A Cost Benefit Analysis of Left Atrial Appendage Closure Versus Warfarin for Stroke Prevention in Atrial Fibrillation

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Objectives

• This analysis sought to compare the cost benefit of left atrial appendage closure (LAAC) to warfarin for stroke prevention in atrial fibrillation (AF)

• Additionally, it sought to estimate the crossover point at which the clinical benefits of LAAC relative to warfarin outweigh the upfront procedural costs of LAAC
Prevalence of AF in the United States was estimated to range from 2.7-6.1 million in 2010\textsuperscript{1}

As many as 12 million Americans may have AF by 2050\textsuperscript{1}

AF patients have roughly 5 times the risk of stroke as non-AF patients\textsuperscript{2}

$11 billion is spent annually on the direct medical costs of stroke in the United States\textsuperscript{1}

AF-related stroke is expensive and cost burden will increase as prevalence of AF increases

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PROTECT-AF Overview

- Randomized FDA-IDE Trial
  - Can the WATCHMAN device replace Warfarin?

- Efficacy Endpoint:
  - Stroke
  - CV death (& Unknown)
  - Systemic embolism

- Safety Endpoint

- Non-inferiority & Superiority
  - Bayesian Sequential Design
  - Analysis at 600 pt-yrs & every 150 pt-yrs thereafter → 1500 pt-yr
  - Follow-up till 5 years

Non-Valvular AF
CHADs ≥ 1

Randomization (1:2)

Warfarin
Watchman

Anticoagulation Regimen
- Implant to 6 weeks
  - Warfarin (INR 2-3) for 6 weeks
  - Aspirin (81 – 325 mg)
- 6 weeks to 6 months
  - Clopidogrel (75 mg)
  - Aspirin (81 – 325 mg)
- After 6 months
  - Aspirin (81 – 325 mg)
Net Clinical Benefit Analysis

- Net clinical benefit (NCB) was calculated as the weighted sum of annualized event rates (difference of warfarin and device)

\[ NCB = (DE_{\text{warfarin}} - DE_{\text{intervention}}) + 0.6 \times (ICH_{\text{warfarin}} - ICH_{\text{intervention}}) \\
+ 0.2 \times (TE_{\text{warfarin}} - TE_{\text{intervention}}) + 0.1 \times (MB_{\text{warfarin}} - MB_{\text{intervention}}) \\
+ 0.1 \times (PEF_{\text{warfarin}} - PEF_{\text{intervention}}). \]

- DE=Death
- ICH=Intracranial Hemorrhage
- TE=Thromboembolism
- MB=Major Bleeding
- PEF=Pericardial Tamponade

- NCB favored WATCHMAN as early as 3 months post implant in CAP registry
- In PROTECT AF the NCB shifted from warfarin to WATCHMAN between 6-9 months post implant

### Annual NCB by Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PROTECT AF</th>
<th>CAP Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1.73</td>
<td>4.97*</td>
</tr>
<tr>
<td>Prior stroke /TIA</td>
<td>4.30</td>
<td>8.68*</td>
</tr>
<tr>
<td>CHADS(_2) score =1</td>
<td>0.70</td>
<td>2.22*</td>
</tr>
<tr>
<td>CHADS(_2) score ≥2</td>
<td>2.00</td>
<td>6.12*</td>
</tr>
</tbody>
</table>

*significant

### NCB as a Function of Time in PROTECT AF and CAP

CBA vs. CEA

- Cost benefit analysis (CBA) and cost effectiveness analysis (CEA) are both established health economic methodologies, although it is more common to see CEA in the clinical literature.

<table>
<thead>
<tr>
<th></th>
<th>Cost Benefit Analysis</th>
<th>Cost Effectiveness Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>A method for systematically calculating and comparing benefits and costs of treatment strategies</td>
<td>A method for comparing relative costs and outcomes of two or more treatment strategies</td>
</tr>
<tr>
<td><strong>Overview</strong></td>
<td>Costs are assessed against monetized benefits</td>
<td>Costs are assessed in terms of clinical outcomes</td>
</tr>
<tr>
<td><strong>Clinical Outcomes</strong></td>
<td>The clinical benefit is monetized through willingness-to-pay, human capital, or costs avoided</td>
<td>Defined clinically such as life years gained, QALYs gained or events avoided</td>
</tr>
<tr>
<td><strong>Output</strong></td>
<td>Net Cost or Net Benefit (Total Incremental Value of Benefits) − (Total Incremental Costs)</td>
<td>Incremental Cost Effectiveness Ratio (Incremental Cost)/(Incremental Effectiveness)</td>
</tr>
<tr>
<td><strong>Challenge</strong></td>
<td>Difficult to monetize benefits</td>
<td>The value of the effectiveness measure is subjective</td>
</tr>
</tbody>
</table>
Cost Benefit of Watchman vs. Warfarin

