The foundation of a new therapy based on RCTs: The TAVR paradigm

Νάσος Μαγγίνας, MD
FACC, FESC
Νοσοκομείο Mediterraneo
Γλυφάδα
Σύγκρουση συμφερόντων

• Καμία σχετικά με αυτή την παρουσίαση
The long bumpy road to TAVR

1985
F.I.M. BAV

1994
Autopsy Study, first drawings

1994-99
Search for a sponsor

1999
First prototypes of THV (PVT)

1999-02
Lab tests and animals

2002
F.I.M. TAVR
1993-1994 Autopsy study
Validation of the concept of intra-valvular stenting

- Coronary ostia
- Diameter 23mm
- Heighth: 14/16 mm
- Post-BAV 23mm balloon
- Post-Stent longitudinal view
- IV Septum
- Mitral Valve
1999- Foundation of PVT
“Percutaneous Valve Technologies”

Funding
Patent applications
Business plan
Development partners
Engineering
Lab investigation

A great little company helped by some of the best and the brightest

Animal implantation programs
Human implantation
Clinical studies
Cadaver study (2002)
Renu Virmani, MD, Washington DC

Circular Palmaz stent opening

Traction force >2kg to dislodge the stent
2002, Rouen, F.I.M – TAVR
Moving from the concept to the clinical demonstration

Lessons from this first TAVR

1- Feasibility of TAVR
2- Accuracy of valve placement
2- No THV embolization
3- No coronary occlusion
4- No MR
5- No AV-heart block
6- Mild AR (paravalvular)
7- Optimal valvular function
8- Excellent hemodynamics
2002-2005: The “trans-septal era” in Rouen
40 patients, I-REVIVE & RECAST trials

Compassionate use (Imminent Death)

- Trans-septal approach (85% success)
- 5 patients survived > 5-y: no device dysfunction

TAVR takes its flight abroad: 100 TAVR cases!

B. O’Neill
Detroit

M. Leon
NYC

A. Colombo
Milano

J. Webb
Vancouver

P. Serruys
Rotterdam
True percutaneous implantation of the CoreValve aortic valve prosthesis by the combined use of ultrasound guided vascular access, Prostar® XL and the TandemHeart®

Peter de Jaegere¹, MD, PhD; Lukas C. van Dijk², MD, PhD; Jean Claude Laborde³, MD; George Sianos¹, MD, PhD; Francisco Javier Orellana Ramos¹, MD; Jurgen Lighart¹, BSc; Arie Pieter Kappetein³, MD, PhD; Martin vander Ent¹, MD, PhD; Patrick W Serruys¹, MD, PhD, FESC, FACC
Trans-catheter aortic valve implantation: Contemporary practice and the future

Omar Aldalati, Philip MacCarthy, Rafal Dworakowski
Kings College Hospital, London, United Kingdom

TAVI implants per million; difference between 2008 and 2011

- Germany: 30 in 2008, 89 in 2011 (X 3)
- Switzerland: 18 in 2008, 65 in 2011
- Denmark: 18 in 2008, 45 in 2011
- France: 3 in 2008, 38 in 2011
- United Kingdom: 6 in 2008, 15 in 2011
Expected growth in the next decade

Global TAVR Units

SOURCE: Credit Suisse TAVR Comment – January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

M Leon, TVT 2016
US Industry Growth in Millions USD

Source: DRG PriceTrack data
Διαδερμική Εμφύτευση Αορτικής Βαλβίδας.
Η Πρώτη Ελληνική Εμπειρία

