Genotype-guided drug prescribing: a systematic review and meta-analysis of randomized control trials

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AIM
Adverse drug events lead to increased morbidity, mortality and health care costs. Pharmacogenetic testing that guides drug prescribing has the potential to reduced adverse drug events and increase drug effectiveness. Our aim was to quantify the clinical effectiveness of genotype-guided prescribing.

METHODS
Three electronic databases were searched from January 1980 through December 2013. Studies were eligible if they were RCTs comparing genotype-guided prescribing with non-genetic informed prescribing, reported drug specific adverse drug events and clinical effectiveness outcomes. Two reviewers independently screened titles and abstracts, extracted data and assessed study quality. Meta-analyses of specific outcomes were conducted where data allowed.

RESULTS
Fifteen studies, involving 5688 patients and 19 drugs, met the inclusion and exclusion criteria. Eight studies had statistically significant results for their primary outcome in favour of genotype-guided prescribing. Nine studies evaluated genotype-guided warfarin dosing. Analysis of percentage of time in therapeutic international normalized ratio range (1952 individuals) showed a statistically significant benefit in favour of genotype-guided warfarin dosing (mean difference = 6.67; 95% CI 1.34, 12.0, I² = 80%). There was a statistically significant reduction in numbers of warfarin-related minor bleeding, major bleeding and thromboembolisms associated with genotype guided warfarin dosing, relative risk 0.57 (95% CI 0.33, 0.99; I² = 60%). It was not possible to meta-analyze genotype-guided dosing for other drugs. Of the six non-warfarin genotype-guided trials, two demonstrated a statistically significant benefit for their primary outcome, odds ratio 0.03 (95% CI 0.00, 0.62, \(P < 0.001\)) for abacavir.

CONCLUSIONS
There is evidence of improved clinical effectiveness associated with genotype-guided warfarin dosing.

Introduction

Many side effects or adverse reactions to medicines are predictable and are accepted risks of treatment. They can be avoided or minimized by careful medicine prescribing and use [1]. Adverse drug events (ADE) are associated with increased morbidity and mortality [2, 3], and elevated health care costs [2, 4, 5]. It is thought that genetic testing could reduce the number of adverse drug events. The application of pharmacogenetic testing in routine clinical care to individualize drug selection, dose and treatment duration has been studied in the areas of cancer,
antiretroviral and cardiovascular drug therapies [6–10]. In response to this growing body of genetic and clinical evidence, the US Food and Drug Administration has issued over 150 drug label recommendations related to pharmacogenetic biomarker testing. The Clinical Pharmacogenetic Implementation Consortium has issued a series of guidelines on genotype-guided drug prescribing including for warfarin, clopidogrel, abacavir and tricyclic antidepressants [11–14]. Despite the guidelines and experimental research there remains a lack of consensus concerning the clinical applicability of pharmacogenetic tests [15].

Genetic factors are known to make the largest contribution to inter-patient variability in warfarin dose requirements [16]. Even though warfarin is the most commonly prescribed oral anticoagulant and a leading cause of ADEs [12, 17], VKORC1 and/or CYP2C9 genotype-guided warfarin dosing fails to improve anticoagulation outcomes [18, 19]. However, previous evidence has been mixed. Some studies have demonstrated clinical utility such as improved time in target range with genotype-guided warfarin dosing [20–22]. Recently, two large RCT reports that evaluated genotype-guided warfarin dosing have stimulated further debate, as they tested related hypotheses yet arrived at different results [6, 23]. These studies vary considerably in follow-up duration and dosing method, yet they are similar with respect to size and choice of primary outcome (time in therapeutic range). The emergence of new evidence and controversy regarding the clinical effectiveness of using genotype-guided warfarin dosing [16, 24, 25] indicates a need for a systematic review of genotype-guided dosing.

The reality of clinical practice is that many patients are on multiple medications and multi-morbidity is now the norm. The consequence is that in primary care and many other settings it is less useful to use a single drug/genetic tests but to use a broader set of tests for multiple drugs. No systematic review has been published that estimates the effectiveness of genotype-guided drug prescribing that is not restricted to the classic single drug/genetic tests approach. This study examines the current randomized controlled trial evidence for the prospective clinical use of pharmacogenetic information to improve effectiveness of drug prescribing as demonstrated by reduced harm and increased relative effectiveness.

Methods

Study design

This was a systematic review and meta-analysis of randomized control trials (RCTs) to answer the question: does genotype-guided prescribing reduce ADEs and improve drug treatment response?

