Cardiovascular Disease Update: A Case-Based Review

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Disclosure

• Dr. Arjomand does not anticipate discussing unlabeled uses of any commercial product

• Dr. Arjomand does not anticipate discussing any investigational products

• Dr. Arjomand has no financial relationships to disclose
Philadelphia

“The Thinker” (Rodin Museum)
Seacoast of Maine & New Hampshire

For people who love New Hampshire’s Seacoast...
Outline

- Antiplatelet therapy in patients undergoing coronary intervention
- Antithrombotic therapy in patients with venous thromboembolism (VTE)
- Advanced management of patients with resistant hypertension
- Endovascular therapy in patients with atrial fibrillation
- Therapeutic options in patients with valvular heart disease (aortic stenosis)
Clinical Case

- 78 y/o man with history of:
  - Smoking, HTN, Dyslipidemia, TIA, asthma
- Presents with:
  - Chest pain at rest
  - EKG: Inferior ST-segment depression
  - Lab: elevated troponin: 3.8
- Management:
  - Underwent cardiac cath and PCI/Stenting
  - Was treated with combination antiplatelet therapy
Combination Anti-platelet Therapy

• Current guidelines:
  • One year after PCI/Stenting
    - Drug-eluting stents: minimum one year
    - Bare-metal stent: minimum one month

• Options:
  • Aspirin + Clopidogrel (Plavix)
  • Aspirin + Prasugrel (Effient)
  • Aspirin + Ticagrelor (Brilinta)
CURE Trial: Primary End Point: MI/Stroke/CV Death

* In combination with standard therapy

TRITON Trial:

Primary Endpoint: CV Death, MI, Stroke

ASA + Clopidogrel

HR 0.81
(0.73-0.90)
P=0.0004

ASA + Prasugrel

HR 0.77
P=0.0001

12.1
(781)

9.9
(643)

NNT= 46

ITT= 13,608

LTFU = 14 (0.1%)
PLATO Trial:

Primary efficacy endpoint

No. at risk

<table>
<thead>
<tr>
<th>Months from randomization</th>
<th>ASA + Clopidogrel</th>
<th>ASA + Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 2 4 6 8 10 12</td>
<td>9.8</td>
<td>11.7</td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI 0.77–0.92), p=0.0003

Primary safety endpoint

No. at risk

<table>
<thead>
<tr>
<th>Months from randomization</th>
<th>ASA + Clopidogrel</th>
<th>ASA + Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 2 4 6 8 10 12</td>
<td>11.20</td>
<td>11.58</td>
</tr>
</tbody>
</table>

HR 1.04 (95% CI 0.95–1.13), p=0.434

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Antiplatelet Therapy:

• Available options:
  • Clopidogrel, Prasugrel, Ticagrelor

• Factoids to know when choosing antiplatelet therapy:
  • Prasugrel & Ticagrelor:
    • More effective than Clopidogrel
    • More expensive than clopidogrel
  • No direct comparison between Prasugrel & Ticagrelor
  • Contraindicated:
    • Prasugrel: patients with prior TIA/Stroke, ?age, ?body weight
    • Ticagrelor: patients with asthma and advanced AV block
Clinical Case (follow-up):

- Ischemic chest pain resolved
- Stopped smoking (reportedly!)
- Discharged on:
  - Combination anti-platelet therapy
    - ASA + Clopidogrel
  - Anti-Ischemic therapy:
    - Statin
    - Beta Blocker
    - ACE inhibitor
Clinical Case

- 56 y/o woman with history of:
  - Smoking and HTN

- Presents with:
  - SOB and Right lower extremity swelling after a long-distance car travel
  - LE Venous Doppler & MRV (Magnetic Resonance Venous): Right iliofemoral vein thrombosis (DVT)
  - Chest CT: positive for pulmonary embolism (PE)

- Management:
  - Anticogulation therapy
    - Inpatient vs Outpatient?
    - Regimen? Iv heparin or Enoxaparin + Warfarin or........?
EINSTEIN PE Trial
Study design

Randomized, open-label, event-driven, non-inferiority study
- Up to 48 hours’ heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed
- Non-inferiority margin: 2.0

Predefined treatment period of 3, 6, or 12 months

Objectively confirmed PE ± DVT

Day 1
- N=4833
- Rivaroxaban 15 mg bid
- Enoxaparin bid for at least 5 days, plus VKA INR 2.5 (range 2.0–3.0)

