Pharmacogenomics and Personalized Medicine

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REVIEW

Drug–Drug–Gene Interactions in Cardiovascular Medicine

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Abstract: Cardiovascular disease remains a leading cause of both morbidity and mortality worldwide. It is widely accepted that both concomitant medications (drug–drug interactions, DDIs) and genomic factors (drug–gene interactions, DGIs) can influence cardiovascular drug-related efficacy and safety outcomes. Although thousands of DDI and DGI (aka pharmacogenomic) studies have been published to date, the literature on drug–drug–gene interactions (DDGIs, cumulative effects of DDIs and DGIs) remains scarce. Moreover, multimorbidity is common in cardiovascular disease patients and is often associated with polypharmacy, which increases the likelihood of clinically relevant drug-related interactions. These, in turn, can lead to reduced drug efficacy, medication-related harm (adverse drug reactions, longer hospitalizations, mortality) and increased healthcare costs. To examine the extent to which DDGIs and other interactions influence efficacy and safety outcomes in the field of cardiovascular medicine, we review current evidence in the field. We describe the different categories of DDIs and DGIs before illustrating how these two interact to produce DDGIs and other complex interactions. We provide examples of studies that have reported the prevalence of clinically relevant interactions and the most implicated cardiovascular medicines before outlining the challenges associated with dealing with these interactions in clinical practice. Finally, we provide recommendations on how to manage the challenges including but not limited to expanding the scope of drug information compendia, interaction databases and clinical implementation guidelines (to include clinically relevant DDGIs and other complex interactions) and work towards their harmonization; better use of electronic decision support tools; using big data and novel computational techniques; using clinically relevant endpoints, preemptive genotyping; ensuring ethnic diversity; and upskilling of clinicians in pharmacogenomics and personalized medicine.

Keywords: drug–drug interactions, drug–gene interactions, drug–drug–gene interactions, drug–gene–gene interactions, pharmacogenomics

Introduction

Cardiovascular disease remains a leading cause of mortality, with heart diseases having caused the highest number of deaths in the United States (21% of ~3.4 million deaths) according to provisional leading cause-of-death rankings for 2020.[1] Globally, cardiovascular diseases (led by ischaemic heart disease, stroke, and hypertensive heart disease) accounted for approximately 17.8 million (95% confidence intervals/CI 17.1 to 19.7 million) deaths and 393 million (95% CI 368 to 417 million) disability-adjusted life years (DALYs) in 2019, making cardiovascular disease the leading cause of both deaths and DALYs.[2] Moreover, the prevalence of cardiovascular disease is increasing due to disparate trends in mortality versus incidence.[3] For instance, the number of new cardiovascular cases (55.5 million, 95% CI 52.3 to 58.9 million) was thrice the number of cardiovascular deaths (17.8 million), leading to an estimated total prevalence of 523 million (95% CI 497 to 550 million) by the end of 2019.[2]

Drug–drug–gene interactions (DDGIs) arise when both another drug (drug–drug interaction, DDI) and an individual's genetic profile (drug–gene interaction, DGI) alter the efficacy and/or safety profile of a specified drug.[4] Advancements in medical knowledge (earlier disease diagnosis, more effective treatments, a realization that lifestyle factors such as smoking can impact disease etc.) have resulted in a remarkable gain in life expectancy.[3] An increasingly ageing population is the main driver of multimorbidity, defined by the Academy of Medical Sciences as the coexistence of

Received: 23 August 2022
Accepted: 21 October 2022
Published: 2 November 2022

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two or more chronic health conditions.[5] Multimorbidity is common in patients with cardiovascular disease (being estimated to be 91% and 93% in 229205 UK,[6] and 3478 Chinese,[7] participants, respectively). Furthermore, this is not restricted to high-income countries.[8] Multimorbidity usually necessitates the administration of multiple medication regimens (to manage the multiple health conditions), often resulting in polypharmacy (most commonly defined as five or more daily medications[9]), higher DDI/DGI/DDGI frequencies, medication-related harm/adverse outcomes (such as adverse drug reactions, longer hospitalizations, and mortality), and increased healthcare costs.[10–15]

