primary Endpoint**

- **PARTNER 3**: All-cause mortality, any stroke, life-threatening bleeding, major vascular complications, or AKI at 30-day
- **CoreValve**: All-cause mortality, myocardial infarction, or any stroke at 1-year
- **NOTION-2**: All-cause mortality, myocardial infarction, or any stroke at 1-year
Can TAVI be superior to surgery;
**TAVI vs SAVR - Patient Prosthesis Mismatch**

P ARTNER A

AS TREATED PATIENT COHORT

SAVR RCT 60% PPM
TAVI RCT 46% PPM
TAVI NRCA 44% PPM

Impact of PPM on LV Mass

SAVR

TAVI

P ARTNER A

SMALL AORTIC ANNULUS (< 20 MM)

P=0.002

SAVR RCT 65% PPM
TAVI RCT 42% PPM
TAVI NRCA 46% PPM

**P Ibarot P et al. J Am Coll Cardiol 2014;64:1323-34**
EARLY DISCHARGE AFTER TRANSFEMORAL TAVI

L AUCK SB ET AL. CIRC CARDIOVASC QUAL OUTCOMES 2016; 9:312-21

- Multidisciplinary
- Multimodality
- Minimalist
  - TF Access
  - Next day discharge

Bar chart showing the distribution of patients by length of stay.

- Early Discharge (EDC): $\leq 48$ hours, 150 (37.8%), [38.2% of patients discharged]
- Standard Discharge (SDC): $> 48$ hours, 243 (61.2%), [61.8% of patients discharged]
**Simplification of Procedure Reduces TAVI Costs**

R EYNOLDS MR ET AL. *J ACCARDIOL* 2012;60:2683–9
B ABALIAROS V ET AL. *J ACCARDIOL I NTV* 2014;7:898–904

Length of stay (TF TAVR)

- **PARTNER 1A TA cohort**: 10 days, $74,721
- **PARTNER 1A TF cohort**: 7 days, $61,297
- **Emory optimized approach**: 3.0 days, $45,485
TAVI Vs SAVR: Mortality in Female Patients

Siontis et al. Eur Heart J 2016

All-cause Mortality at 2 years (N = 3,806)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Trials</th>
<th>$\tau^2$</th>
<th>HR (95% CI)</th>
<th>P-inter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>0.002</td>
<td>0.99 (0.77, 1.28)</td>
<td>0.050</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>&lt;0.001</td>
<td>0.68 (0.50, 0.91)</td>
<td></td>
</tr>
</tbody>
</table>

Overall 0.87 (0.76-0.99), P=0.038
In the next 10 years, TAVR growth will increase X4!
BICUSPID AORTIC VALVE DISEASE

- BICUSPID AORTIC VALVES HAVE A HIGH PREVALENCE IN YOUNGER PATIENTS WITH AS, BUT EVEN IN THE ELDERLY BICUSPID VALVES COMPRISE APPROXIMATELY 20% OF SURGICAL CASES.

- TAVI IS SAFE AMONG PATIENTS WITH BICUSPID AORTIC VALVES, WITH A 5% 30-DAY AND 17.5% 1-YEAR MORTALITY.

- HOWEVER, POST-IMPLANTATION MODERATE TO SEVERE PARAVALVULAR AORTIC REGURGITATION WAS FOUND IN 28.4% OF PATIENTS, ALTHOUGH THIS APPEARED TO BE MITIGATED SOMEWHAT BY CT-BASED THV SIZING.
Future TAVI indication: bicuspid morphology

5/44 11.4%
Type 0
No raphe

31/44 70.5%
Type 1
One raphe

1/44 2.3%
Type 2
Two raphe

L - R
R - N
L - N
L - N / R - N

5/44 11.4%
2/44 4.5%


Future TAVI indication: bicuspid morphology

TF S3 8/44 18.2%
TF CV/Evo 4/44 9.1%
TF SYM 1/44 2.7%
TA SAP 31/44 70.5%
Conclusions

TAVI: future developments

TAVI – a disruptive technology.

Technical evolution in imaging simplifies pre-procedural planning and intra-procedural guidance.

