CYP2C9 genotyping in acenocoumarol treatment: is it a cost-effective addition to international normalized ratio monitoring?

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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.

Health technology
The study examined the addition of CYP2C9 genotyping to international normalised ratio (INR) monitoring in patients receiving acenocoumarol treatment.

Type of intervention
Primary prevention (monitoring).

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients requiring oral anticoagulants.

Setting
The setting was secondary care. The economic study was carried out in the Netherlands.

Dates to which data relate
The clinical data were derived from studies published in 2004. No dates for resource use were explicitly reported. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and a key authors' assumption.

Modelling
A simple decision tree was constructed to model the costs and benefits of the two alternative strategies. Patients on acenocoumarol could undergo or not undergo genotyping, which preceded or was performed shortly after the initiation of acenocoumarol. For both main arms of the tree, the possible outcomes were bleeding and no bleeding. A short time horizon was probably used, but was not explicitly reported.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the prevalence of CYP2C9 polymorphisms *2 and *3;

the prevalence of CYP2C9 polymorphisms *2 and *3 after the selection of genotyping candidates based on the first
INR on day 4;

the incidence rate of major bleeding in CYP2C9*1/*1 patients;

the incidence rate of major bleeding in carriers of CYP2C9 polymorphism; and

the relative risk of major bleeding in carriers of CYP2C9 polymorphism compared with wild-type patients.

**Study designs and other criteria for inclusion in the review**

It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. Limited information on the primary studies was provided. All clinical data were obtained from Dutch studies, but no information on the design was given. Prevalence of CYP2C9 polymorphisms *2 and *3 was obtained from three Dutch studies that involved a total of 1,591 individuals.

**Sources searched to identify primary studies**

Not reported.

**Criteria used to ensure the validity of primary studies**

Not reported.

**Methods used to judge relevance and validity, and for extracting data**

Not reported.

**Number of primary studies included**

Four primary studies provided the clinical data used in the model.

**Methods of combining primary studies**

The approach used to pool the patient data was not described. A weighted average might have been used for prevalence of CYP2C9 polymorphisms *2 and *3.

**Investigation of differences between primary studies**

Not reported.

**Results of the review**

The prevalence of CYP2C9 polymorphisms *2 and *3 was 0.36.

The prevalence of CYP2C9 polymorphisms *2 and *3 after the selection of genotyping candidates based on the first INR on day 4 was 0.44.

The incidence rate of major bleeding in CYP2C9*1/*1 patients per 100 patient-years was 4.16 (range: 2.00 to 6.00).

The incidence rate of major bleeding in carriers of CYP2C9 polymorphism per 100 patient-years was 6.8.

The relative risk of major bleeding in carriers of CYP2C9 polymorphism compared with wild-type patients was 1.649 (range: 1.05 to 2.2).

**Methods used to derive estimates of effectiveness**
The authors made a key assumption that was used in the decision model.

**Estimates of effectiveness and key assumptions**
It was assumed that the reduction in incidence rate of major bleedings in carriers of CYP2C9 polymorphism after genotyping was 0.8 (range: 0.6 to 1.0).

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of bleeding episodes. This was derived using the decision model approach.

**Direct costs**
The perspective chosen for the analysis was not reported, but it might have been that of the health care system. Only the direct medical costs of CYP2C9 genotyping, INR monitoring by anticoagulation clinics, additional number of INR measurements needed for adapting care in carriers of a CYP2C9 allele, acenocoumarol tablets for 1 year, and the treatment of major bleeding were considered. With the exception of the cost of treating major bleeding, which was presented as a macro-category, the unit costs were reported for most items. Some details of resources used, which were based mainly on authors' opinions or published sources, were reported. The costs were derived from published studies and Dutch official sources. The price year was 2004. Discounting was not relevant as the costs were incurred during a short timeframe.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered in the economic analysis.

**Currency**
Euros (EUR).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the robustness of the base-case estimates to variations in the prevalence of polymorphism, cost of genotyping, incidence rate of major bleeding, relative risk of major bleeding, relative risk reduction of major bleeding, cost of additional INR monitoring, and cost of major bleeding. The ranges of values were derived from the literature or were based on plausible assumptions. A threshold analysis was also performed to define the critical value of key model inputs which would affect the cost-effectiveness of the genotyping strategy.

**Estimated benefits used in the economic analysis**
Bleeding episodes per 100 patient-years were 4.6392 with genotyping and 5.1334 without genotyping (difference 0.4942) if all patients were genotyped.

In the case of selecting only patients in whom an initial INR of greater than 2.5 was assessed on the fourth day of therapy, the corresponding values would have been 4.7457 with genotyping and 5.3497 without genotyping (difference 0.6040).