A systematic review reported that the median percentage of preventable drug-related hospital admissions was 3.7% (range 1.4 to 15.4, 13 studies) and that most preventable drug-related admissions (n = 1406, 9 studies) involved antiplatelets including aspirin (n = 225, 16.0%), diuretics (n = 223, 15.9%), nonsteroidal anti-inflammatory drugs (n = 155, 11.0%) or anticoagulants (n = 117, 8.3%).[16] In a later systematic review that also reported hospitalization resulting from adverse drug reactions (ADRs) or adverse drug events (ADEs), all included studies reported involvement of cardiovascular medicines, with these medicines being responsible for a median of 33.9% (interquartile range/IQR 19.9 to 58.6%) of ADRs (n = 21 studies) and 42.3% (IQR 30 to 72.2%) of ADEs (n = 6 studies).[17] More recently, in a prospective observational study conducted in the Liverpool University Hospital Foundation National Health Service (NHS) Trust, England, 218 (18.4%) of 1187 patients were admitted with an adverse drug reaction, with these admissions being estimated to cost the UK NHS approximately £2.21 billion each year.[12] In this study, cardiovascular drugs (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, anticoagulants, antiplatelets, and diuretics) and DDIs were implicated in 82 (37.6%) and 64 (29.4%) of the 218 patient episodes with adverse drug reactions, respectively.[12] It should be pointed out that the number of potential DDIs far outweighs the number of clinically relevant adverse reactions.[18,19] However, DDIs are more likely to be clinically relevant if they involve drugs with low therapeutic indices (eg, warfarin for anticoagulation or digoxin for atrial fibrillation), are given to vulnerable patients (eg, those who are elderly or have multiple morbidities including renal/hepatic impairment), or involve novel therapeutic agents (whose mechanisms of actions are less likely to be fully understood).[18]

Pharmacogenomics is the study of the genomic basis of variability in drug response, and it is often used interchangeably with pharmacogenetics, which focuses on specific genes.[20] More advanced and cheaper genotyping technology have enabled the conduct of several pharmacogenomic (DGI) studies, including genome-wide association studies, that have increased pharmacogenomic awareness and the realization that most patients would benefit from the use of pharmacogenomic information in their clinical management. For instance, McInnes et al have previously reported that 99.5% of 487,409 participants in the UK Biobank had at least one clinically actionable genotype, defined as a genotype associated with a clinically relevant DGI.[21] Other studies have reported similar estimates including 99.8% of 42,092 Estonians,[22] 91.4% of 9589 Vanderbilt pharmacogenotyping program participants,[23] 99.5% of 6045 Qataris,[24] 95.9% 5408 Australians,[25] 99.0% of 1013 Mayo Clinic Biobank participants,[26] 98.7% of 713 UK patients,[27] 99.4% of 498 Dutch participants,[28] and, 96.9% of 98 Canadian paediatric patients[29] having at least one clinically actionable genotype/diplotype. To enable the translation of pharmacogenomic knowledge into clinical practice, clinical implementation guidelines such as the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), the Dutch Pharmacogenetics Working Group (DPWG), and the French National Network (Réseau) of Pharmacogenetics (RNPGx) have been developed.[30] However, these guidelines, like most pharmacogenetic studies, focus on DGIs, which means evidence pertaining to DDGIs remains limited.[15,31] As stated above, multimorbidity and polypharmacy, which are common in cardiovascular disease and ageing populations, increase the frequencies of both DDIs and DGIs, which makes it necessary to increase efforts to avoid these interactions and to understand how DDIs interact with DGIs (DDGIs). Using pharmacogenomic and other evidence, we therefore examine the extent to which DDGIs and other interactions influence efficacy and safety outcomes in the field of cardiovascular medicine. We describe the different categories of DDIs and DGIs and illustrate how they interact to produce DDGIs and other complex interactions. We provide examples of studies that have reported the prevalence of clinically relevant interactions and the most implicated cardiovascular medicines, outline the challenges associated with dealing with these interactions in clinical practice and recommendations on how to manage these challenges.