Next generation devices will minimize the limitations of TAVI:
- paravalvular regurgitation
- heart block and conductance disturbances
- vascular complications

The indication shift towards lower risk patients will continue.
Severe Aortic Regurgitation
The Limitation

- In untreated patients with symptomatic severe aortic regurgitation, mortality may be as high as 10-20% per year\(^1\)
- ESC\(^2\) and ACC/AHA\(^3\) guidelines recommend SAVR for these patients, however an alternative is needed for those at very high surgical risk

Isolated Aortic Insufficiency

- Non-calcified, thin leaflets
- Dilated annulus
- Dilated root
- Dilated aorta
- Dilation may progress even after AVR

Patients with severe aortic regurgitation typically have large, non-calcified annuli, which may continue to dilate after treatment\(^4\)

\(^1\) Jung, et al., Eur Heart J 2003; 24: 1231-43; \(^2\) Vahanian, et. al., Eur Heart J 2012; 33: 2451-2496; \(^3\) Nishimura, et al., Circulation 2014; 129: e521-e643; \(^4\) Webb, et al., EuroPCR 2013
Severe Aortic Regurgitation
The Current Evidence

- Early mortality was high, but may reflect the high-risk status of the patients.
- The positive PVL outcomes achieved with JenaValve suggest that devices with "active fixation" are well suited for this anatomy.

---

30-Day Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>Stroke</th>
<th>Pacemaker</th>
<th>Mod/Severe PVL (Post-Procedure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JenaValve (Seiffert)</td>
<td>12.9%</td>
<td>0.0%</td>
<td>4.7%</td>
<td>21.0%</td>
</tr>
<tr>
<td>CoreValve (Roy)</td>
<td>9.3%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>23.0%</td>
</tr>
<tr>
<td>CoreValve (Testa)</td>
<td>23.0%</td>
<td>0.0%</td>
<td>5.0%</td>
<td>23.0%</td>
</tr>
</tbody>
</table>

---

Severe Aortic Regurgitation
The Future Need

- There are limited available treatment options for patients with severe aortic regurgitation who cannot undergo surgery
- Early clinical experience shows the need for a dedicated TAVR system with:
  - Transfemoral delivery
  - Active fixation for anchoring within the annulus
  - Sizes appropriate for large or dilated anatomy
  - Recapturability
Concomitant Mitral Disease
Feasibility of Dual Transcatheter Procedures

Select high-risk or inoperable patients with concomitant disease may have improved prognosis if both valves are treated percutaneously, either during a single procedure or through a staged approach.

TAVR in 2011 followed by TMVR in 2015 for severe mitral stenosis with annular calcification\(^1\)

Simultaneous TAVR, MitraClip, and AMPLATZER Cardiac Plug\(^2\)

Concomitant Mitral Disease
The Future Need

- A significant proportion of TAVR patients present with concomitant mitral disease. Treatment may improve outcomes for certain patients.

- Further study is needed to understand which patients have the potential to benefit from a dual procedure.

- Once we understand patient selection, this could become common practice. Future needs include:
  ✓ A toolbox of transcatheter mitral repair and replacement technologies
  ✓ Transcatheter aortic and mitral valve technologies which are designed to work in tandem
Antithrombotic regimen in TAVI

In patient undergoing TAVI with CoreValve, with concurrent AF, treatment with clopidogrel plus acenocoumarol for 3 months, followed by acetylsalicylic acid plus acenocoumarol since then, seems safe and effective enough in long-term follow-up. Further research for new and even safer antithrombotic regimen combinations is required.
4D-CT Image – Case 1

Immobile Leaflet

Thrombus overlying stent frame
GALILEO trial design

1520 patients after successful TAVR procedure

R 1:1

Rivaroxaban 10 mg od + ASA 75–100 mg od

Clopidoogrel* 75 mg od + ASA 75–100 mg od

At 3 months: Drop one antiplatelet

Rivaroxaban 10 mg od

ASA 75–100 mg od

Primary endpoint: Composite of death, MI, stroke, systemic embolism, symptomatic valve thrombosis and VTE (DVT or PE) over follow-up**

*In subjects who are clopidogrel naïve at randomisation, at least 300 mg of clopidogrel should be administered followed by clopidogrel 75 mg od

**GALILEO is an event driven study – the duration of the study depends on the efficacy cut-off date (event rate)

ClinicalTrials.gov. NCT02556203
ATLANTIS trial Design

Apixaban in Patients Who Underwent a Clinically Successful TAVI Procedure

N = 1509

Stratum 1
Indication for anticoagulation

Stratum 2
No indication for anticoagulation

SOC* - VKA

Apixaban 5 mg twice daily
2.5 mg twice daily in select patients*

SOC-DAPT/ SAPT

Primary endpoint: Composite of death, MI, stroke/TIA/systemic emboli, intracardiac or bioprosthesis thrombus, episode of DVT/PE, major bleeding, over 6 months of follow-up.