ΚΩΝΣΤΑΝΤΙΝΟΣ ΣΙΑΡΓΙΑΣ, ΑΘΑΝΑΣΙΟΣ ΜΑΤΙΝΑΣ, ΓΡΗΓΟΡΗΣ ΠΑΥΛΙΔΗΣ, ΜΑΖΕΝ ΚΙΟΥΡΥ,
ΓΕΩΡΓΙΟΣ ΣΤΑΥΡΙΔΗΣ, ΠΑΝΑΓΙΩΤΑ ΡΕΛΙΑ, ΑΝΝΑ ΣΜΥΡΗ, ΑΠΟΣΤΟΛΟΣ ΘΑΝΟΠΟΥΛΟΣ,
ΜΑΡΙΝΑ ΜΠΑΛΑΝΙΚΑ, ΣΠΥΡΟΣ ΠΟΛΥΜΕΡΟΣ, ΣΩΦΙΑ ΘΩΜΟΠΟΥΛΟΥ,
ΓΕΩΡΓΙΟΣ ΑΘΑΝΑΣΙΟΠΟΥΛΟΣ, ΓΕΩΡΓΙΟΣ ΚΑΡΑΤΑΖΑΚΗΣ, ΡΕΝΑΤΑ ΜΑΣΤΟΡΑΚΟΥ,
ΣΤΑΥΡΟΥΛΑ ΛΑΚΟΥΜΕΝΤΑ, ΑΛΚΗΣ ΜΙΧΑΛΗΣ, ΠΕΤΡΟΣ ΑΛΙΒΙΖΑΤΟΣ, ΔΙΟΝΥΣΙΟΣ ΚΟΚΚΙΝΟΣ

1η Καρδιολογική, 1η και 2η Καρδιοχειρουργική Κλινική, Τμήμα Αναισθησιολογίας και Τμήμα Ακτινολογίας
Εθνικού Καρδιοχειρουργικού Κέντρου, Αθήνα
The TAVR paradigm

• 1. Επιμονή για μία νέα, υποσχόμενη θεραπεία.

• Ποια είναι τα χαρακτηριστικά της εξέλιξης της διακαθετηριακής αορτικής εμφύτευσης (TAVR) που θα μπορούσαν να χρησιμεύσουν σε άλλες νέες μεθόδους;
2. SAVR risk assessment: the Heart Team

<table>
<thead>
<tr>
<th>STS PROM</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Inoperable</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TAVR reasonable for patients with contraindications to SAVR:

Absolute: Porcelain aorta, hostile chest, radiation damage, previous severe thoracotomy complications
Relative: frailty, cirrhosis, CABG/vulnerable grafts, severe PHTN, severe RV failure
Combine TAVR and SAVR risks

Contraindications:

Absolute (ann. size, other valves, LV thrombus, coronary risk, frailty)

Relative (CAD, instability, no Ca, HOCM, PHTN, COPD, recent MI…)

Alternative access

No contraindications

TAVR Risk

SAVR Risk

Low                        Mod       High     Inoperable

Contraindications
Learning Who Not to Treat

Patients in whom the presence of multiple comorbidities, especially frailty, overwhelm the likelihood of functional recovery despite successful TAVR

TAVR

Medical therapy

Porcelain aorta
Hostile chest
RIMA/LIMA anatomy

Severe COPD
Liver cirrhosis

Dementia

Severe frailty
3. Industry, technology
<table>
<thead>
<tr>
<th>Prosthesis</th>
<th>Size [mm]</th>
<th>Delivery system</th>
<th>Femoral sheath size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapien XT</td>
<td>20</td>
<td>NovaFlex</td>
<td>16 Fr eSheath</td>
</tr>
<tr>
<td>Sapien S3</td>
<td>23</td>
<td>Commander</td>
<td>14 Fr eSheath</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Commander</td>
<td>14 Fr eSheath</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>Commander</td>
<td>16 Fr eSheath</td>
</tr>
<tr>
<td>CoreValve</td>
<td>23</td>
<td>DCS-C4-18FR-23</td>
<td>18 Fr</td>
</tr>
<tr>
<td></td>
<td>26–31</td>
<td>DCS-C4-18FR</td>
<td>18 Fr</td>
</tr>
<tr>
<td>Evolut R</td>
<td>23–29</td>
<td>EnVeo R 14Fr-equivalent</td>
<td>14 Fr</td>
</tr>
<tr>
<td>Lotus</td>
<td>23</td>
<td>Lotus valve system</td>
<td>18 Fr</td>
</tr>
<tr>
<td></td>
<td>26–29</td>
<td>Lotus valve system</td>
<td>20 Fr</td>
</tr>
<tr>
<td>Portico</td>
<td>23–25</td>
<td>Portico TF delivery system</td>
<td>18 Fr</td>
</tr>
<tr>
<td>Direct Flow</td>
<td>25–27</td>
<td>Direct Flow delivery system</td>
<td>18 Fr</td>
</tr>
</tbody>
</table>