Day 21
- Rivaroxaban 20 mg od

30-day post-study treatment period

- Primary efficacy outcome: first recurrent VTE
- Principal safety outcome: first major or non-major clinically relevant bleeding
**EINSTEIN PE Trial: Primary efficacy outcome analysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (N=2419)</th>
<th>Enoxaparin/VKA (N=2413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>First symptomatic recurrent VTE</td>
<td>50 (2.1)</td>
<td>44 (1.8)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>18 (0.7)</td>
<td>17 (0.7)</td>
</tr>
<tr>
<td>Recurrent DVT + PE</td>
<td>0</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>22 (0.9)</td>
<td>19 (0.8)</td>
</tr>
<tr>
<td>Fatal PE/unexplained death where PE cannot be ruled out</td>
<td>10 (0.4)</td>
<td>6 (0.2)</td>
</tr>
</tbody>
</table>

HR

0.75 1.12 1.68*

\[\text{HR} = 1.00 \text{ (95\% CI: 0.75 to 1.68)}\]

**Rivaroxaban superior**
p=0.57 for superiority (two-sided)

**Rivaroxaban non-inferior**

\[P=0.0026 \text{ for non-inferiority (one-sided)}\]

**Rivaroxaban inferior**

*Potential relative risk increase <68.4%; absolute risk difference 0.24% (–0.5 to 1.02)*
**EINSTEIN PE Trial:**
Principal safety outcome: major or non-major clinically relevant bleeding

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Cumulative event rate (%)</th>
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<tbody>
<tr>
<td></td>
<td>Rivaroxaban N=2412</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin/VKA N=2405</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>0.1</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
</tr>
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<td>2</td>
<td>15</td>
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<tr>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
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<tr>
<td>5</td>
<td>15</td>
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<tr>
<td>6</td>
<td>15</td>
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<tr>
<td>7</td>
<td>15</td>
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<tr>
<td>8</td>
<td>15</td>
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<td>9</td>
<td>15</td>
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<td>10</td>
<td>15</td>
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<td>11</td>
<td>15</td>
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<td>12</td>
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<td>13</td>
<td>15</td>
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<td>14</td>
<td>15</td>
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<td>15</td>
<td>15</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Rivaroxaban N=2412</th>
<th>Enoxaparin/VKA N=2405</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>249/2412 (10.3)</td>
<td>274/2405 (11.4)</td>
<td>0.90 (0.76–1.07)</td>
<td>p=0.23</td>
</tr>
</tbody>
</table>

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Enoxaparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2412</td>
<td>2405</td>
</tr>
<tr>
<td>at risk</td>
<td>2183</td>
<td>2184</td>
</tr>
<tr>
<td>0—30</td>
<td>2133</td>
<td>2115</td>
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<tr>
<td>31—60</td>
<td>2024</td>
<td>1990</td>
</tr>
<tr>
<td>61—90</td>
<td>1953</td>
<td>1923</td>
</tr>
<tr>
<td>91—120</td>
<td>1913</td>
<td>1887</td>
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<tr>
<td>121—150</td>
<td>1211</td>
<td>1092</td>
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<tr>
<td>151—180</td>
<td>696</td>
<td>687</td>
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<tr>
<td>181—210</td>
<td>671</td>
<td>660</td>
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<td>211—240</td>
<td>632</td>
<td>620</td>
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<tr>
<td>241—270</td>
<td>600</td>
<td>589</td>
</tr>
<tr>
<td>271—300</td>
<td>588</td>
<td>574</td>
</tr>
<tr>
<td>301—330</td>
<td>313</td>
<td>251</td>
</tr>
</tbody>
</table>

Safety population
**EINSTEIN PE Trial:**

**Major bleeding**

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Cumulative event rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>n/N (%)</td>
</tr>
<tr>
<td>26/2412 (1.1)</td>
<td>52/2405 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Rivaroxaban</th>
<th>Enoxaparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2412</td>
<td>2412</td>
<td>2405</td>
</tr>
<tr>
<td>N=2281</td>
<td>2216</td>
<td>2270</td>
</tr>
<tr>
<td>N=2248</td>
<td>2156</td>
<td>2224</td>
</tr>
<tr>
<td>N=2091</td>
<td>2063</td>
<td>2116</td>
</tr>
<tr>
<td>N=1317</td>
<td>761</td>
<td>2063</td>
</tr>
<tr>
<td>N=735</td>
<td>700</td>
<td>1176</td>
</tr>
<tr>
<td>N=669</td>
<td>669</td>
<td>746</td>
</tr>
<tr>
<td>N=659</td>
<td>658</td>
<td>719</td>
</tr>
<tr>
<td>N=350</td>
<td>278</td>
<td></td>
</tr>
</tbody>
</table>