*2.5 mg twice daily if CrCl 15 to 29mL/min or if 2 of the following criteria: age ≥ 80 y, weight ≤ 60 kg, or Cr ≥ 1.5 mg/dL (133 μmol).

ClinicalTrials.gov. NCT02664649
A Trial to Assess the Safety and Efficacy of Prophylactic Ticagrelor With Acetylsalicylic Acid Versus Clopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular Embolic Events During Transcatheter Aortic Valve Implantation (TAV) (PTOLEMAICS)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02989558

**Sponsor:**
University of Athens

**Information provided by (Responsible Party):**
Dr. Emmanuel Vavuranakis, University of Athens

**Study Details**

**Study Description**

**Brief Summary:**
Ticagrelor administered with Acetylsalicylic Acid (ASA) will provide better cerebrovascular protection from microembolization in the cerebral circulation during Transcatheter Aortic Valve Implantation (TAVI) and 30 days afterwards, than Clopidogrel plus ASA. This hypothesis will be investigated by measuring the number of High Intensity Transient Signals (HITS) as assessed with transcranial Doppler (TCD) on middle cerebral arteries.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/Treatment</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Valve Stenosis</td>
<td>Drug: Ticagrelor plus ASA</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Drug: Clopidogrel plus ASA</td>
<td></td>
</tr>
</tbody>
</table>

**Study Design**

**Study Type:** Interventional (Clinical Trial)

**Estimated Enrollment:** 90 participants

**Allocation:** Randomized

**Intervention Model:** Parallel Assignment

**Masking:** None (Open Label)

**Primary Purpose:** Prevention

**Official Title:** A Prospective, Multicentre, Randomized, Open Label, Blinded Endpoint Phase 3 Trial to Assess the Safety and Efficacy of Prophylactic Ticagrelor With Acetylsalicylic Acid Versus Clopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular Embolic Events During Transcatheter Aortic Valve Implantation (TAVI) Operations - the PTOLEMAICS Study

**Study Start Date:** December 2016

**Estimated Primary Completion Date:** December 2018

**Estimated Study Completion Date:** December 2018
A Trial to Assess the Safety and Efficacy of Prophylactic Ticagrelor With Acetylsalicylic Acid Versus ClOpidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular Embolic Events During TAVI (PTOLEMAIOS)
MODERATE AS AND CLINICAL HEART FAILURE

• THE TRANSCATHETER AORTIC VALVE REPLACEMENT TO UNLOAD THE LEFT VENTRICLE IN PATIENTS WITH ADVANCED HEART FAILURE STUDY (TAVR-UNLOAD; NCT02661451)

• WILL COMPARE CLINICAL OUTCOMES AMONG SYMPTOMATIC PATIENTS [NEW YORK HEART ASSOCIATION CLASS ≥2] IN HEART FAILURE [LEFT VENTRICULAR EJECTION FRACTION 20–50 %] AND MODERATE AS UNDERGOING TAVI WITH THE SAPIEN 3 VALVE VERSUS OPTIMISED HEART FAILURE THERAPY.
TAVI IN NON-CARDIAC SURGERY SITES
TAVI IN NON-CARDIAC SURGERY SITES

• Owing to the continued evolution of TAVI to become an effective and safe treatment modality, the need for emergency cardiac surgery for complications during TAVI is currently low and about 1%.

• A recent German multicentre registry comparing outcomes after TAVI among patients treated in centres with and without on-site cardiac surgery reported that

• While patients undergoing TAVI at hospitals without on-site cardiac surgery were older and at higher predicted surgical risk, major complications and in-hospital mortality were not statistically different.

