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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, $I^2 = 80\%$). 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; $I^2 = 60\%$). 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 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

Table 1
Medline search

#1: (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab])OR drug therapy[sh] OR randomly[tiab] OR trial[tiab]) NOT (animals[mh] NOT humans[mh])
#2: 'Genotype'[Mesh] OR 'Genotyping Techniques'[Mesh] OR 'Genetic Association Studies'[Mesh] OR 'Pharmacogenetics'[Mesh] OR 'Genetics'[Mesh] OR 'Reverse Genetics'[Mesh] OR 'Genetics, Population'[Mesh] OR 'Genetics, Medical'[Mesh] OR 'Genetics, Behavioral'[Mesh] OR 'Genetics, Microbial'[Mesh] OR 'Physical Chromosome Mapping'[Mesh] OR 'Dosage Compensation, Genetic'[Mesh] OR 'Regulatory Sequences, Nucleic Acid'[Mesh] OR 'Polymorphism, Genetic'[Mesh] OR 'Polymorphism, Genetic'[Mesh] OR 'Amplified Fragment Length Polymorphism Analysis'[Mesh] OR 'Polymorphism, Single Nucleotide'[Mesh] OR 'Polymorphism, Single-Stranded Conformational'[Mesh] OR 'Polymorphism, Restriction Fragment Length'[Mesh] OR 'DNA Copy Number Variations'[Mesh]
#3: abacavir OR ziagen OR acenocoumarol OR sintrom OR acepromazine OR acetophenazine OR allopurinol OR alloprin OR maloprim OR zyloprim OR amisulpride OR aripiprazole OR abilify OR azathioprine OR imuran OR azadan OR bupropion OR zyban OR wellbutrin OR capecitabine OR xeloda OR carbamazepine OR tegretol OR carbuterol OR epitol OR equetro OR chlorproguanil OR chlorpromazine OR chlorprothixene OR cisplatin OR citalopram OR celexa OR cladribine OR clofarabine OR clolar OR clozapine OR clozaril OR cytarabine OR cytosar OR dapsone OR droperidol OR erlotinib OR tarceva OR fludarabine OR fludara OR fluorouracil OR fluphenazine OR modecate OR fluspirilene OR gefitinib OR iressa OR gemcitabine OR gemzar OR haloperidol OR haldol OR ivacaftor OR kalydeco lithium OR carvolth OR duralit OR lithane OR lithman OR lithobid OR loxapine OR xyloc OR loxitane OR loxapac OR mercaptopurine OR purinethol OR mesoridazine OR methotrexate OR rheumatrex OR truxall OR methotrimeprazine OR methopromazine OR mepazine OR nozinan OR nelarabine OR adriance OR arranon OR olanzapine OR zyprexa OR paliperidone OR invega OR peginterferon alfa-2a OR pegasys OR sylatron OR peginterferon alfa-2b OR pegintron OR sylatron OR perazine OR perphenazine OR phenprocoumon OR pimozide OR orap OR pipothiazine OR piportil OR prochlorperazine OR comoro OR nu-prochlor OR promazine OR quetiapine OR seroquel OR remoxipride OR ribavirin OR virazole OR copegus OR rebetol OR ribasphere OR ribapak OR risperidone OR risperidal OR sertindole OR simvastatin OR zocor OR sulpiride OR tacrolimus OR advagraf OR prograf OR protopic OR ecori OR tegafur OR orzel OR thioguanine OR lanvis OR tabloid OR thioproperazine OR thioridazine OR thiothixene OR navane OR trifluoperazine OR terfluzine OR triflupromazine OR warfarin OR coumadin OR jantova OR ziprasidone OR zeldow OR geodon
#4: #1 AND #2 AND #3

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 I^2 statistics, which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. $I^2 < 25\%$ was considered as low in heterogeneity and $I^2 > 75\%$ 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 (*CYP3A5*), 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