Safety population
In patients with acute symptomatic PE with or without DVT, Rivaroxaban (Xarelto) showed:

- Non-inferiority to LMWH/VKA for efficacy:
  - HR=1.12 (0.75–1.69);
  - $p_{\text{non-inferiority}} = 0.0026$ for non-inferiority margin of 2.0

- Similar findings for principal safety outcome:
  - HR=0.90 (0.76–1.07); $p=0.23$

- Superiority for major bleeding:
  - HR=0.49 (0.31–0.79) $p=0.0032$
Anticoagulation Therapy & PE

- **Available options:**
  - Bridge therapy, Warfarin, Xarelto

- **Factoids to consider when choosing anticoagulation therapy:**
  - Cost
  - Co-existing diseases:
    - ? Mechanical prosthetic valve
  - Concomitant therapy
    - Anti-platelet therapy
  - Adherence with INR testing
Clinical Case (follow-up):

- Due to extensive Right lower extremity thrombosis and leg swelling, patient received inpatient treatment:
  - Treatment with iv heparin and Warfarin
  - Underwent endovascular ultrasound-accelerated thrombolysis of Right iliofemoral DVT
  - Was discharged home on Warfarin (insurance reasons)
Clinical Case

- 71 y/o man with history of:
  - HTN, dyslipidemia, prior stroke

- Presents with:
  - Suboptimal BP control while on 4 antihypertensive medications
  - Work-up: no evidence of secondary HTN (no renal artery disease, normal serology, ...)

- Management:
  - Available options: ?
    - Renal denervation?
Radiofrequency catheter positioned in the right renal artery.          Contrast injection into the right renal artery.
Simplicity HTN-2 Trial: Change in office-based blood pressure

![Graph showing change in office-based blood pressure over 6 and 12 months post-randomization.](image)

- **6-month post randomization**
  - RDN*: -12
  - Crossover †: +7

- **12-month post randomization**
  - RDN*: -28
  - Crossover (6-mo post-RDN)*: -10
  - Crossover SBP: -24

*P = 0.16

### Simplicity HTN-3 Trial:

#### Patient selection

- **Design:**
  - Multi-center, prospective, randomized trial study of

- **Goal:**
  - Assess safety and effectiveness of renal denervation in subjects with uncontrolled hypertension

- **Primary outcome:**
  - Change in Office Systolic Blood Pressure [Time Frame: Baseline to 6 months post-randomization]

<table>
<thead>
<tr>
<th>Estimated Enrollment:</th>
<th>530</th>
</tr>
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<tbody>
<tr>
<td>Study Start Date:</td>
<td>September 2011</td>
</tr>
<tr>
<td>Estimated Primary Completion Date:</td>
<td>June 2013 (Final data collection date for primary outcome measure)</td>
</tr>
</tbody>
</table>
Eligible Patients for Renal Denervation:

- Office-based blood pressure >160 mm/Hg (>150 mm/Hg in patients with type diabetes)
- Three or more antihypertensive drugs have been used in adequate dosage and combination, including use of a diuretic.
- Have attempted to modify blood pressure with lifestyle changes.
- Secondary hypertension has been excluded.
- Pseudoresistance has been excluded with the use of ambulatory blood-pressure monitoring.
- Patients have preserved renal function (glomerular filtration rate >45 mL/min/1.732).
- Absence of polar or accessory arteries, no renal artery stenosis, and no prior renal revascularization.
Clinical Case

- 82 y/o man with history of:
  - HTN, gastric ulcer, GI bleeding
- Presents with:
  - Transient right-sided weakness (Left hemispheric TIA)
  - EKG: atrial fibrillation
  - Echo: normal LV function
  - TEE: clot in left atrial appendage
  - Carotid: mild plaque
- Management:
  - Anticoagulation
  - ? Additional therapy given risk of bleeding with long-term anticoagulation
Non-Valvular Atrial Fibrillation