Cardiovascular Medicine

Cardiovascular medicine deals with the diagnosis and treatment of cardiovascular disease (CVD), which is a general term that describes a group of disorders affecting the heart and/or blood vessels.[32] The major disorders vary in terms of underlying

pathologies, other organ systems involved (eg endocrine, hematologic, immune, neurologic and/or pulmonary), and the population segments affected.[33] Although each CVD disorder has a distinct pathology, they all have a common set of risk factors including atherosclerosis (build-up of fatty deposits within arteries), hypertension and related organ damage, infection (including streptococcal-related heart valve damage or rheumatic heart disease), and anatomic deformities (both congenital and acquired).[32–35] Examples of CVD disorders include those involving the heart muscles (eg, atrial fibrillation and myocardial infarction), heart valves (eg, rheumatic heart disease) and blood vessels. Blood vessel disorders include ischaemic heart disease (occlusion of the coronary arteries), cerebrovascular disease (blockage of brain-supplying blood vessels), peripheral arterial disease (restriction of blood supply to the arm and leg muscles) and deep vein thrombosis (clots/thrombi forming in the deep veins found in the legs, calf or elsewhere).[32,34] When thrombi in deep veins become dislodged, they can travel to the lungs and block the pulmonary vessels resulting in a condition termed pulmonary embolism.[32,34] Strokes, on the other hand, result from the blockage (eg, by atherosclerotic plaques or blood clots or emboli) of the arteries supplying the brain (ischaemic strokes), although they can also be caused by other events (eg bleeding in haemorrhagic strokes).[32,34]

CVD management generally involves three main stages.[34,36] In the first, an assessment is conducted to evaluate the causes, if any, of the CVD disorder, evaluate the severity (for instance damage to other organs) and determine concomitant or underlying conditions (such as diabetes) that may add to the cardiovascular burden. Depending on the initial assessment (severity of the disease, risk factors, etc.), both non-pharmacological (second stage) and pharmacological (third stage) interventions may be offered at the same or different time(s), acutely or chronically and therapeutically or prophylactically (primary or secondary prophylaxis). Non-pharmacological treatment includes advice on lifestyle interventions (ie, weight reduction, diet changes, alcohol consumption, smoking and exercise) and mechanical interventions (such as elastic compression stockings or percutaneous coronary intervention/coronary angioplasty). If non-pharmacological treatment is insufficient, pharmacotherapy (cardiovascular medicines) to aid symptom relief, control the disease, retard disease progression, prevent complications, reduce risk factors and improve the length and quality of life is (are) required.[34,36,37] Due to the high prevalence of cardiovascular disease, it is unsurprising that cardiovascular medicines are among the most commonly used drugs.[38–40] For example, based on the US National Health and Nutrition Examination Survey (2015–2016) and Canadian Health Measures Survey (2016–2017), lipid-lowering drugs were used by 45.0% and 34.3% of US and Canadian adults aged 60–79, respectively.[39] Example categories of cardiovascular medicines/drugs are shown in Table 1.**Note:** Data from Chapter 2 of the British National Formulary.[37]

Drug–Drug Interactions

Drug–drug interactions (DDIs) occur when one drug (the perpetrator drug) affects how the body acts on a victim drug (pharmacokinetic effects) and/or how the victim drug acts on the body (pharmacodynamic effects).[4,18] There is a third mechanism by which drugs can interact (pharmaceutical DDIs, caused by inappropriate mixing of drugs before administration eg, precipitation of phenytoin solution for injection when mixed with a glucose solution)[18] but these are not common and are therefore not discussed further.

Table 1 Example Categories of Cardiovascular Medicines/Drugs

Categories	Drug Classes and/or Examples	Main Uses
Anti-arrhythmic drugs	Class I (membrane stabilizing drugs like lidocaine, flecainide and propafenone), class II (beta blockers like esmolol, see below), class III (eg amiodarone and dronedarone) and class IV (calcium-channel blockers that are not dihydropyridines eg verapamil).	To control the ventricular rate and/or restore and maintain sinus rhythm for atrial fibrillation, ectopic beats, atrial flutter, paroxysmal supraventricular tachycardia, ventricular tachycardia or arrhythmias after myocardial infarction.
Beta-adrenoceptor blocking drugs	Propranolol, atenolol, carvedilol, metoprolol, esmolol, sotalol, nebivolol etc.	Angina, hypertension, myocardial infarction, arrhythmias, heart failure and others (thyrotoxicosis, anxiety, migraine prophylaxis, glaucoma etc).

(*Continued*)

Table 1 (Continued).

