The New Drugs: Are They Worth It?
A PHARMACOECONOMIC PERSPECTIVE

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Outline

1. The epidemic of AF and the potential of novel oral anticoagulants
2. Why should we care about costs?
3. Are the new drugs worth their added benefits?
Atrial fibrillation is an epidemic

RISING PREVALENCE

Projected number of persons with AF in the United States between 2000 and 2050, assuming no further increase in age-adjusted AF incidence (solid curve) and assuming a continued increase in incidence rate as evident in 1980 to 2000 (dotted curve).

**SOURCE:** Miyasaka Y et al. Circulation 2006;114:119-125
AF accounts for substantial morbidity and health spending

**Resource utilization**

- With AFib (n=3,944)
  - Hospital Inpatient: 6.6%
  - Emergency: 47.8%
  - Outpatient/Physician Visit: 99.8%

- Without AFib (n=3,944)
  - Hospital Inpatient: 10.4%
  - Emergency: 38.3%
  - Outpatient/Physician Visit: 11.1%

**Health spending**

- $2.93 billion (44%)
- $1.53 billion (23%)
- $1.95 billion (29%)
- $235 million (4%)

**SOURCE:** afstat.com
Warfarin has been the mainstay of AF treatment for decades

- FDA approved in 1950s
- Most commonly used anticoagulant in US
- Highly efficacious for preventing thromboembolic stroke in AF

![Relative risk reduction chart]

- Aspirin vs placebo: 22%
- Warfarin vs placebo: 64%
- Warfarin vs aspirin: 38%
Warfarin is underused even in high-risk patients

% PATIENTS ON ANTICOAGULANT BY CHADS$_2$ SCORE

<table>
<thead>
<tr>
<th>CHADS2 score 0</th>
<th>CHADS2 score 1-2</th>
<th>CHADS2 score 3-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>44</td>
<td>42</td>
</tr>
</tbody>
</table>

SOURCE: Am J Med 2010; 123: 446
Even for patients on warfarin, patients are very frequently not adequately controlled with tremendous consequences.

- 3 times odds of major bleeding (compared to therapeutic) explains 26% - 44% of all bleeding events.

- 5 times the odds of stroke (compared to therapeutic) explains 11% of all thromboembolic events.
Novel anticoagulants
Adapted from Weitz & Bates, J Thromb Haemost 2005

ORAL
- TTP889
- Rivaroxaban
- LY517717
- YM150
- DU-176b
- PRT-054021
- Ximelagatran
- Dabigatran

PARENTERAL
- TFPI (tifacogin)
- APC (drotrecogin alfa)
- sTM (ART-123)
- Fondaparinux
- Idraparinux
- DX-9065a
- Otamixaban

Relevant Pathways:
- TF/VIIa
- X
- IX
- IXa
- VIIIa
- Va
- Xa
- II
- Ila
- Fibrinogen
- Fibrin
The novel oral anticoagulants appear to have great promise.

**Hazard of thromboembolism (compared with warfarin)**

- **Dabigatran**: -34%
- **Apixaban**: -21%
- **Rivaroxaban**: -21%

**Hazard of major bleeding (compared with warfarin)**

- **Dabigatran**: 3%
- **Apixaban**: -7%
- **Rivaroxaban**: -31%

The uptake of these drugs has been brisk

**SOURCE:** Kirley et al. Circ Cardiovasc Qual Outcomes. 2012;5:615-621
But...these drugs are very expensive

- **Warfarin**: $4
- **Dabigatran**: $257
- **Rivaroxaban**: $242
Total spending on dabigatran already exceeds that on warfarin

**SOURCE:** Kirley et al. Circ Cardiovasc Qual Outcomes. 2012;5:615-621
Why care about costs?

- Health care costs are rising and the availability of health-related interventions exceeds our ability to afford them (i.e. constrained budgets)

**SOURCE:** http://www.cms.gov/NationalHealthExpendData/02_NationalHealthAccountsHistorical.asp
Even for patients with insurance cost is an issue AMONG MANAGED CARE MEDICAL INPATIENTS, OVER THE PAST YEAR:

- Did not fill prescription because it was too expensive: 20%
- Skipped doses to make medicine last longer: 12%
- Took less than prescribed to make medicine last longer: 11%
- Split pills to make medicine last longer: 4%
- At least 1 of above strategies: 23%

