

CYP2C9 gene variants, drug dose and bleeding risk in warfarin treated patients: a HuGE systematic review and meta-analysis

Protocol for a HuGE association review

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Background

Warfarin is the most commonly used oral anticoagulant drug in the UK and USA, and it is being prescribed more frequently. Clinical indications include venous thrombo-embolism, mechanical prosthetic heart valves, and in patients with atrial fibrillation at risk of arterial thrombo-embolism. It acts by antagonising the effects of vitamin K and dependant clotting factors. The main adverse effect is bleeding. Warfarin has a narrow therapeutic range and interacts with many other drugs. Warfarin is metabolised primarily in the liver by cytochrome P450 CYP2C9, which also metabolises phenytoin, losartan, tolbutamide and NSAIDs. The functional effectiveness of this system is influenced by genetic polymorphisms, with some variants leading to slower drug metabolism. Published studies have demonstrated these effects in vitro and in vivo and a small group of studies has shown that these variants do impact on clinically relevant outcomes, such as warfarin dose requirements and risk of bleeding complications.

Warfarin requires close clinical and laboratory monitoring during induction and maintenance treatment to obtain optimal control and to prevent bleeding. Although clinical guidelines are available evidence demonstrates that warfarin therapy is difficult to manage. Studies have also demonstrated that patients' and doctors' attitudes to using warfarin are predominantly negative. These factors suggest that the management of warfarin treated patients could be improved, with potential benefits for patients who need the drug. It is also likely that there are patients who could benefit from warfarin treatment but are not receiving it because of negative attitudes, in part based upon real concerns about the risk of adverse effects.

It is possible that genetic testing of patients prior to initiation of treatment or testing currently treated patients may provide additional information to improve prescribing decisions. The results of testing could help patients make informed decisions about warfarin treatment and its' risk.

Objectives

To ascertain the impact of CYP2C9 gene variants on daily drug dose and bleeding risk in warfarin treated patients.

Methods

Criteria for considering studies

Polymorphisms

CYP2C9 gene variants, especially *2 and *3.

Clinical outcomes

- Reduction in daily drug dose
- Risk of bleeding
- In warfarin treated patients

Types of studies

Population based genetic association studies

Search methods

- Electronic database searches: PubMed, EMBASE, BIOSIS, HuGENet, Centre for Reviews and Dissemination, Cochrane Library
- Reference lists of identified studies
- Direct contact with authors of primary studies and experts in the field to identify other or unpublished studies

Quality assessment

Criteria will be based on the HuGENet guidelines for the reporting of genetic association studies (Little *et al.*); no quantitative methods will be used.

Data extraction

Two reviewers independently extracting data using a pre-piloted proformas, with a third available for arbitration.

Data synthesis

Random effects meta-analysis using a per-allele method, and the odds ratio/relative risk for bleeding events. Heterogeneity investigated using chi-squared methods and the I^2 statistic.

Potential conflict of interest

None known

References:

1) Little et al. Guidelines for the reporting of genetic association studies. American Journal of Epidemiology.