Background

- Lifetime risk of atrial fibrillation in men & women above 40 years old is 1 in 4
- Up to 20% of ischemic strokes occur in patients with atrial fibrillation
- Need for long-term anticoagulation
- Contraindications to anticoagulation exist in 30-40% of patients
- Bleeding risk with lifelong anticoagulation
Non-Valvular Atrial Fibrillation

Stroke Pathology

- Causes of stroke in atrial fibrillation:
  - Insufficient contraction of left atrial appendage (LAA) leads to stagnant blood flow
  - 90% of thrombus found in LAA
  - embolization of LAA clot leads to stroke
- TEE-based risk factors
  - Enlarged LAA
  - Reduced inflow and outflow velocities
  - Spontaneous Echo contrast
WATCHMAN® LAA Closure Technology

Fact:
90% of thrombus found in LAA

Question:
Why NOT Occlude it?
PROTECT AF Clinical Trial Design

- Prospective, randomized study of WATCHMAN LAA Device vs long-term warfarin therapy
- 2:1 allocation ratio device to control
- 800 patients enrolled from Feb 2005 to Jun 2008
  - Device group (463)
  - Control group (244)
  - Roll-in group (93)
- 59 enrolling centers (U.S. & Europe)
- Follow-up requirements
  - TEE follow-up at 45 days, 6 months and 1 year
  - Clinical follow-up biannually up to 5 years
  - Regular INR monitoring while taking warfarin
- Enrollment continues in Continued Access Protocol (CAP Study)
**PROTECT AF Trial: Primary Efficacy Results**

**Intent-to-Treat**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Device Events (no.)</th>
<th>Total pt-yr (95% CI)</th>
<th>Rate (95% CI)</th>
<th>Control Events (no.)</th>
<th>Total pt-yr (95% CI)</th>
<th>Rate (95% CI)</th>
<th>RR (95% CI)</th>
<th>Posterior probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 pt-yr</td>
<td>18</td>
<td>409.3</td>
<td>4.4 (2.6, 6.7)</td>
<td>13</td>
<td>223.6</td>
<td>5.8 (3.0, 9.1)</td>
<td>0.76 (0.39, 1.67)</td>
<td><strong>0.992</strong></td>
</tr>
<tr>
<td>900 pt-yr</td>
<td>20</td>
<td>582.3</td>
<td>3.4 (2.1, 5.2)</td>
<td>16</td>
<td>318.0</td>
<td>5.0 (2.8, 7.6)</td>
<td>0.68 (0.37, 1.41)</td>
<td><strong>0.998</strong></td>
</tr>
</tbody>
</table>

Posterior probability estimates indicate a non-inferiority to superiority.

**Event-free probability over time**

- **Watchman**
- **Control**

**Randomization allocation** (2 device:1 control)

**ITT cohort**: patients analyzed based on their randomly assigned group (regardless of treatment received).
**PROTECT AF Trial: Primary Safety Results**

### Intent-to-Treat

#### Event-free probability

<table>
<thead>
<tr>
<th>Days</th>
<th>Event-Free Probability</th>
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<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>365</td>
<td>0.9</td>
</tr>
<tr>
<td>730</td>
<td>0.8</td>
</tr>
<tr>
<td>1095</td>
<td>0.7</td>
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</table>

#### Device vs. Control

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 pt-yr</td>
<td>45</td>
<td>386.4</td>
<td>11.6 (8.5, 15.3)</td>
<td>9</td>
<td>220.4</td>
<td>4.1 (1.9, 7.2)</td>
<td>2.85 (1.48, 6.43)</td>
</tr>
<tr>
<td>900 pt-yr</td>
<td>48</td>
<td>554.2</td>
<td>8.7 (6.4, 11.3)</td>
<td>13</td>
<td>312.0</td>
<td>4.2 (2.2, 6.7)</td>
<td>2.08 (1.18, 4.13)</td>
</tr>
</tbody>
</table>

**Randomization allocation (2 device:1 control)**

ITT cohort: patients analyzed based on their randomly assigned group (regardless of treatment received)