The pharmacoeconomics question:

Are the added benefits of the novel agents worth their added costs?
Other outputs of a cost-effectiveness analysis

Extend results of a trial
- longer duration of treatment or follow-up, other populations, related interventions, other settings

Allows for comparisons between treatments
- most trials are placebo controlled

Estimate “real world” impact
- clinical trials often performed in atypical settings, under-represent specific populations, have small N’s, are short, use surrogate endpoints, achieve high compliance
Must consider drug costs and those of their downstream consequences

“Downstream costs”
• Strokes avoided
• Bleeding prevented
• Monitoring

“Upstream costs”
• Drug costs
Decision modeling: basic example
Decision modeling: a real-world example
COST-EFFECTIVENESS OF THE ROSUVASTATIN FOR PATIENTS WITH HIGH HS-CRP

SOURCE: Choudhry et al. J Am Coll Cardiol 2011; 57: 784-91
Incremental cost-effectiveness ratio

\[
\text{ICER} = \frac{\text{COST}_{\text{NEW TREATMENT}} - \text{COST}_{\text{OLD TREATMENT}}}{\text{EFFECT}_{\text{NEW TREATMENT}} - \text{EFFECT}_{\text{OLD TREATMENT}}}
\]

\[
= \frac{\Delta \text{COST}}{\Delta \text{HEALTH EFFECT}}
\]
Health outcomes can be compared using measures that combine quantity and quality of life.

- Quantity of life measured in “life years” (i.e. years of survival)
- Quality of life measured in “utilities” (lower values for impaired physical and emotional function)
- Resulting units are in quality-adjusted life years
Calculating QALYs

Weight the time spent in a given health state by the utility score for that health state.
Incremental cost-utility ratio

\[ ICUR = \frac{\text{COST}_{\text{NEW TREATMENT}} - \text{COST}_{\text{OLD TREATMENT}}}{\text{UTILITY}_{\text{NEW TREATMENT}} - \text{UTILITY}_{\text{OLD TREATMENT}}} = \frac{\Delta \text{COST}}{\Delta \text{UTILITY}} \]
Comparing quality-adjusted life expectancy for different programs
Defining whether something is cost-effective

- The threshold for defining whether something is “cost-effective” is somewhat arbitrary
- $50,000/QALY was proposed in 1982
  - Adjusting for inflation, today this would equal $120,000/QALY
- Most interventions covered by Medicare have cost-effectiveness thresholds of <$109,000/QALY
- The WHO suggests a threshold of 3 times the per capita gross domestic products of a country

<table>
<thead>
<tr>
<th>Adopt new treatment?</th>
<th>Improved Outcomes</th>
<th>Worse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saves money</td>
<td>YES (&quot;dominant strategy&quot;)</td>
<td>PROBABLY NOT</td>
</tr>
<tr>
<td>Costs money</td>
<td>MAYBE (usually if &lt;$50K/QALY)</td>
<td>NO (&quot;dominated strategy&quot;)</td>
</tr>
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</table>
Cost-effectiveness of commonly-used technologies

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost-Effectiveness Ratio</th>
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<tr>
<td><strong>Preventive measures</strong></td>
<td></td>
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<tr>
<td><em>Haemophilus influenzae</em> type b vaccination of toddlers</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>One-time colonoscopy screening for colorectal cancer in men 60–64 years old</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Newborn screening for medium-chain acyl-coenzyme A dehydrogenase deficiency</td>
<td>$160/QALY</td>
</tr>
<tr>
<td>High-intensity smoking-relapse prevention program, as compared with a low-intensity program</td>
<td>$190/QALY</td>
</tr>
<tr>
<td>Intensive tobacco-use prevention program for seventh- and eighth-graders</td>
<td>$23,000/QALY</td>
</tr>
<tr>
<td>Screening all 65-year-olds for diabetes as compared with screening 65-year-olds with hypertension for diabetes</td>
<td>$590,000/QALY</td>
</tr>
<tr>
<td>Antibiotic prophylaxis (amoxicillin) for children with moderate cardiac lesions who are undergoing urinary catheterization</td>
<td>Increases cost and worsens health</td>
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<tr>
<td><strong>Treatments for existing conditions</strong></td>
<td></td>
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<tr>
<td>Cognitive-behavioral family intervention for patients with Alzheimer’s disease</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Cochlear implants in profoundly deaf children</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Combination antiretroviral therapy for HIV-infected patients</td>
<td>$29,000/QALY</td>
</tr>
<tr>
<td>Liver transplantation in patients with primary sclerosing cholangitis</td>
<td>$41,000/QALY</td>
</tr>
<tr>
<td>Implantation of cardioverter–defibrillators in appropriate populations, as compared with medical management alone</td>
<td>$52,000/QALY</td>
</tr>
<tr>
<td>Left ventricular assist device, as compared with optimal medical management, in patients with heart failure who are not candidates for transplantation</td>
<td>$900,000/QALY</td>
</tr>
<tr>
<td>Surgery in 70-year-old men with a new diagnosis of prostate cancer, as compared with watchful waiting</td>
<td>Increases cost and worsens health</td>
</tr>
</tbody>
</table>