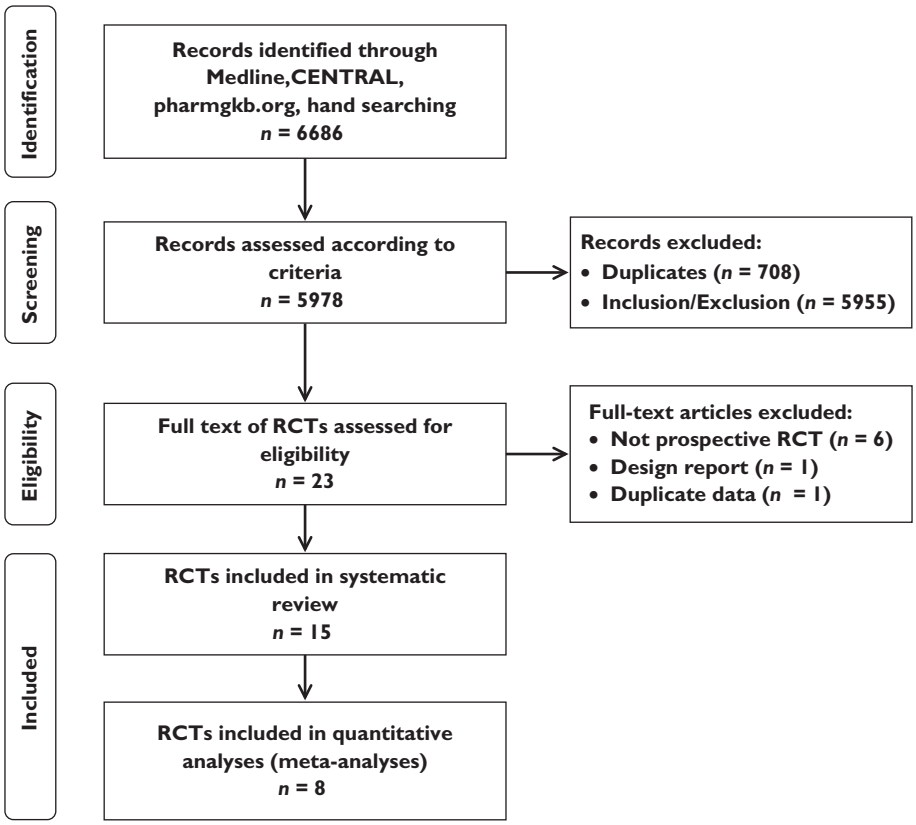

Figure 1
PRISMA flow diagram of study selection

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 (C_0) 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

Table 2

Characteristics of studies

Study	Country of study	Population Total number in trial (Intervention/ Control) % Male 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 2.95, 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 (514/501) 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) 73% 42 years 83% 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)	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 91% Caucasian	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 99% 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, 51.2) Control = 29.1% (95% CI 22.8, 35.5) $P = 0.03$
Verhoef *et al.* [34]	Greece Netherlands	484 (239/245) 60% 68 years 97% Caucasian	Acenocoumarol/ phenprocoumon	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, 3.28), favours genotype model.