Evolution of the Edwards Balloon-Expandable Transcatheter Valves
## 4. RCTs in TAVR

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>STS PROM</th>
<th>RCTs</th>
<th>Observational, Registries, Meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoperable</td>
<td>&gt; 50%</td>
<td>PARTNER B</td>
<td>CoreValve extreme risk</td>
</tr>
<tr>
<td>High risk</td>
<td>8-50 %</td>
<td>PARTNER A</td>
<td>STS, France Registries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US CV high risk Study</td>
<td>UK, Asian Registries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GARY, Australian Registries</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>4-8 %</td>
<td>PARTNER 2A</td>
<td>S3, Thourani, Lancet 2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SURTAVI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>US Pivotal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOTION</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>STACCATO (TA)</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt; 4 %</td>
<td>NOTION</td>
<td></td>
</tr>
</tbody>
</table>
Transcatheter Valve Therapy

Edwards Sapien and CoreValve receive CE Mark

Edwards Sapien receives FDA Approval

Sapien 3 and Evolut R Approved

2000

2005

PARTNER Trial Started

CoreValve US Pivotal

2010

Feb 8, 2006 – First Retrograde TF TAVR (REVIVAL II Trial)

2015

Edwards Sapien XT and Medtronic CoreValve receive FDA Approval
Five year mortality PARTNER IB
Inoperable patients

Kapadia S et al, Lancet 2015;385:2485

Number at risk

Standard treatment group
TAVR group

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>179</td>
<td>179</td>
<td>138</td>
<td>124</td>
<td>110</td>
<td>101</td>
<td>89</td>
<td>81</td>
<td>72</td>
<td>63</td>
<td>53</td>
<td>35</td>
</tr>
</tbody>
</table>

HR 0.50, 95% CI 0.39–0.65; p\textsubscript{log-rank} < 0.0001

STS 11 to 12

93.6%  
71.8%  
40%
Two year mortality, CV extreme risk
Observational study, inoperable pts

STS 10.3%
EuroScore 22.6%
Five year mortality PARTNER I
High surgical risk

HR 1.04, 95% CI 0.86–1.24; p=0.76

67.8%
62.4%

STS 11 to 12

Mack M et al, Lancet 2015;385:2477
CoreValve high risk group

1 year mortality

3 year mortality/CVA

Adams DH et al, NEJM 2014;370:1790

Deeb GM et al, JACC 2016;67:2565
Intermediate risk patients

Intermediate Risk Symptomatic Severe Aortic Stenosis

Intermediate Risk ASSESSMENT by Heart Valve Team STS>4

P2 S3i
n = 1078

ASSESSMENT:
Optimal Valve Delivery Access

- Transfemoral (TF)
  - TF TAVR SAPIEN 3
- Transapical / Transaortic (TA/TAo)
  - TA/TAo TAVR SAPIEN 3

Leon M et al, NEJM 2016;374:1609

P2A
n = 2032

ASSESSMENT:
Transfemoral Access

- Yes
  - Transfemoral (TF)
    - 1:1 Randomization
      - TF TAVR SAPIEN XT vs Surgical AVR
    - TA/TAo TAVR SAPIEN 3
- No
  - Transapical / TransAortic (TA/TAo)
    - 1:1 Randomization
      - TA/Tao TAVR SAPIEN 3 vs Surgical AVR

Thourani VH et al, Lancet 2016;387:2218

STS 5.8%
Intermediate risk patients

STS 4.5%
EuroSCORE 11.9%

Trial Design

Intermediate Surgical Risk
Predicted risk of operative mortality ≥3% and <15%

Heart Team Evaluation
Assess inclusion/exclusion
Risk classification

Randomization
Stratified by need for revascularization

Screening Committee
Confirmed eligibility

Baseline neurological assessments

TAVR
TAVR only
TAVR + PCI

SAVR
SAVR only
SAVR + CABG

Reardon MJ et al, NEJM 2017;376:1321
Intermediate risk patients

P2 SURTAVI
Low risk patients

Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis
1-Year Results From the All-Comers NOTION Randomized Clinical Trial