*Cost-Effectiveness of Selected Preventive Measures and Treatments for Existing Conditions (2006 Dollars).*

**SOURCE:** Cohen at al. N Engl J Med 2008; 358: 661
## Cost-effectiveness of dabigatran vs warfarin

**SHAH AND GAGE. CIRCULATION. 2011;123:2562-2570**

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>Quality adjusted life years</th>
<th>Incremental cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>$23,000</td>
<td>8.40</td>
<td>…</td>
</tr>
<tr>
<td>Dabigatran 150mg</td>
<td>$43,700</td>
<td>8.65</td>
<td>…</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td><strong>$20,700</strong></td>
<td><strong>0.25</strong></td>
<td><strong>$86,000/QALY</strong></td>
</tr>
</tbody>
</table>
Cost-effectiveness of dabigatran v warfarin
ONE-WAY SENSITIVITY ANALYSIS

The problem with existing analyses

- Overestimated warfarin costs
- Assumed patients with AF had perfect quality of life
- Don’t evaluate the cost-effectiveness of rivaroxaban or apixaban
Take home points

1. Atrial fibrillation imposes a large and increasing clinical and economic burden

2. The novel anticoagulants offer significant therapeutic benefits but are very expensive

3. When considering efficacy, safety and cost, dabigatran appears to offer reasonable value but existing cost-effectiveness analyses have methodological limitations
Oral vitamin K antagonists such as warfarin dramatically reduce the risk of thromboembolism in patients with atrial fibrillation (AF) but are challenging to use as they interact with numerous other drugs and foods, and demonstrate wide inter-patient variability in metabolism. These factors have contributed to warfarin’s substantial underuse in potentially eligible patients while simultaneously making it the most commonly implicated drug in emergency hospitalizations for adverse drug events.

To improve the risk profile of anticoagulation treatment in AF, alternative strategies have recently become available. Novel agents, which act by inhibiting Factor Xa or thrombin and which do not require routine monitoring, may provide more consistent anticoagulation and remove the inconvenience of warfarin monitoring. Two of these agents, dabigatran and rivaroxaban, are non-inferior to warfarin and were approved by the FDA for use in AF in October 2010 and July 2011, respectively. Apixaban appears to be superior to warfarin and is currently being reviewed for approval by the FDA.

Unfortunately, these novel oral anticoagulants are extremely expensive. For example, the price of dabigatran is approximately $8 per day, which is about 60 times the cost of warfarin. These differences are particularly relevant in the context of rapidly rising health care spending and the challenges that many patients have affording their essential medications.

Cost-effectiveness analysis provides a method of evaluating whether the clinical benefits associated with these novel agents represent good value for money. This research technique also allows for the projection of clinical and economic outcomes over a longer time horizon than observed in typical trials and for patients who may be underrepresented in them. Most commonly cost-effectiveness analyses produce estimates of the added cost for each quality-adjusted life year (QALY) gained from a new therapy. In the U.S., technologies that have cost-effectiveness ratios of less than $50,000-$100,000/QALY are generally considered to be economically attractive.

Economic analyses of dabigatran suggest that compared with warfarin the cost-savings from avoided monitoring and averted embolic and bleeding events do not outweigh this drug’s higher costs, but that it nevertheless represents reasonable value for money. Unfortunately, these analysis have methodological limitations. The cost-effectiveness of the other novel oral anticoagulants is the subject of forthcoming analyses.
References