Search strategy

Medline, Cochrane Central Register of Controlled Trials (CENTRAL) and pharmgkb.org databases were searched from January 1980 through December 2013. Pharmgkb.org is a pharmacogenomics knowledge resource that gathers, curates and distributes knowledge about the influence of human genetic variation on drug responses. The search strategy was developed by the authors with a librarian and piloted in Medline (Table 1). Reference lists from reviews and included articles were searched for relevant items by SW and RG. Abstracts were downloaded for articles considered to be potentially relevant and the inclusion criteria were then applied to these articles by two independent reviewers (RG, DD, SW). Disagreements were resolved through discussion.

Inclusion criteria

We included studies if physicians, in a clinical setting, were assigned randomly to use genetic information such as single nucleotide polymorphism (SNP) or copy number variation (CNV) to guide drug prescription (e.g. dose, choice of drug/no drug if no alternative) and measured clinical outcome or outcomes that determine benefit of using the genetic information. We excluded studies that retrospectively determined the association of genotype with drug response.

Data extraction

Independent double data extraction was performed using pre-designed and pilot-tested forms (RG, DD, SW). We contacted the authors of the included studies when reported outcome data were inadequate for meta-analysis. We extracted data on study design, clinical and safety outcomes. Any disagreements between the reviewers were resolved by discussion. For the purposes of this review, minor bleeding is defined as a bleeding event that required no additional testing and treatment, major bleeding is categorized as fatal bleeding, symptomatic bleeding in a critical area or organ, or a fall of haemoglobin requiring hospitalization or blood transfusion and thromboembolism is defined as a deep venous thrombosis, pulmonary embolism, or embolic stroke and the percentage of time in a critical area or organ, or a fall of haemoglobin requiring hospitalization or blood transfusion and thromboembolism is defined as a deep venous thrombosis, pulmonary embolism, or embolic stroke and the percentage of time in the therapeutic international normalized ratio (INR) range was defined as between 2.0 and 3.0, except by Anderson et al. [18] (1.8 to 3.2), Burmester et al. [36] (2.0 to 3.5), Hilman et al. [19] (1.9 to 3.0) and Huang et al. [37] (1.8 to 3.0).

Assessment of risk of bias and analysis

Two review authors independently assessed the risk of bias in each included study according to Cochrane Collaboration’s tool for assessing risk of bias [26]. Any disagreements between the reviewers were resolved by discussion.

Data synthesis was performed using Review Manager version 5.2 [27]. Where the interventions were the same, or
similar enough, and if there was no important clinical heterogeneity, we synthesized results in a meta-analysis. For measures of effect we used risk ratios (RR) with 95% confidence intervals (CI) for binary outcomes and mean differences (MD) with 95% CI for continuous outcomes. Due to significant statistical heterogeneity, we synthesized the data using a random effects analysis. All analyses included all participants in the treatment groups to which they were allocated (intention-to-treat analyses) as far as possible. Meta-analyses based on the random effects model were performed for warfarin dosing studies for percentage time in therapeutic INR, and for warfarin related minor, major and thromboembolism ADEs. Heterogeneity was assessed using I² statistics, which is the proportion of total variance explained between trials rather than to sampling error. I² < 25% was considered as low in heterogeneity and I² > 75% was of high heterogeneity [28].

Results

Study characteristics
Fifteen of 6686 identified studies satisfied the inclusion criteria (Figure 1) and evaluated clinical outcomes of genotype-guided interventions for 19 different drugs (Table 2). Studies analyzed a total of 5688 patients, varying in size, ranging from 26 to 1650 participants in the analysis of the primary outcome. Demographic characteristics of participants varied between studies. Of the 13 studies reporting ethnicity, one was 100% Caucasian participants and two studies were carried out with a 100% Chinese population. Studies were carried out in hospital settings in various countries, with the largest study being an international study involving 19 countries.

Six RCTs evaluated genotype-guided prescribing for drugs other than warfarin (Table 2): abacavir selection as HIV antiretroviral therapy (HLA-B*5701), azathioprine dosing as inflammatory therapy (TMPT), clopidogrel vs. prasugrel selection as antiplatelet therapy prior to angioplasty (CYP2C19), tacrolimus dosing as an immunosuppressant post-transplantation (CYP3A4), acenocoumarol/phenprocoumon dosing as vitamin K antagonist therapy for atrial fibrillation or venous thrombosis (CYP2C9 and VKORC1) and antiretroviral selection as second line HIV therapy (various HIV resistance mutations) [29–34]. Follow-up times for these studies ranged from 7 days to 4 months.