STS 2.9%

EuroSCORE 8.4%
One year mortality
RCTs vs Registries

• RCTs 15-22%
• Registries 18-24% (~ 5% more than RCTs)

<table>
<thead>
<tr>
<th>Registry</th>
<th>Country</th>
<th>Cases</th>
<th>Year</th>
<th>Mortality at 1 year</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRANCE II</td>
<td>France</td>
<td>3,195</td>
<td>2012</td>
<td>24%</td>
<td>4.1%</td>
</tr>
<tr>
<td>STS/AAC</td>
<td>United States of America</td>
<td>12,182</td>
<td>2015</td>
<td>23.7%</td>
<td>4.1%</td>
</tr>
<tr>
<td>GARY</td>
<td>Germany</td>
<td>3,876</td>
<td>2014</td>
<td>24.3%</td>
<td>4.2%</td>
</tr>
<tr>
<td>UK TAVI</td>
<td>United Kingdom</td>
<td>3671</td>
<td>2015</td>
<td>18.3%</td>
<td></td>
</tr>
<tr>
<td>Asian TAVR</td>
<td>Multiple</td>
<td>848</td>
<td>2016</td>
<td>10.8%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Australian-New Zealand</td>
<td></td>
<td>540</td>
<td>2014</td>
<td>11.9%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

Aldalati O et al,
## Upcoming RCTs in TAVR

<table>
<thead>
<tr>
<th>Trial</th>
<th>Objective</th>
<th>Date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER 3</td>
<td>To determine safety and effectiveness of Sapien 3 in low risk patients in comparison to sAVR</td>
<td>2027</td>
</tr>
<tr>
<td>UK TAVI</td>
<td>To determine clinical effectiveness and cost-utility of TAVI in comparison to sAVR (high and intermediate risk)</td>
<td>2016</td>
</tr>
<tr>
<td>ACTIVATION</td>
<td>Percutaneous coronary intervention prior to TAVI</td>
<td></td>
</tr>
<tr>
<td>GALILEO</td>
<td>Effect of rivaroxaban anticoagulation strategy in comparison to dual anti-platelet therapy</td>
<td>2018</td>
</tr>
<tr>
<td>TAVR UNLOAD</td>
<td>To determine safety and efficacy of TAVI in patients with moderate aortic stenosis and heart failure in comparison to optimal medical therapy</td>
<td>2020</td>
</tr>
<tr>
<td>STEP for patients prior to undergoing TAVR</td>
<td>Whether supervised exercise would improve frailty status of TAVI patients</td>
<td>2017</td>
</tr>
</tbody>
</table>
5. RCTs in TAVR Complications

<table>
<thead>
<tr>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular complications</td>
<td>Hospital stay</td>
</tr>
<tr>
<td>PPM</td>
<td>Transfusions</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>Kidney damage</td>
</tr>
<tr>
<td>Transapical worse</td>
<td>Afib</td>
</tr>
<tr>
<td>Gender difference (F&gt;M)</td>
<td>Smaller AVA</td>
</tr>
<tr>
<td>Cost?</td>
<td></td>
</tr>
</tbody>
</table>
RCTs in TAVR