Categories	Drug Classes and/or Examples	Main Uses
Positive inotropic drugs	Cardiac glycosides (eg digoxin) and phosphodiesterase type-3 inhibitors (eg enoximone and milrinone).	To increase the force of myocardial contraction in conditions such as heart failure and atrial fibrillation
Anti-anginal drugs	Nitrates (eg glyceryl trinitrate and ranolazine), calcium-channel blockers (eg verapamil and dihydropyridines like nifedipine), potassium channel activators (eg nicorandil), peripheral vasodilators (eg cilostazol) and others (eg ivabradine).	Cause coronary vasodilation and/or reduce venous return/left ventricular work hence managing angina (and other conditions such as hypertension, arrhythmias and peripheral vascular disease).
Antifibrinolytics	Eg tranexamic acid.	Impair fibrin dissolution to prevent or treat bleeding associated with excessive fibrinolysis (eg thrombolytic overdose, dental extraction, surgery, traumatic hyphaemia and obstetric disorders).
Blood-related products	Includes dried human prothrombin complex (contains clotting factors IX, II, VII and X) and specific coagulation factors (eg recombinant factor VIIa/activated eptacog alfa, dried factor IX fraction and protein C concentrate).	Treatment/perioperative prophylaxis of haemorrhage in patients with congenital or acquired (including anticoagulant overdose) deficiencies of specific coagulation factors.
Calcium-channel blockers	Dihydropyridines (eg felodipine, nifedipine and amlodipine) and non-dihydropyridines (eg diltiazem and verapamil).	Angina, hypertension, subarachnoid haemorrhage and arrhythmias (verapamil).
Anticoagulants	Parenteral (eg heparin, low molecular weight heparins such as enoxaparin, heparinoids such as danaparoid and hirudins such as bivalirudin) and oral anticoagulants that include Vitamin K antagonists (eg warfarin, acenocoumarol) and direct oral anticoagulants (eg apixaban, rivaroxaban and dabigatran).	Prevent thrombus formation or extension eg in venous thromboembolism and prevention of clots due to atrial arrhythmias and prosthetic cardiac valves.
Antiplatelets	Include aspirin, clopidogrel, ticagrelor, cilostazol and others.	Prophylaxis of myocardial infarctions, reduction of thrombosis after angioplasty and coronary stenting and stroke prophylaxis after prosthetic valve replacement or in cerebrovascular ischemia
Fibrinolytics/ thrombolytic agents	Human tissue plasminogen activators (alteplase), reteplase, tenecteplase, streptokinase and urokinase.	Clot resolution during myocardial infarction, thromboembolism or cerebral stroke.
Drugs affecting the renin-angiotensin system	Angiotensin-converting enzyme inhibitors like captopril, angiotensin II receptor antagonists like losartan and renin-inhibitors like aliskiren.	Used in heart failure, hypertension, diabetic nephropathy and prophylaxis of cardiovascular events.
Diuretics	Thiazides (eg bendroflumethiazide), loop diuretics (eg furosemide and torsemide), potassium-sparing diuretics and aldosterone antagonists (eg amiloride, triamterene, eplerenone and spironolactone), osmotic diuretics (eg mannitol), and carbonic anhydrase inhibitors (eg acetazolamide).	To relieve cardiovascular disease-related oedema (eg oedema due to chronic heart failure) and blood pressure (usually in lower doses).
Lipid-modifying drugs	Statins (eg atorvastatin, lovastatin, simvastatin), fibrates (eg bezafibrate, gemfibrozil), bile acid sequestrants (eg colestipol and cholestyramine) and others (eg lomitapide, nicotinic acid and omega-3 fatty acid compounds).	Altering the balance between low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides in hyperlipidaemias and prevention of cardiovascular events.