We identified nine RCTs evaluating genotype-guided warfarin dosing as vitamin K antagonist therapy for various indications [6, 18, 19, 21, 23, 35–38]. Seven of nine studies involved a combination of indications including atrial fibrillation, atrial flutter, deep venous thrombosis and pulmonary embolism, two studies included prosthetic valve and joint patients, one included pre-operative orthopaedic patients and two studies initiated warfarin prior to heart valve replacement. All nine studies reported on drug specific clinical effectiveness outcomes, with eight evaluating warfarin related ADEs and time within therapeutic INR, and five evaluating outcomes of adverse drug events. Seven studies used different dosing models for their genotype-guided and control dosing arms, whereas
Huang et al. and Wang et al. used the same dosing algorithms for both genotype-guided and control and Kimmel et al. and Pirmohamed et al. used the same pharmacogenetic but different control algorithms [6, 23, 37, 38]. For the genotype-guided arm, two studies used dosing models that accounted only for CYP2C9 variants, while all other studies incorporated both CYP2C9 and VKORC1 variants and one study incorporated CYP2C9, VKORC1 and CYP4F2 variants. Follow-up times for our outcomes of interest (warfarin related ADEs and time within therapeutic range) ranged from 14 days to 12 weeks.

Risk of bias for all studies
Four studies were of very high methodological quality with all items categorized as low risk of bias (Figure 2A) and a further three were of high methodological quality with all items categorized as low risk of bias except one that was uncertain/unclear risk of bias. The greatest source of bias was observed in performance bias, the blinding of participants and personnel (Figure 2B).

Non-warfarin trials
Of the six non-warfarin genotype-guided trials, two demonstrated a statistically significant benefit for their primary outcome. In renal transplant patients receiving tacrolimus either according to CYP3A5 genotype or according to the standard regime the proportion within the targeted therapeutic trough concentration (C₀) after six doses was 43.2% (95% CI 36, 51.2) vs. 29.1% (95% CI 22.8, 35.5), respectively, P = 0.03 [33]. In patients infected with immunodeficiency virus type 1 excluding HLA-B*5701-positive patients, in the experimental arm, abacavir treatment resulted in a reduction in the incidence of hypersensitivity reactions, OR 0.03 (95% CI 0.00, 0.62, P < 0.001) [29]. The other four non-warfarin trials did not show statistically significant improvements in the primary outcome that they defined. It was not possible to perform a meta-analysis on these studies due to clinical heterogeneity.

Genotype-guided warfarin dosing
Time within therapeutic INR range. Data were available for meta-analysis from eight studies, the study by Burmester et al. [36] was not included as data were available for only the first 14 days, when the estimate of the median times to stable therapeutic dose were 31 days (95% CI, 23, 36). A total of 1952 patients from seven studies are included in the meta-analysis (Figure 3) [6, 18, 19, 21, 23, 35, 37]. The statistically significant mean difference is

Figure 1
PRISMA flow diagram of study selection
## Table 2
Characteristics of studies