Aortic regurgitation

Vascular complications

PARTNER 2

PARTNER 1A – 1B
Table 4. Rate of complications as per trials and registries.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>CVA</th>
<th>Pacing</th>
<th>Vascular</th>
<th>Bleeding</th>
<th>AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER B [31]</td>
<td>2010</td>
<td>6.7%</td>
<td>3.4%</td>
<td>30.7%</td>
<td>16.8%$</td>
<td>0</td>
</tr>
<tr>
<td>PARTNER A [32]</td>
<td>2011</td>
<td>5.5%</td>
<td>3.8%</td>
<td>17%</td>
<td>9.3%$</td>
<td>1.2%</td>
</tr>
<tr>
<td>CoreValve Extreme Risk [33]</td>
<td>2014</td>
<td>4%</td>
<td>21.6%</td>
<td>8.2%</td>
<td>12.7%*</td>
<td>11.8%</td>
</tr>
<tr>
<td>CoreValve High Risk [34]</td>
<td>2014</td>
<td>4.9%</td>
<td>19.8%</td>
<td>5.9%</td>
<td>13.6%*</td>
<td>6%</td>
</tr>
<tr>
<td>PARTNER II [35]</td>
<td>2016</td>
<td>6.4%</td>
<td>8.5%</td>
<td>7.9%</td>
<td>10.4%*</td>
<td>1.3%</td>
</tr>
<tr>
<td>NOTION [36]</td>
<td>2015</td>
<td>2.8%</td>
<td>34.1%</td>
<td>5.6%</td>
<td>11.3%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Registry</th>
<th>Year</th>
<th>CVA</th>
<th>Pacing</th>
<th>Vascular</th>
<th>Bleeding</th>
<th>AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRANCE II [8]</td>
<td>2012</td>
<td>4.1%</td>
<td>15.6%</td>
<td>4.7%</td>
<td>1.2%*</td>
<td>N/R</td>
</tr>
<tr>
<td>UK TAVI [6]</td>
<td>2016</td>
<td>2.6%</td>
<td>10.2%</td>
<td>3.5%</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>STS/AAC# [9]</td>
<td>2014</td>
<td>2.2%</td>
<td>11%</td>
<td>4.2%</td>
<td>4.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>GARY# [7]</td>
<td>2015</td>
<td>1.5%</td>
<td>17.5%</td>
<td>4.1%</td>
<td>26.3%</td>
<td>N/R</td>
</tr>
<tr>
<td>Asian# [10]</td>
<td>2016</td>
<td>3.8%</td>
<td>9.5%</td>
<td>5%$</td>
<td>6.4%*</td>
<td>3.3%</td>
</tr>
<tr>
<td>Australian-New Zealand [37]</td>
<td>2014</td>
<td>5.3%</td>
<td>28.4%</td>
<td>7.6%</td>
<td>7%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

$Major bleeding; *Life threatening or disabling bleed; ^Outcomes of year 2014; #In-hospital outcomes; CVA — cerebrovascular accident; AKI — acute kidney injury; N/R — not reported
CVA and TAVR


30 day CVAs

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TAVR Events</th>
<th>Total</th>
<th>SAVR Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, random, 95% CI</th>
<th>Odds ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muneretto 2015</td>
<td>0</td>
<td>55</td>
<td>1</td>
<td>55</td>
<td>3.3%</td>
<td>0.33 [0.01, 8.21]</td>
<td>0.33 [0.01, 8.21]</td>
</tr>
<tr>
<td>Latib 2012</td>
<td>4</td>
<td>111</td>
<td>9</td>
<td>111</td>
<td>23.6%</td>
<td>0.42 [0.13, 1.42]</td>
<td>0.42 [0.13, 1.42]</td>
</tr>
<tr>
<td>Tamburino 2015</td>
<td>8</td>
<td>650</td>
<td>14</td>
<td>650</td>
<td>45.0%</td>
<td>0.57 [0.24, 1.36]</td>
<td>0.57 [0.24, 1.36]</td>
</tr>
<tr>
<td>Thyregod 2015</td>
<td>4</td>
<td>139</td>
<td>4</td>
<td>135</td>
<td>17.4%</td>
<td>0.97 [0.24, 3.96]</td>
<td>0.97 [0.24, 3.96]</td>
</tr>
<tr>
<td>Schymik 2015</td>
<td>3</td>
<td>216</td>
<td>4</td>
<td>210</td>
<td>10.7%</td>
<td>1.51 [0.25, 9.11]</td>
<td>1.51 [0.25, 9.11]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1171</strong></td>
<td><strong>1167</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1167</strong></td>
<td><strong>0.63 [0.35, 1.14]</strong></td>
<td><strong>0.63 [0.35, 1.14]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 19

Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 4 (P = 0.76); I² = 0%

Test for overall effect: Z = 1.53 (P = 0.13)

French Registry, JACC 2014
6. Multi-imaging
• Ευχαριστώ

για την προσοχή σας