Pharmacokinetic DDIs

Many DDIs are pharmacokinetic in nature and occur when a perpetrator drug alters the absorption, distribution, metabolism (Figure 1A and B), elimination/excretion and/or transcellular transport of the victim drug, resulting in increased or decreased exposure of the victim drug.[18]

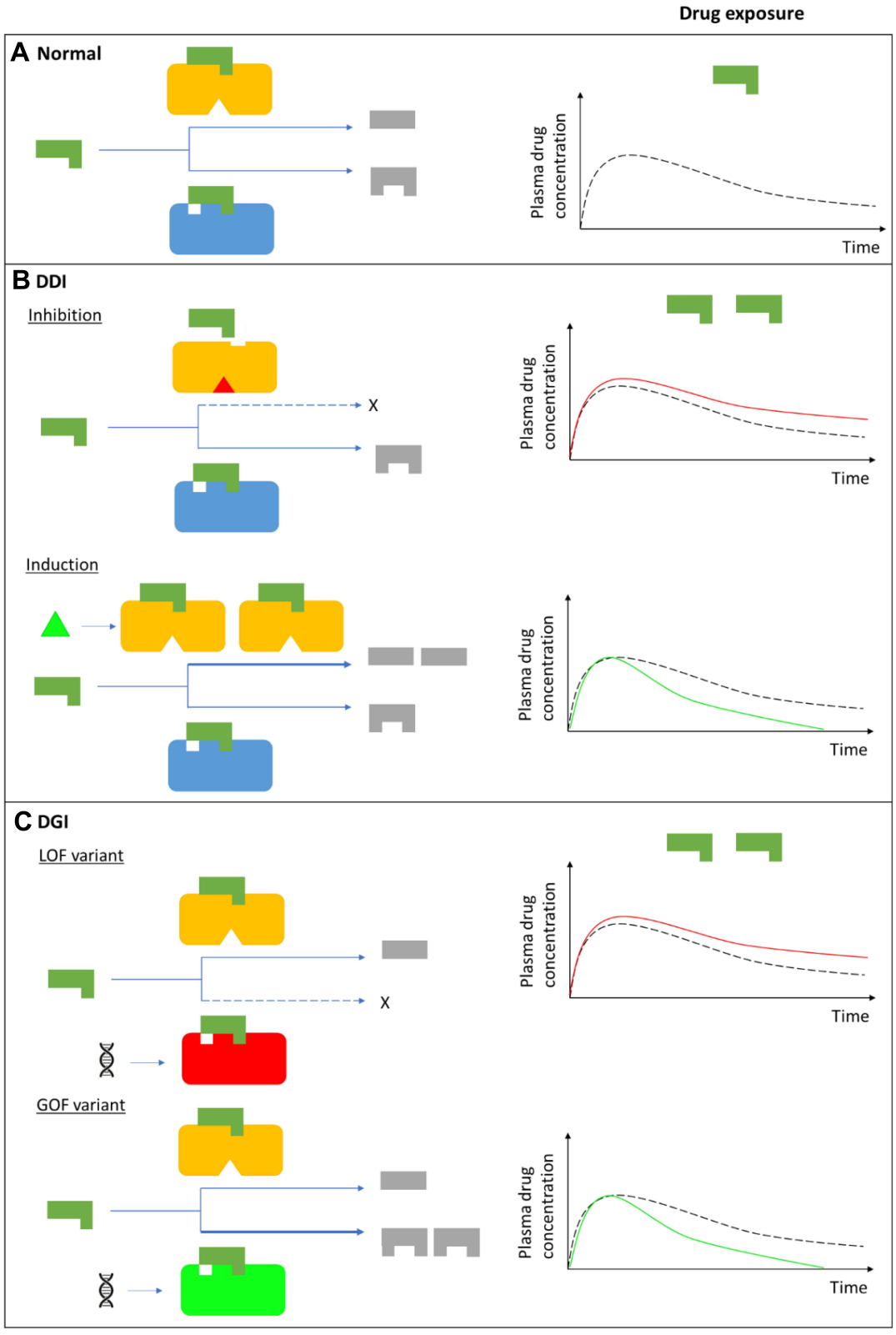

Figure 1 Continued.