**Cost results**
The expected costs per 100 patient-years were EUR 79,899 with genotyping and EUR 77,807 without genotyping (difference EUR 2,092) if all patients were genotyped.

In the case of selecting only patients in whom an initial INR of greater than 2.5 was assessed on the fourth day of therapy, the corresponding values would have been EUR 81,440 with genotyping and EUR 80,105 without genotyping (difference EUR 1,135).

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios (ICERs; i.e. the incremental cost per bleeding episode avoided) were calculated to combine the costs and benefits of the alternative strategies.

Under the base-case assumptions, the ICER with genotyping over no genotyping was EUR 4,233 if all patients were genotyped. In the case of selecting only patients in whom an initial INR of greater than 2.5 was assessed on the fourth day of therapy, the ICER would have been EUR 2,210.

The sensitivity analysis showed that a reduction in the cost of genotyping to EUR 20 or EUR 30 (it was EUR 55 in the base-case) made the genotyping strategy dominant (i.e. more effective and less expensive) under most scenarios. The incidence rate of major bleeding was a key assumption affecting the cost-effectiveness of genotyping. With an incidence rate of only 2.4 per 100 patient-years, as reported in a published study, the ICER would have been EUR 15,126. Another important parameter was the relative risk reduction of major bleeding. With a 5% risk reduction (20% in the base-case), the cost of the genotyping strategy varied from EUR 20,000 to EUR 49,000 for all patients and from EUR 17,500 to EUR 40,700 for selected patients with an initial INR of greater than 2.5. If the bleeding rate was reduced by 30%, genotyping became the dominant strategy.

The cost of major bleeding episodes was also a key parameter, especially in settings where genotyping was very expensive. The threshold analysis revealed that if genotyping was between EUR 20 and EUR 30, only scenarios with a low bleeding rate reduction (relative risk 0.9) failed to achieve dominance. However, a marginal cost-effectiveness of EUR 4,000 was possible if the bleeding rate incidence in wild-type patients was greater than 3.0 per 100 patient-years (4.16 in the base-case). Even if genotyping was relatively expensive (EUR 50), dominance or a marginal cost-effectiveness of EUR 4,000 was achieved in many scenarios.

**Authors' conclusions**

CYP2C9 genotyping is a potentially cost-effective tool to manage patients requiring oral anticoagulation therapy in the Netherlands. However, the analysis revealed the importance of defining clinical and economic factors that might have a substantial impact on the cost-effectiveness of this health technology. There was a high uncertainty around these key model inputs.

**CRD COMMENTARY - Selection of comparators**

The rationale for the choice of the comparators was clear. The new intervention was compared with the conventional approach, which was represented by INR monitoring alone. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state explicitly whether a systematic review of the literature was undertaken to identify the primary studies, which might have been identified selectively. The design of the primary studies was unclear and the methods used to combine their data were not described. Likewise, it was not reported whether the primary studies were comparable in terms of the study populations and interventions. An assumption was also made on the basis of the authors' opinions. Both assumed and literature-based values were varied in the sensitivity analysis which extensively addressed the issue of variability in the clinical estimates.
Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. It will not be comparable with the benefits of other health care interventions.

Validity of estimate of costs
The authors did not state explicitly which perspective was adopted for the analysis of the costs. However, given the categories of costs included in the analysis, the viewpoint of the health service payer appears to have been chosen. Some information on the unit costs and resource consumption was provided, which will assist reflation exercises in other settings. Further, the authors investigated the impact of changing cost estimates in the sensitivity analysis. The source of all the cost data was reported, whereas the sources of quantities of resources used were not reported for all items. The price year was reported, which will facilitate reflation exercises in other time periods. Given the short time horizon of the analysis, discounting was not relevant and was not performed. No statistical analyses of the costs were carried out.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. However, extensive sensitivity analyses were carried out, which enhance the external validity of the study results. Moreover, the sensitivity analysis focused on the impact of variations in bleeding rates, which represent a crucial aspect of the analysis since these rates might vary in different sub-groups of patients within a population. Finally, different values for cost estimates were used and this will help in extrapolating the results to other settings.

Implications of the study
The cost-effectiveness of CYP2C9 genotyping should be corroborated in a prospective clinical trial. The authors pointed out that future studies should investigate the potential role of the VKORC1 genotype in comparison with CYP2C9 genotyping in patients taking oral anticoagulants. It is likely that the VKORC1 genotype is also associated with major bleeding in coumarin users, and that this association may be even stronger that that of the CYP2C9 genotype.

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Other publications of related interest


Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient


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MeSH
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