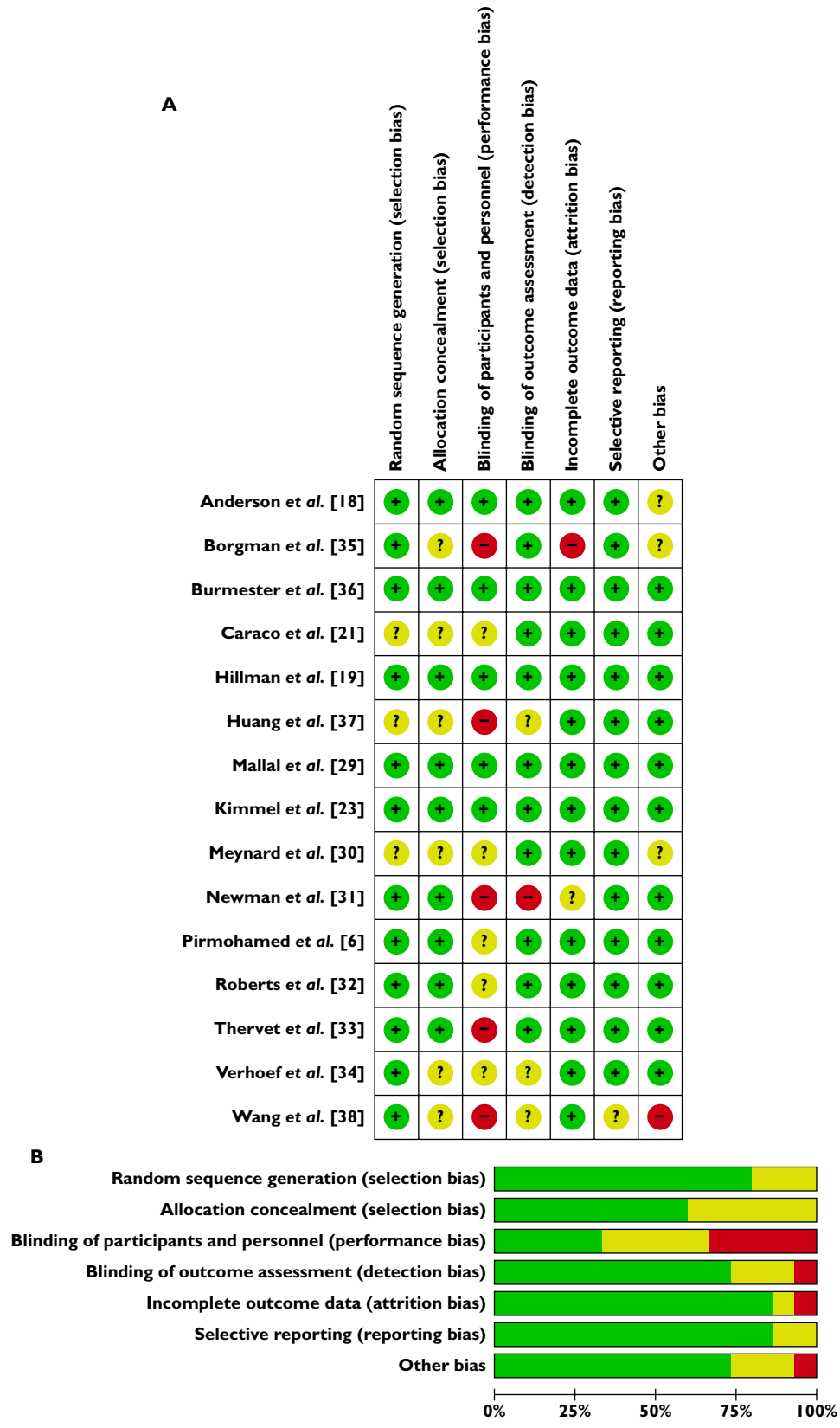

Figure 2

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

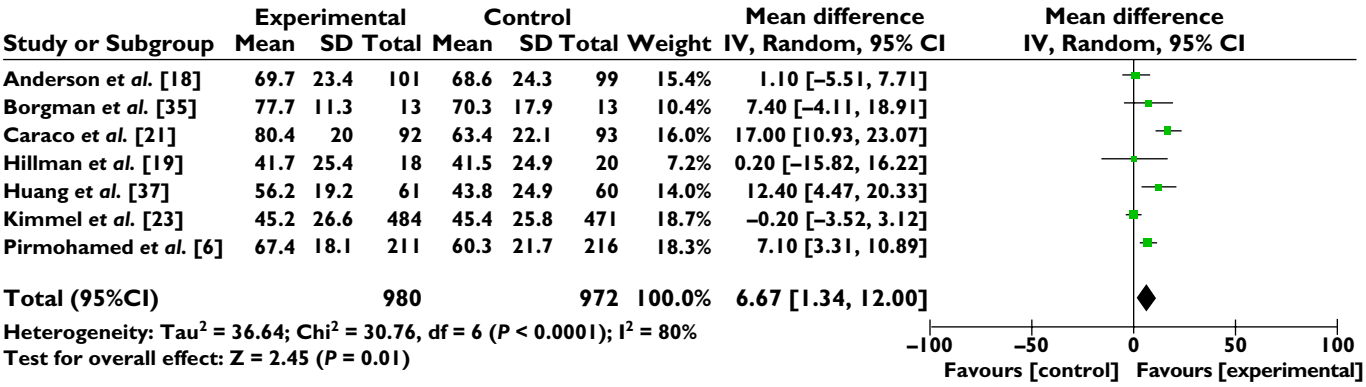

Figure 3

Forest plot: meta-analysis of genotype-guided prescribing to improve warfarin dosing; time within therapeutic international normalized ratio range (%), 14 to 60 days. Size of square reflects the study statistical weight, the horizontal lines indicate 95% confidence intervals (CI) and the diamond indicates summary mean difference estimate with the corresponding 95% CI

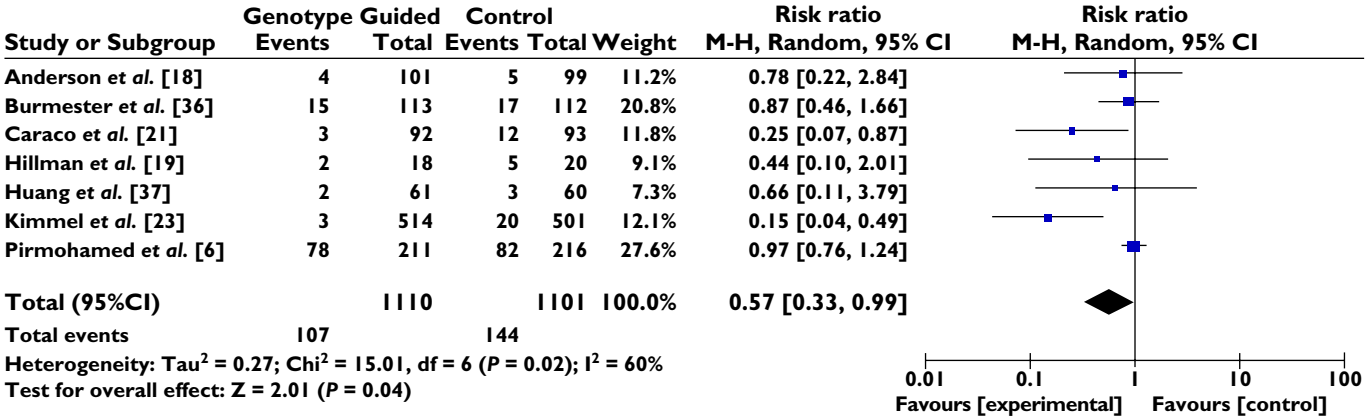

Figure 4

Forest plot of comparison: meta-analysis of genetically-guided prescribing to improve warfarin dosing; risk of adverse haemorrhagic and thromboembolic events. Size of square reflects the study statistical weight, the horizontal lines indicate 95% confidence intervals (CI) and the diamond indicates summary risk ratio estimate with the corresponding 95% CI

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, $I^2 = 80\%$.

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, $I^2 = 60\%$.

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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