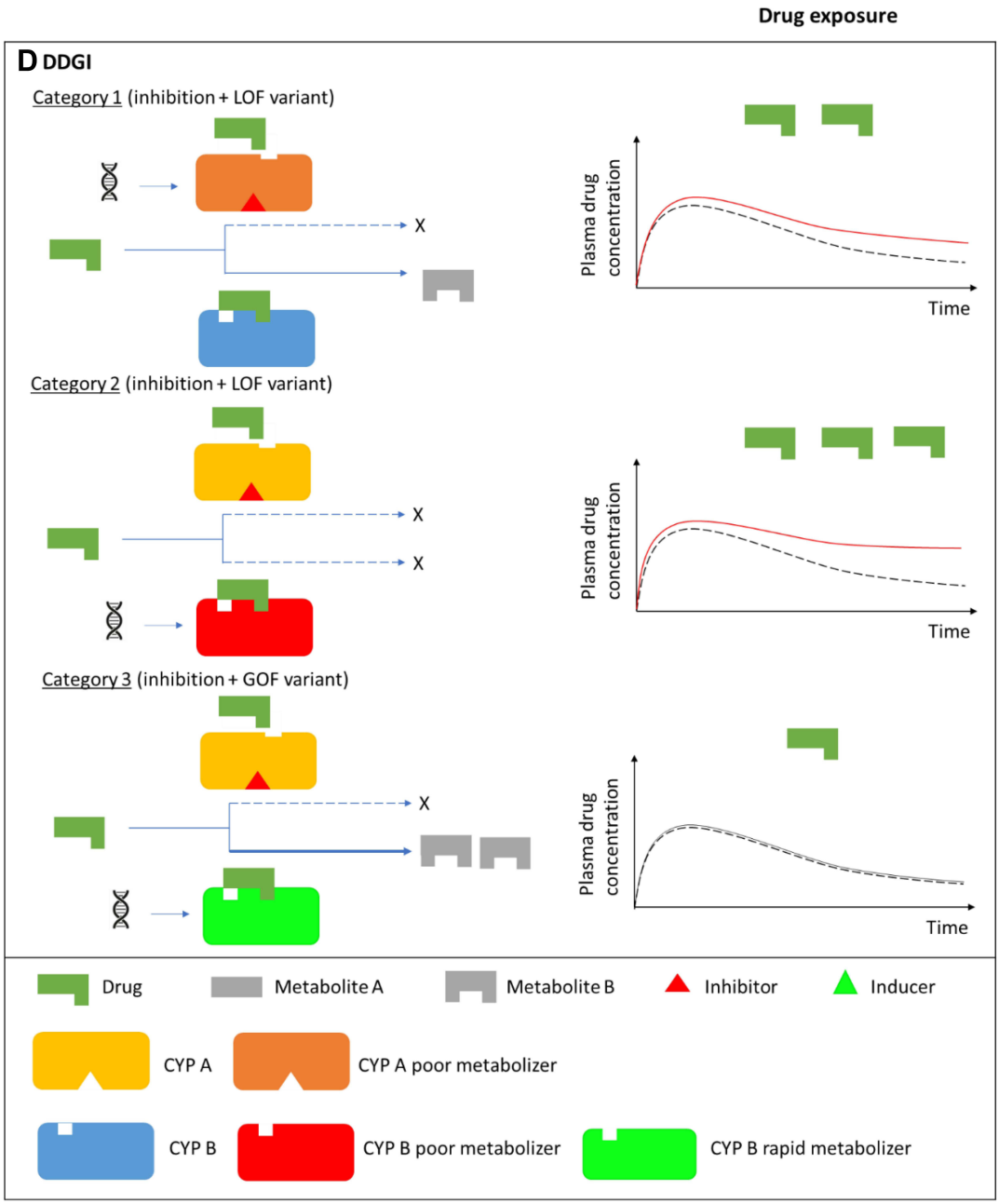

Figure 1 Drug-drug, drug-gene, and drug-drug-gene interactions.[13,52] (**A**) Normal metabolism: expected drug exposure (black dotted line in plasma drug concentration–time curve, single exposure) for a drug/substrate that is metabolized by two cytochrome P450 (CYP) enzymes. (**B**) Drug–drug interaction (DDI): inhibition (eg null activity) or induction (eg increased enzyme copies) of CYP A by co-medications resulting in increased (red line in plasma drug concentration–time curve) or decreased (green line in plasma drug concentration–time curve) drug exposures, respectively. (**C**) Drug–gene interaction (DGI): genetic variation inactivates/reduces (loss-of-function/LoF variant) or increases (gain-of-function/GoF variant) CYP B activity resulting in increased or decreased drug exposures, respectively. (**D**) Drug-drug-gene interaction (DDGI): cumulative effects of comedications (DDIs) and genetic variations (DGIs). In a category 1 DDGI, a DDI and DGI on the same pathway (eg CYP **A**) and direction (eg inhibitor with a LOF variant) interact to significantly increase (or decrease) drug exposure while in a category 2 DDGI, the DDI and DGI act on different pathways but still in the same direction to also increase (or decrease) drug exposure. Lastly, category 3 comprises DDIs and DGIs with opposing effects (eg inhibitor with a GOF variant) that leads to increased (inhibitor effects greater than GOF variant effects), decreased (inhibitor effects lower than GOF variant effects) or unchanged (inhibitor effects similar to GOF variant effects) drug exposure. The above interactions also apply to bioactivation of prodrugs (in which decreased metabolism results in decreased systemic exposure) and other pathways (eg drug- and/or gene-mediated changes to drug transporters or drug targets). If a drug has a comparable clinical effect with its metabolites, the effects of metabolism-based DDIs, DGIs and DDGIs may not be apparent. Any compensation by CYP A for the loss (or increase) in CYP B's activity, and vice-versa, is not depicted/accounted for in this over-simplified schematic.

Absorption

During absorption in the gastro-intestinal tract, DDIs can occur when one drug alters: a) intestinal blood flow/motility (eg, metoclopramide increases gastric emptying and can increase the rate but not extent of absorption of some drugs); b)

the stomach pH/acidity (eg, proton pump inhibitors, histamine type 2 receptor antagonists or antacids that increase gastric pH facilitate the absorption of weakly acidic drugs like aspirin); c) the formulation of the victim drug (eg, some antacids can damage enteric coatings that are designed to prevent dissolution in the stomach); d) the proportion of drug available for absorption (eg, some antacids can bind drugs such as tetracycline); e) bacterial flora resident in the intestine (eg, broad-spectrum antibiotics can decrease the populations of gut microbes that are important in modulating the bioavailability of oral drugs such as oral contraceptives), among other mechanisms.[18,37,41]