TAVR Accessory Devices

**Balloon Aortic Valvuloplasty (1)**

- Locks into annulus for stability (doesn’t need PM)
- Overextends leaflets safely
- Good for post-dilation

**WHY?**

- Kevlar composite materials
- Non-compliant and rupture resistant (precise sizing)
- Good for post-dilation

- Scoring elements improve stability (doesn’t need PM)
- Enhance valvuloplasty effect
Additional tools

BARD True Flow balloon: continuous cardiac blood flow independent of the heart’s rhythmic state
**Leafflex AVRT**

- Mechanical shock waves fracture leaflet calcium and improve leaflet mobility
- 13 Fr catheter
- Non-occlusive (no PM)
- Can be used as (1) stand-alone, (2) bridge to TAVR/SAVR or (3) preparation for TAVR (esp. bicuspid valves)
Lithoplasty for Aortic Leaflet Restoration

- Electro-hydraulic lithotripsy in a balloon; microsecond bubble expansion and collapse travels thru balloon and disrupts calcium
- Supra-avalvular approach
- Procedural hemodynamic stability; no need for PM
- Trans-femoral access
- Preparation for TAVR preparation or stand-alone therapy
Future generations (MEDTRONIC)

Evolut NG
- Low Profile
- Improved Visualization
- Controlled Release
- Consistent Implant Depth

Horizon
- Concentric Deployment
- Enhanced Sealing
- Superior Hemodynamics
- Complete Control

courtesy of MEDTRONIC
Neurologic Injury
The Clinical Need for Embolic Protection

Van Mieghem, et al., have examined the contents of Claret Montage filters which were placed within the brachiocephalic and left common carotid arteries during TAVR.

The key findings:
- Macroscopic debris was released into the circulation in ~90% of TAVR procedures.
- The debris was composed of thrombotic material, bits of valve leaflet, calcified particles, myocardial tissue, or plastic fragments from interventional tools.

![Graph showing percentages of different debris types.]

Van Mieghem, et al., *J Am Coll Cardiol Intv* 2015; 8: 718-24
Montage (Claret)
CLEAN-TAVI | Day 7 Imaging

- 98% of patients (protected and unprotected) showed some form of neurologic injury on MRI
- Montage significantly reduced total lesion number by 50% and total lesion volume by 57%

Lesion Number per Patient

- Median New Lesion Number (n): 10 (Control), 5 (With Claret Medical CPS)
- 50% Reduction

Total Lesion Volume per Patient

- Median Total New Lesion Volume (mm³): 472 (Control), 205 (With Claret Medical CPS)
- 57% Reduction

Linke, et al., presented at TCT 2014
Embolic Protection Devices
Potential to Attenuate the Risk of Stroke

TriGuard Embolic Deflection Device (Keystone Heart)¹
- Pore Size: 130 μm
- Delivery Sheath: 9F
- Access: Transfemoral
- Coverage: Brachiocephalic, left common carotid, left subclavian

Sentinel Cerebral Protection System (Claret Medical)²
- Pore Size: 140 μm
- Delivery Sheath: 6F
- Access: Brachial or radial
- Coverage: Brachiocephalic, left common carotid

Embrella Embolic Deflector System (Edwards Lifesciences)³
- Pore Size: 100 μm
- Delivery Sheath: 6F
- Access: Brachial
- Coverage: Brachiocephalic, left common carotid

Permanent Pacemakers
A Better Solution?

Early implantation of a COST EFFECTIVE, leadless pacemaker could:

✓ Encourage earlier mobility
✓ Reduce complications such as pocket infection
✓ Decrease length of stay
✓ Provide VVIR pacing as a bridge to a dual chamber device, if the pacing indication persists

Transcatheter Leadless Pacemaker Implantation for Complete Heart Block Following CoreValve Transcatheter Aortic Valve Replacement

MARAT FUDIM, M.D., JOSEPH L. FREDI, M.D., STEPHEN K. BALL, M.D., and CHRISTOPHER R. ELLIS, M.D.