| Study                  | Country of study | Population Total number in trial (Intervention/Control) | Mean age | Ethnicity | Drug prescribed | Genotype(s) used | Primary outcome(s) | Primary outcome result |
|------------------------|------------------|---------------------------------------------------------|----------|-----------|-----------------|------------------|--------------------|------------------------|
| Anderson et al. [18]   | USA              | 200 (101/99); 53% 61 years                             |          | 94% Caucasian | Warfarin         | CYP2C9 VKORC1     | % out-of-range INRs | Relative % reduction = 7.3, P = 0.47 |
| Borgman et al. [35]    | USA              | 26 (13/13); 54% 52 years                               |          | 92% Caucasian | Warfarin         | CYP2C9 VKORC1     | % time within therapeutic range | Experimental = 70.3 ± 17.9, Control = 77.7 ± 11.3, P = 0.441 |
| Burmester et al. [36]  | USA              | 225 (112/113); 59% 68 years (median)                   |          | 100% Caucasian/Hispanic | Warfarin         | CYP2C9 VKORC1 CYP4F2 | 1. Absolute prediction error relative to therapeutic dose, 2. Time in therapeutic target range for 1st 14 days | 1. Median difference = 0.39 mg day⁻¹ (95% CI 0.26, 0.57), favours genotype model, 2. Median for both arms = 28.6%, P = 0.564 |
| Caraco et al. [21]     | Israel           | 191 (95/96); 52% 59 years (median)                     |          | Not stated | Warfarin         | CYP2C9           | 1. Time to reach therapeutic INR range, 2. Time to reach stable anticoagulation | 1. Adjusted HR 3.95 (95% CI 2.77, 5.65), favours genotype model, 2. HR 4.23 (95% CI 2.96, 6.07), favours genotype model |
| Hillman et al. [19]    | USA              | 38 (18/20); 45% 70 years                               |          | 100% Caucasian | Warfarin         | CYP2C9 VKORC1     | Feasibility        | Application of a CYP2C9 gene-based multivariate warfarin dosage calculator is feasible |
| Huang et al. [37]      | China            | 121 (61/60); 31% 42 years                              |          | 100% Chinese | Warfarin         | CYP2C9 VKORC1     | Time to reach stable warfarin dose | HR 1.93 (95% CI 1.26, 2.97), favours genotype model |
| Kimmel et al. [23]     | USA              | 955 (514/511); 51% 58 years (median)                   |          | 27% Black, 73% Non-Black | Warfarin         | CYP2C9 VKORC1     | % time within therapeutic range | Adjusted mean difference: -8.3%, P = 0.01, favours control |
| Mallal et al. [29]     | 19 Countries     | 1650 (803/847); 23% 42 years (median)                  |          | 83% 42 years 91% Caucasian | Abacavir         | HLA-B*5701       | Reduced incidence of hypersensitivity reaction | OR 0.03 (95% CI 0.00, 0.62), favours genotype model |
| Meynard et al. [30]    | France           | 525 (187/186/152); 81% 41 years unknown               |          | Antiretroviral agents (12) | Warfarin         | CYP2C9 VKORC1     | HIV anti-retroviral resistance mutations | Proportion with plasma HIV-1 RNA <200 copies ml⁻¹ at week 12 | Phenotyping = 35%, Genotyping = 44%, Controls = 36%, No significant difference between arms |
| Newman et al. [31]     | UK               | 322 (163/159); 83% 42 years                            |          | Azathioprine | TMPT             | Stopping azathioprine due to adverse drug reaction | OR 1.1 (95% CI 0.66, 1.8) |
| Pirmohamed et al. [6]  | UK, Sweden       | 427 (211/216); 62% 68 years                            |          | 91% Caucasian | Warfarin         | CYP2C9 VKORC1     | % time within therapeutic range | Adjusted mean difference: 7% (95% CI 3.3, 10.6), favours genotype model |
| Roberts et al. [32]    | Canada           | 187 (91/96); 78% 60 years                              |          | 95% Caucasian | Clopidogrel/prasugrel | CYP2C19         | Proportion with P2Y12 reactivity unit >234 after 1 week dual therapy treatment. | Experimental = 9 (10%), Control = 16 (17%), Adjusted P = 0.07 |
| Thervet et al. [33]    | France           | 236 (116/120); 67% 47 years                            |          | 90% Caucasian | Tacrolimus       | CYP3A5           | Proportion within targeted therapeutic trough concentration after six doses. | Experimental = 43.2% (95% CI 36.5, 51.2), Control = 28.1% (95% CI 22.8, 35.5), P = 0.03 |
| Verhoef et al. [34]    | Greece, Netherlands | 484 (239/245); 60% 68 years                            |          | Azenocoumarol/phenprocoumon | Warfarin         | CYP2C9 VKORC1     | % time within therapeutic range. | Experimental = 61.6 ± 23.3, Control = 60.2 ± 23.2, Difference: 1.4 (95% CI –2.8, 5.5), P = 0.52 |
| Wang et al. [38]       | China            | 101 (50/51); 31% 42 years                              |          | 100% Chinese | Warfarin         | CYP2C9 VKORC1     | Time to reach stable warfarin dose | HR 1.57 (95% CI 1.10, 2.28), favours genotype model |
Figure 2
Risk of bias. (A) Risk of bias summary: review authors’ judgements about each risk of bias item for each included study. (B) Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies. ■ low risk of bias; □ unclear risk of bias; ▼ high risk of bias.
6.67% (95% CI 1.34, 12.0) time within therapeutic international normalized ratio range, in favour of genotype-guided warfarin dosing. There is considerable heterogeneity in this analysis, I² = 80%.

Risk of adverse haemorrhagic and thromboembolic events

Data were available for 2211 patients from seven studies for the meta-analysis of the risk of haemorrhagic and thromboembolic events (Figure 4) [6, 18, 19, 21, 23, 35–37]. Unpublished data from one study was used in this analysis. There was a total of 251 events observed, 107 in the genotype-guided group and 144 in the control group. The RR was significant, RR = 0.57 (95% CI 0.33, 0.99), with moderate heterogeneity, I² = 60%.