Distribution

Distribution-related DDIs mostly occur through two mechanisms.[18] The first involves the distribution of a victim drug to its site of action, with perpetrator drugs that can alter cardiac output (eg, inotropic drugs) or tissue perfusion (eg, vasodilators or vasoconstrictors) resulting in either increased exposure/drug effect (increased cardiac output and/or tissue vasodilation) or reduced exposure/drug effect (decreased cardiac output and/or tissue vasodilation). The second mechanism involves displacement of highly protein-bound drugs such as warfarin (~99% protein-bound), with the addition of other highly protein-bound drugs such as tizoxanide resulting in the displacement of warfarin, an increase in the unbound (free) fraction, and an increase in pharmacodynamic response.[18,42,43] However, these effects are likely to be short-lived and of limited clinical significance since the metabolism of the displaced drug usually increases, which offsets the increase in the unbound drug fraction.[18,42]

Metabolism

The most studied pharmacokinetic DDIs are those involving the family of cytochrome P450 (P450 or CYP) hepatic metabolizing isoenzymes, with CYP3A4 being the most commonly implicated enzyme.[18] Examples of substrates, inducers and inhibitors for the CYP metabolizing enzymes are shown in Table 2 (cardiovascular medicines are highlighted in bold). Although some DDIs can involve only cardiovascular drugs (eg, the antiarrhythmic amiodarone increasing plasma concentrations of the anticoagulant warfarin, through the inhibition of CYP2C9), other pairs of interacting drugs involve drugs from other drug classes (eg, the triazole antifungal fluconazole also potentiating warfarin's anticoagulation effect through CYP2C9 inhibition or the macrolide antibiotic clarithromycin inhibiting the CYP3A4-mediated metabolism of simvastatin, increasing its exposure and the risk of myopathy/rhabdomyolysis). Therefore, Table 2 is not restricted to cardiovascular drugs. Additionally, as stated earlier, patients with CVD usually take multiple medications including non-cardiovascular drugs, and some non-cardiovascular drug pairs can produce clinically significant cardiovascular side effects (eg, increased risk of QT interval prolongation and Torsades de Pointes when the antihistamine terfenadine is co-administered with the antibiotic erythromycin),[49] which makes it important to also study these drugs.