From the Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Final Position of the Micra

Vascular Complications
The Limitation

• For those treated with an iliofemoral approach, ~5% experience a major vascular complication
• Until this rate is zero, we have room to improve

<table>
<thead>
<tr>
<th>Device</th>
<th>% Patients with MVC (VARC 2, 30 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN</td>
<td>15.5%</td>
</tr>
<tr>
<td>SAPIEN XT</td>
<td>9.6%</td>
</tr>
<tr>
<td>Evolut R</td>
<td>8.3%</td>
</tr>
<tr>
<td>LOTUS REPRISE II</td>
<td>5.2%</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>5.0%</td>
</tr>
<tr>
<td>ACURATE</td>
<td>3.4%</td>
</tr>
<tr>
<td>N=276</td>
<td>N=284</td>
</tr>
<tr>
<td>N=60</td>
<td>N=250</td>
</tr>
<tr>
<td>N=583</td>
<td>N=89</td>
</tr>
</tbody>
</table>

Minimum Vessel Diameter (mm) | 7.0 | 7.0 | 5.0 | 6.0 | 5.5 | 6.0

Additional tools

PerQseal: percutaneous closure up to 24F, intravascular patch (resorbable synthetic polymer)
TAVR Accessory Devices

**Large Hole Vascular Closure**  
*(novel technologies)*

- **MANTA**  
  Collagen seal with footplate and footplate (14 and 18 Fr) lasure

- Large hole vascular closure is an integral component of the transfemoral TAVR procedure
- Safety concerns are “moderate” – early and late – requiring reasonable demonstration of device performance in observational registries with 30-90 day clinical follow-up
TAVR Accessory Devices

**Novel Imaging Systems**

Multi-modality Imaging is the RULE

- Patient Follow-up
- Patient Screening, Procedural Planning
- Intra-procedural Guidance

Images: Angio, CTA, TTE, TEE + 3D
CT guided TAVI

HeartNavigator 3
Image Guidance – VinV Mitral

M-ViV Implant – TEE-Fluoro-Fusion-Imaging
Image Guidance – D-VinV Mitral

M-ViV Implant; TEE-Fluouro-Fusion Imaging
TAVI predictive modelling

Result validation with post-procedural data

- Preop CT
- Segmentation
- Modelling
- Virtual Stent Placement
- Virtual Stent Release
- Comparison between Simulation & Measurement
- Postoperative Stent Geometry
- Postop CT

FNS SNF
Swiss National Science Foundation
TAVI predictive modelling

Virtual stent release
TAVI modelling and forecasting

Analysis of calcium displacement and loss

Preoperative Calcium (white) and postoperative calcium (green)
TAVI modelling and forecasting

Analysis of local stress/strain and valve deformation
Post-Discharge Monitoring
The Limitation

A recent study of 720 TAVR patients looked at the causes of hospital readmission in more detail

- 43.9% of TAVR patients experienced a re-admission within the first year
- 41% of the readmissions were due to cardiac causes

Readmission for Cardiac Causes

- Heart Failure: 56.7%
- Arrhythmia: 21.2%
- Acute Coronary Syndrome: 13.0%
- Prosthesis-Related: 9.0%

\[1\text{Nombela-Franco, et al., J Am Coll Cardiol Intv 2015; 8:1748-1757}\]
Post-Discharge Monitoring
The Limitation

The TVT Registry shows that ~60% of TAVR patients in the US are discharged home

18.6% of patients alive at 12 months had been re-hospitalized for stroke, heart failure, or repeat aortic valve intervention

^Holmes, et al., JAMA 2015; 313: 1019-28
Post-Discharge Monitoring
Medtronic SEEQ Mobile Cardiac Telemetry

SEEQ is an external patch monitor that patients could wear for the first month at home.

**Patch-based ECG monitoring**
- Up to 30 days of continuous monitoring\(^1\)
- Automatic and patient marked events recorder

**Wireless Communication**
- Automatic transmission of data to Medtronic Monitoring Center

**Medtronic Monitoring Center**
- Attended 24/7 by trained cardiographic technicians
- Proactive assessment of data and patient compliance
- Customizable physician reporting
Post-Discharge Monitoring
Medtronic Reveal LINQ Insertable Cardiac Monitor

LINQ is a small subcutaneous ECG monitor which lasts 3 years.
1. Atrial Fibrillation During or After TAVI: Incidence, Implications, and Therapeutical Considerations.
   Vavuranakis M, Kolokathis AM, Vrachatis DA, Kalogeras K, Magkoutis NA, Fradi S, Ghostine S, Karamanou M, Tousoulis D.
   PMID: 26642773
   Similar articles