Discussion

The aim of this systematic review was to examine the evidence for the prospective clinical use of genotype information to improve the effectiveness of drug prescribing as demonstrated by reduced harm and increased relative effectiveness. Previous reviews have focussed on the use of genotype-guided prescribing for a single drug and we aimed to use a broader approach. We identified a reasonable size of literature relevant to our aim, but it was only possible to meta-analyze the studies of warfarin dosing. The limited literature outside warfarin dosing may reflect that warfarin is a commonly prescribed drug with a narrow therapeutic index and a wide variation in the dose required to reach therapeutic range. While there is an
increase in RCTs that go beyond using genotyping to evaluate warfarin dosing, high level evidence is lacking regarding the clinical utility of testing for genetic variations associated with drug response. This is the first systematic review to incorporate data from the two most recent warfarin genotype-guided dosing RCTs, demonstrating that the use of genotype-guided dosing increases time within therapeutic international normalized ratio range, mean difference 6.67% (95% CI 1.34, 12.0). This is not in accordance with a 2012 systematic review that states ‘there is little evidence to support the use of genotyping, which conflicts with the US Food and Drug Administration (FDA) statement. . . Our overall findings are in accordance with an older systemic review that did not find sufficient evidence to support the use of pharmacogenetics to guide warfarin therapy (Kangelaris, 2009). In addition, an editorial by Ansell, 2009 notes, “most problematic is that the intervention arm of each trial is considerably different”. Therefore, current use of genotyping is not underpinned by the evidence and should be discouraged.’ [39]. The differences of opinion are partially due to the studies used in the systematic review. They included Anderson et al. [18], Burmester et al. [36] Caraco et al. [21] and Hillman et al. [19]. Borgman et al. [35], Kimmel et al. [23], Pirmohamed et al. [6] and Wang et al. [38] were not published at the time of their review, an added 1509 patients. However there is still significant variability in terms of design quality, medical indication, length of follow-up and intervention design, indicating that our meta-analysis of time within therapeutic range should be interpreted with caution.

For the warfarin studies there were differences in study design related to the experimental vs. control algorithms employed to determine loading dose and in some cases dose revision and/or maintenance. For example, whereas the pharmacogenetic experimental loading dose and dose adjustment protocols were similar in the two most recent RCTs, the control dosing protocols were very different. Kimmel et al. [23] used CYP2C9 + VKORC1 genotype and the Gage clinical variable algorithm vs. the Gage clinical variable algorithm, Pirmohamed et al. [6] used CYP2C9 + VKORC1 genotype and the Avery clinical variable algorithm vs. 10 mg on day 1 and 5 mg on day 2. Kimmel et al. [23] saw no difference in time within therapeutic INR range, whereas Pirmohamed et al. [6] saw a modest difference in time within therapeutic INR range. The benefits of the genetic components of the pharmacogenetic algorithm in the study by Pirmohamed et al. [6] are hard to separate from the benefits of the clinical algorithm. It has been suggested that it was not surprising that differences were not seen between the Kimmel et al. [23] trial arms as they were comparing two multivariate models [16]. The contribution of genetic variables to the success of warfarin dosing could have been masked by the fact that using a clinical only multivariate model for dose prediction and adjustment that requires rigorous INR testing and management is highly likely to be substantially better than real world settings that have standard local practice.

There are six genotype-guided warfarin dosing trials registered in clinicaltrials.gov that are currently actively recruiting or completed and awaiting study results. One of these is a large RCT of an estimated 1600 patients (the GIFT trial), which will compare therapeutic warfarin dosing using genotype and clinical information with warfarin dose requirements using clinical information only. This trial is powered for ADEs as a primary outcome measure (http://clinicaltrials.gov/ct2/show/NCT01006733?term=NCT01006733%26). Our results are not definitive because of the statistical heterogeneity between trials. Although the overall quality of the included studies was high there was evidence of performance bias in many of the studies. This was mitigated by use of a ‘hard’ outcome measure, of ‘time within therapeutic INR range’. In summary, this study has examined the evidence for the prospective clinical use of genotype-guided prescribing to improve effectiveness of drug prescribing and the evidence supports the use of genotype-guided prescribing for warfarin, tacrolimus and abacavir. RCTs of the more pragmatic clinical approach of using a multidrug/SNP process to inform prescribing need to be undertaken.

Competing Interests

All authors have completed the Unified Competing Interest form at and declare no support from any organization for the submitted work. MD reports grants from Rx&D and pharmaceutical companies, outside the submitted work in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

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