Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation
Patrick AR, Avorn J, Choudhry NK

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The objective was to determine the circumstances in which genotyping before warfarin initiation could be cost-effective for patients with atrial fibrillation. Genotyping was cost-effective only if it reduced the out-of-range international normalised ratios by more than five to nine percentage points. There was uncertainty surrounding the effectiveness of genotyping and its widespread use could not be advocated. The methods were good and, given the uncertain effectiveness data, the authors’ conservative conclusions appear to be warranted.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to determine the circumstances in which genotyping before warfarin initiation could be cost-effective for patients with atrial fibrillation.

Interventions
The use of cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) genotyping before warfarin initiation was compared with no genotyping.

Location/setting
USA/secondary care.

Methods
Analytical approach:
A decision analytic Markov model was used to assess the costs and outcomes of the two interventions for a hypothetical cohort of 70-year-old patients, with newly diagnosed atrial fibrillation. There was conflicting data on the effectiveness of genotyping so the authors performed a threshold analysis to assess the test characteristics at which genetically-guided dosing would be cost-effective. The time horizon was the lifetime of the patient and the authors reported that a societal perspective was adopted.

Effectiveness data:
The effectiveness and clinical parameters used in the model were from published literature, and wherever possible meta-analyses were used. The relevant articles were identified through MEDLINE searches. The main effectiveness estimate was the absolute increase in the international normalised ratios (INRs) with genetically-guided dosing of warfarin. This was from two published studies.

Monetary benefit and utility valuations:
The quality of life estimates were from studies identified in the Cost-Effectiveness Analysis Registry.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs).

Cost data:
The authors included the direct costs relating to: genotyping; phlebotomy; warfarin; treatment of bleeding events and strokes, which included the costs of hospitalisation, physician services, and post-acute care; and (in a sensitivity analysis only) the costs associated with deaths attributable to events other than bleeding or stroke. The costs of genotyping and
phlebotomy were from published literature. Those of warfarin were from the average wholesale price and those of deaths due to other events were from end-of-life information published by Medicare. The price year was 2007, with costs inflated using the medical care component of the Consumer Price Index. All costs were reported in US dollars ($) and future costs were discounted.

Analysis of uncertainty:
A series of one-way sensitivity analyses was performed by varying the individual parameters over plausible ranges of values. A probabilistic sensitivity analysis was also performed and each parameter was fitted with a distribution then varied simultaneously for 10,000 Monte Carlo simulations.

Results
The average discounted QALYs gained for patients receiving usual care were 7.28 and the average discounted costs were $22,541.

The authors reported that if genotyping increased the time spent within the INR range by less than five percentage points (e.g. from 57.7 to 62.7%), the incremental cost-utility ratio would be more than $100,000 per QALY gained, compared with usual care. The incremental cost-utility ratio would be less than $50,000 per QALY gained if genotyping increased the time spent in the INR range by nine percentage points, and the incremental cost-utility ratio would be about $8,000 per QALY gained with a 30 percentage point increase.

The results of the probabilistic sensitivity analysis showed that at a willingness to pay threshold of $100,000 per QALY gained, the probability of genetically-guided warfarin being cost-effective was 70%. At a threshold of $50,000 per QALY gained, the probability of the intervention being cost-effective decreased to 42%.

Authors' conclusions
The authors concluded that genotyping before warfarin initiation was cost-effective only if it reduced the out-of-range INR values by more than five to nine percentage points, compared with usual care. There was uncertainty surrounding the effectiveness of genotyping and its widespread use could not be advocated.

CRD commentary
Interventions:
The interventions were clearly reported and the usual care was appropriately included.

Effectiveness/benefits:
The authors reported that the clinical and effectiveness measures were from studies identified through MEDLINE searches. It appears that a full systematic review of the literature was not conducted and it is not possible to determine if all the relevant information was included. The objective was to assess the effectiveness required for genotyping to be cost-effective, given the various effectiveness estimates reported in the literature, and this was appropriate.

Costs:
The authors reported that a societal perspective was adopted, but indirect costs, such as productivity costs due to early mortality or morbidity, were not included. All the direct medical costs appear to have been analysed and their sources were adequately reported. The time horizon, price year, inflation indices, and currency details were all adequately reported, but the discount rate was not.

Analysis and results:
All the outcome and cost data were synthesised using a decision analytic Markov model. Adequate details of the model were provided, including a diagram. The costs and benefits of the genotyping strategies were not reported. The impact of uncertainty on the model's results was assessed using probabilistic sensitivity analyses. This type of analysis is considered to be the gold-standard in the UK for assessing the overall model uncertainty. The authors adequately reported the limitations of their study, namely that the long-term data were not available and had to be extrapolated.

Concluding remarks:
The methods were good and, given the poor quality or lack of effectiveness data, the authors’ conservative conclusions
appear to be warranted.

**Funding**
Funded by a grant from the Partners Healthcare System.

**Bibliographic details**

**PubMedID**
20031873

**DOI**
10.1161/CIRCOUTCOMES.108.808592

**Original Paper URL**
http://circoutcomes.ahajournals.org/content/2/5/429.abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aged; Anticoagulants /administration & dosage /adverse effects /economics; Aryl Hydrocarbon Hydroxylases /genetics; Atrial Fibrillation /drug therapy /economics /genetics /mortality; Brain Ischemia /epidemiology; Cost-Benefit Analysis; Cytochrome P-450 CYP2C9; Drug Costs; Genetic Testing /economics; Genotype; Hemorrhage /chemically induced /epidemiology; Humans; Incidence; Markov Chains; Mixed Function Oxygenases /genetics; Models, Econometric; Precision Medicine /economics; Quality of Life; Stroke /epidemiology; Vitamin K Epoxide Reductases; Warfarin /administration & dosage /adverse effects /economics

**AccessionNumber**
22010000692

**Date bibliographic record published**
21/07/2010

**Date abstract record published**
22/12/2010