Cost-Effectiveness of Pharmacogenomic-Guided Warfarin Therapy

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PROBLEM
Randomized clinical trials have produced conflicting results on the clinical superiority of pharmacogenomic-guided warfarin dosing protocols (PG-protocols) when compared to current non-PG warfarin protocols. Clinical trials that have demonstrated improved clinical outcomes for PG-protocols during the first 90 days, their results demonstrate only small clinical benefits with respect to adverse clinical events. However, adverse clinical events such as ischemic stroke (IS) and intracranial hemorrhage (ICH) related to sub-optimal warfarin therapy have high mortality and lifelong morbidity resulting in substantial healthcare expenditure. Additionally, the cost of genotyping patients for PG-protocols has dropped substantially in recent years. Therefore, the cost-effectiveness of PG-therapy is an open and valuable question in any large healthcare system such as Aurora Health Care (AHC).

BACKGROUND
With over 40 years of demonstrated clinical efficacy, warfarin remains the world’s most used pharmaceutical to prevent thromboembolic events like IS in patients with atrial fibrillation (AF). However, warfarin has many challenges including a wide inter-individual dose response and a narrow therapeutic range. Thus, despite known effectiveness, warfarin is a leading cause to drug induced morbidity and mortality globally. Over 50 different warfarin therapy protocols with as many as 14 independent clinical and genomic variables have been developed hoping to improve safety and efficacy of warfarin protocols, thus reducing IS and ICH. Our team has previously conducted a number of simulated anticoagulation protocol comparative effectiveness studies. In this study we capitalized on the results from our most recent experiment comparing five PG and non-PG warfarin therapy protocols including AHC’s ‘Best Practice’ warfarin therapy protocol currently in use throughout the AHC system. Secondary outcomes from this most recent experiment included the predicted IS and ICH rates over a 90-day period for an AHC AF patient population.

OBJECTIVE
To determine the price point at which using a PG-protocol would result in a neutral cost difference for the AHC patient population given the predicted rates of IS and ICH.

METHODS
We used five different PG and non-PG warfarin therapy protocols with differing degrees of personalization. Each warfarin therapy protocol had differences in one or more of the algorithms for initial, adjustment and maintenance warfarin dosing. In each of the five warfarin therapy protocols, we determined the acute and five-year care costs associated with predicted IS and ICH. Care costs are based on nationwide average costs for acute IS and ICH inpatient visits and subsequent five-year care. Care costs are calculated based on whether the IS or ICH event is major, minor or resulted in death. All price estimates were then adjusted according to annual Medical Care Component of the Consumer Price Index. Then, using retrospective EMR analysis, we estimated the annual number of patients starting warfarin therapy for AF within the AHC system. We then be able to calculate the predicted annual healthcare costs savings per patient initiating warfarin under each of the studied PG and non-PG protocols.

RESULTS
The AHC ‘Best Practice’ protocol had higher rates of IS and ICH compared to the four other protocols tested within the first 90 days of therapy. The PG-protocol 3 with a highest degree of personalization, incorporating patients’ genotype into the initial and adjustment dosing algorithms had the lowest rates of IS and ICH (Table 1).

<table>
<thead>
<tr>
<th>Protocol</th>
<th>AHC Best Practice</th>
<th>Clinical Protocol</th>
<th>PG-protocol 1</th>
<th>PG-protocol 2</th>
<th>PG-protocol 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>2.2</td>
<td>2.07</td>
<td>1.9</td>
<td>1.72</td>
<td>1.72</td>
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<tr>
<td>Intracranial Hemorrhage</td>
<td>6.94</td>
<td>5.78</td>
<td>5.28</td>
<td>5.37</td>
<td>5.17</td>
</tr>
</tbody>
</table>

We calculated acute care and five year care costs related to both IS and ICH for each protocol, costs were averaged across 1,000 patients initiating warfarin therapy for AF over 90 days. We found that current AHC ‘Best Practice’ warfarin therapy protocol had the highest predicted costs for IS resulting in $163,463 for acute care costs, and $171,280 for five-year care costs related to ICH. The current AHC protocol also had the highest associated costs for IS at $51,333 for acute care, and $58,507 for five-year care costs. In contrast, PG-protocol 3 had the lowest predicted acute care and five-year care costs associated with ICH at $119,824 and $125,463 respectively, and the lowest costs associated with IS at $39,672 and $45,126 as well (Figure 1).

CONCLUSIONS
Using patients’ clinical and genetic information in warfarin therapy protocols can significantly reduce IS and ICH related healthcare expenditures over a five-year period. The PG-protocol 3 generates the greatest total average savings at $78.98 per patient over five-years. The clinical and PG-protocols only modestly reduce the absolute event rate for IS and ICH when compared to the current AHC ‘Best Practice’ warfarin therapy protocol. However, with an average of 3,000 patients annually initiating warfarin for AF and the large acute care and five-year care costs associated with IS and ICH, even incremental reductions in adverse events through PG-guided care can produce savings. Given the substantial reduction in costs associated with genotyping patients, $78.98 per patient is likely an achievable price point at which using a PG-protocol would result in a neutral cost difference. Next steps include developing expense estimates to include PG-guidance into the warfarin therapy work flow.

REFERENCES