900 patient year analysis
Summary

- Long-term anticoagulation treatment of patients with AF has been found effective, but presents difficulties and risk.
- PROTECT AF trial evaluated the WATCHMAN device compared to warfarin and found:
  - Hemorrhagic stroke risk is significantly lower with the device.
  - When hemorrhage occurred, risk of death was markedly increased.
  - All cause stroke and all cause mortality risk are equivalent to that with warfarin.
  - There are early safety events, specifically pericardial effusion; these events have decreased over time.
Clinical Case

- 69 y/o woman with history of:
  - Smoking, COPD (on home oxygen)
- Presents with:
  - Syncope
  - Work-up: no arrhythmia/conduction disease, no anemia, no neurologic abnormality
  - Echo: normal LV function, severe aortic stenosis (AS)
- Management:
  - Treatment of aortic valve disease (AS)
Aortic Stenosis

• Symptoms: SAD
  • Syncope
  • Angina
  • Dyspnea (CHF)

• Management:
  • Treatment of aortic valve disease (AS)
    • SAVR – Surgical Aortic Valve Replacement
    • TAVR – Transcatheater Aortic Valve Replacement
Percutaneous Access and Closure

(A) The femoral artery is punctured and a guidewire placed within the artery. Percutaneous sutures are placed using a “pre-closure” device.
(B) The large vascular access sheath is inserted.
(C) Following sheath removal the sutures are tightened.
PARTNER Study Design
(Placement of AoRTic TraNscathetER Valve)

Symptomatic Severe Aortic Stenosis

ASSESSMENT: High-Risk AVR Candidate
3,105 Total Patients Screened

N = 699
High Risk

Total = 1,057 patients
2 Parallel Trials: Individually Powered

ASSESSMENT: Transfemoral Access

Yes

Transfemoral (TF)

1:1 Randomization

N = 244
TF TAVR

VS

No

Transapical (TA)

1:1 Randomization

N = 248
AVR

1:1 Randomization

N = 104
TA TAVR

VS

N = 103
AVR

Primary Endpoint: All-Cause Mortality at 1 yr (Non-inferiority)

Inoperable

N = 358

ASSESSMENT: Transfemoral Access

Yes

TF TAVR

N = 179

VS

No

Not In Study

N = 179

Standard Therapy

Primary Endpoint: All-Cause Mortality Over Length of Trial (Superiority)
Co-Primary Endpoint: Composite of All-Cause Mortality and Repeat Hospitalization (Superiority)

PARTNER Study Design
(Placement of AoRTic TraNscathetER Valve)
Current Widely Available Transcatheter Valves

(A) The Edwards SAPIEN THV balloon-expandable valve (Edwards Lifesciences, Irvine, California) incorporates a stainless steel frame, bovine pericardial leaflets, and a fabric sealing cuff.

(B) The SAPIEN XT THV (Edwards Lifesciences) utilizes a cobalt chromium alloy frame and is compatible with lower profile delivery catheters.

(C) The Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) incorporates a self-expandable frame, porcine pericardial leaflets, and a pericardial seal.
The PARTNER 1B Trial Compared Transarterial TAVR to Medical Management in Extremely High-Risk (Inoperable) Patients. Time to event analyses of death (A), death due to cardiac causes (B), rehospitalization (C), and the combined endpoint of death or stroke (D). PARTNER = Placement of AoRTic TranScathetER Valve.
The PARTNER 1A 2-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement

Kaplan-Meier time-to-event curves are shown for death by intention to treat (A) and as-treated (B), stroke (C), and the composite of death or stroke (D). Mortality and stroke rates were similar. Reprinted from Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98, with the permission of the Massachusetts Medical Society. PARTNER = Placement of AoRTic TranscathetER Valve.
PARTNER 1A Trial All-Cause Mortality (ITT)

No. at Risk

TAVR 348
AVR 351

HR [95% CI] = 0.93 [0.74, 1.15]
p (log rank) = 0.483
Conclusions:

- At 3 years, in patients with symptomatic severe AS who were high-risk candidates for surgical AVR...
  - There was no difference in all-cause mortality between TAVR and surgery
  - Baseline predictors of mortality were different for TAVR (e.g. BMI, PVD) and surgery (e.g. STS score, mod/severe MR)
  - Symptom improvement was similar in both groups and maintained thru three years

- At 3 years, strokes were similar in TAVR and surgery patients, despite increased peri-procedural neurologic events in TAVR patients
  - There was no late (after 30 days) stroke hazard in TAVR compared with surgery