   PMID: 25863809
   Similar articles

3. Inferior epigastric artery as a landmark for transfemoral TAVI: Optimizing vascular access?
   PMID: 23197457
   Similar articles

   PMID: 26888915
   Similar articles

5. Percutaneous paravalvular leak closure after TAVI: a demanding approach.
   Vavuranakis M, Vrachatis DA, Tousoulis D.
   PMID: 25251978
   Similar articles
Team work
Past & present

6. Tropin levels after TAVI are related to the development of distinct electrocardiographic changes.
   TAVI in the case of pre-existing mitral prosthesis. Tips & tricks and literature review.
   Vavuranakis M, Karori M, Voudris V, Thomopoulos S, Aznaouridis K, Kalogeraki K, Vrachatis D,
   PMID: 23084110
   Similar articles

7. TAVI in the case of pre-existing mitral prosthesis. Tips & tricks and literature review.
   Vavuranakis M, Vrachatis DA, Kanori MG, Moldovan C, Kalogeraki K, Lavda M, Aznaouridis K, Stefanadis C.
   PMID: 23366003 Free Article
   Similar articles

8. A Modified Technique to Safely Close the Arterial Puncture Site After TAVI.
   Vavuranakis M, Kalogeraki KI, Vrachatis DA, Kanori MG, Aznaouridis K, Moldovan C, Stefanadis C.
   PMID: 23293175 Free Article
   Similar articles

9. "Balloon withdrawal technique" to correct prosthetic malposition and treat paravalvular aortic regurgitation during TAVI.
   Vavuranakis M, Kanori M, Vrachatis D, Aznaouridis C, Kalogeraki K, Moldovan C, Stefanadis C.
   PMID: 23549394 Free Article
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    PMID: 22689848
    Similar articles

    PMID: 23763705
    Similar articles

    Vavuranakis M, Siasos G, Zografos T, Cikonomou E, Vrachatis D, Kalogeraki K, Papaioannou T, Kolokathis MA, Moldovan C, Tousoulis D.
    PMID: 27762328
    Similar articles

13. Impact of inflammatory process on left ventricular recovery after Transcatheter Aortic Valve Implantation.
    PMID: 23388331
    Similar articles

14. First in Greece Transcatheter Aortic Valve Implantation using the CoreValve Evolut-R Retractable and Repositionable Prosthesis with the InLine Sheath and the FitVeo Loading Guiding Catheter: A Major Advantage for Small Diameter Access Vessels.
    PMID: 26133778
    Similar articles

15. Four-year clinical results of transcatheter self-expanding Medtronic CoreValve implantation in high risk patients with severe aortic stenosis.
    PMID: 27013900
    Similar articles

    PMID: 27524611
    Similar articles

17. "String sign": a mismatch of currently available self-expandable valve and the annulus stringing.
    Vavuranakis M, Kanori M, Aznaouridis K, Moldovan C, Kalogeraki K, Stefanadis C.
    PMID: 24574437
    Similar articles
18. **Transcatheter aortic valve implantation, patient selection process and procedure: two centres’ experience of the intervention without general anaesthesia.**
   
   
   PMID: 21169181  Free Article
   
   Similar articles

19. **Antithrombotic therapy in TAVI**
   
   
   PMID: 29434628  Free PMC Article
   
   Similar articles

20. **Transcatheter aortic-valve implantation by the subclavian approach complicated with vessel dissection and transient left-arm paralysis.**
   
   
   PMID: 20656500
   
   Similar articles

21. **Successful Transcatheter Aortic Valve Implantation of a Low-Profile Last-Generation Aortic Bioprosthesis in a Patient With Coarctation of the Aorta.**
   
   
   PMID: 27006314
   
   Similar articles

22. **Antiplatelet and Anticoagulation Therapy in Structural Heart Disease Interventions Beyond TAVI.**
   
   
   PMID: 28603014
   
   Similar articles

23. **Impact of balloon aortic valvuloplasty on transcatheter aortic valve implantation with self-expandable valve.**
   
   
   PMID: 27177535
   
   Similar articles