- A cost benefit model was constructed to estimate the total costs and benefits of LAAC versus warfarin from a US-payer perspective
- Clinical probabilities were taken from the PROTECT AF trial at 1065 patient years\(^1,2\)
- US DRGs\(^3\) were used to assign acute treatment costs and long-term disability costs were taken from the literature\(^4\)
- Value of 1 year of life was varied across a range of published sources\(^5-8\), ranging from $25,000 to $200,000

<table>
<thead>
<tr>
<th>Source</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption based on NICE value for 1 year of quality life(^5)</td>
<td>$25,000</td>
</tr>
<tr>
<td>Internationally accepted value for 1 year of quality life(^6)</td>
<td>$50,000</td>
</tr>
<tr>
<td>Low end of values used in FDA analyses(^7)</td>
<td>$76,000</td>
</tr>
<tr>
<td>Results of Meta-Analysis on 3 decades of studies on value of statistical life(^8)</td>
<td>$200,000</td>
</tr>
</tbody>
</table>

\(^7\) Department of Health and Human Services: Center for Food Safety and Applied Nutrition; Food Labeling; Gluten-free labeling of foods, final regulatory impact analysis. Food and Drug Administration. Docket No. FDA-2008-N-0404.
Characterizing Costs and Benefits

- Costs were defined as the incremental cost of treatment and complications, both procedural and anticoagulant-related complications.
- Benefits were defined as the savings achieved through reduction in ischemic stroke, systemic embolism and mortality.

\[
\text{Net Cost Benefit} = (c_{\text{Stroke (warf)}} - c_{\text{Stroke (laac)}} + v \times \text{LifeYearsGained}) - (c_{\text{Treatment (laac)}} + c_{\text{Complications (laac)}} - c_{\text{Treatment (warf)}} + c_{\text{Complications (warf)}})
\]
Clinical Probabilities and Costs

Clinical probabilities were taken from the PROTECT AF trial of the Watchman Device compared to warfarin at 1065 patient years\(^1,2\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Event Probability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAAC</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Procedural Stroke</td>
<td>0.011</td>
<td>NA</td>
</tr>
<tr>
<td>Pericardial Effusion</td>
<td>0.048</td>
<td>NA</td>
</tr>
<tr>
<td>Device Embolization</td>
<td>0.006</td>
<td>NA</td>
</tr>
<tr>
<td>Procedural Major Bleeding</td>
<td>0.018</td>
<td>NA</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.001</td>
<td>0.016</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.014</td>
<td>0.041</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.013</td>
<td>0.016</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.003</td>
<td>0.000</td>
</tr>
<tr>
<td>All-cause mortality (LAAC)</td>
<td>0.030</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Results

- At 5 years, cost benefit varied depending on the value assigned for 1 year of life.
Results

- The costs of LAAC outweigh the benefits in the immediate years following the procedure.
- This is to be expected since the entirety of treatment costs for LAAC are accrued in the first year while benefits accrue over time.

Cumulative Net Costs and Benefits of LAAC versus warfarin at $76,000 Value of 1 Year of Life

- Benefits are 11% of costs.
- Benefits are 33 times greater than costs.
Results

Net Benefit of LAAC compared to Warfarin Over 10 Years with 4 Values for Year of Life

- Year 1: $25,000
- Year 2: $50,000
- Year 3: $76,000
- Year 4: $200,000
Sensitivity Analysis

- One-way sensitivity analysis reveals mortality rates to be the biggest drivers of cost benefit.
- LAAC procedure costs and the value of one year of life were also significant drivers.
- No other model parameters influenced outcomes enough to change 5-year cost benefit results.
Conclusions

• A positive cost benefit is achieved with LAAC relative to warfarin in the early years following device implantation

• LAAC costs are incurred up front, and benefits accrue over time

• Conversely, with warfarin, costs accrue slowly, but benefits diminish over time as patients age into higher risk of bleeding complications

• LAAC represents a net benefit within 3-6 years depending on how 1 year of life is valued

• This analysis provides decision makers with a tool for considering the value of reduced mortality when assessing comparative effectiveness of stroke prevention in AF

• LAAC represents substantial long-term value to the US healthcare system