It is important to note that for drugs that are administered as prodrugs such as clopidogrel (metabolism by a CYP enzyme is required to generate the active drug), DDIs will have the opposite effect eg CYP2C19 induction by rifampicin, will increase the rate of production of clopidogrel's active metabolite, increasing the likelihood of toxicity (haemorrhagic events). Another thing worth pointing out is that enzyme inhibition can take many forms including non-competitive, competitive, uncompetitive, and mixed-type inhibition, with the two most common types being non-competitive (the inhibitor binds at an allosteric site and is not affected by substrate concentration) and competitive (inhibitor binds at the active site and "competes" with the substrate).[50] Inhibition can also be reversible (inhibitor noncovalently binds to the enzyme) or irreversible (inhibitor covalently binds to the enzyme) and in terms of clinical relevance means the effects of reversible inhibitors are usually short-lived, once the inhibitor is withdrawn. Lastly, whereas the effects of enzyme inhibition usually occur relatively early after administration of the inhibitor, those of drug induction usually take some time (1–2 weeks) as these require the formation of new enzyme.[18]

Excretion

The most common excretion/elimination DDIs involve drugs that are excreted by the kidney, with drugs that reduce renal elimination eg aminoglycoside antibiotics (alter glomerular filtration rate) or some nonsteroidal anti-inflammatory drugs (NSAIDs, compete for renal tubular excretion) increasing the risk of toxicity for drugs that are predominantly excreted by the kidneys, such as the cardiac glycoside digoxin.[18]

https://doi.org/10.2147/PGPM.S338601 DovePress

Table 2 Examples of Substrates, Inducers and Inhibitors for Cytochrome P450 Isoenzymes and Transporters[a] (Data from Turner et al[27])

Enzymes	Subtrates[b,c]	Inducers[d,e]	Inhibitors[f,g]
CYP isoenzymes			
CYP1A2	Sensitive (alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine) Moderate sensitive (clozapine, pirfenidone, ramosetron) Other (cyclobenzaprine, fluvoxamine, haloperidol, imipramine, **mexiletine**, nabumetone, naproxen, olanzapine, riluzole, tacrine, **triamterene**, zileuton, zolmitriptan)	Moderate (phenytoin, rifampicin, ritonavir, tobacco, teriflunomide) Other (carbamazepine)	Strong (ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) Moderate (methoxsalen, **mexiletine**, oral contraceptives) Weak (acyclovir, allopurinol, cimetidine, peginterferon 2a, piperine, zileuton) Other (**amiodarone**, efavirenz, **ticlopidine**, levofloxacin)
CYP3A4/5	Sensitive (alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, **dronedarone**, ebastine, eletriptan, **eplerenone**, everolimus, **felodipine**, ibrutinib, indinavir, lomitapide, **lovastatin**, lurasidone, maraviroc, midazolam, naloxegol, **nisoldipine**, quetiapine, saquinavir, sildenafil, **simvastatin**, sirolimus, tacrolimus, **ticagrelor**, tipranavir, tolvaptan, triazolam, vardenafil) Moderate sensitive (alprazolam, aprepitant, **atorvastatin**, colchicine, eliglustat, pimozide, rilpivirine, **rivaroxaban**, tadalafil) Other (astemizole, chlorphenamine, ciclosporin, cisapride, clarithromycin, diazepam, erythromycin, nevirapine, **quinidine**, ritonavir, telithromycin)	Strong (carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin, St. John's wort) Moderate (**bosentan**, efavirenz, etravirine, modafinil) Weak (armodafinil, rufinamide) Other (nevirapine, phenobarbital, pioglitazone, rifabutin, troglitazone)	Strong (boceprevir, clarithromycin, cobicistat, conivaptan, **diltiazem**, grapefruit juice, idelalisib, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, troleandomycin, voriconazole) Moderate (aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, ciclosporin, **dronedarone**, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, **verapamil**) Weak (chlorzoxazone, **cilostazol**, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, **ranolazine**, tacrolimus, **ticagrelor**) Other (**amiodarone**, suboxone)
CYP2B6	Sensitive (bupropion) Moderate sensitive (efavirenz) Other (artemisinin, cyclophosphamide, ifosfamide, ketamine, meperidine, methadone, nevirapine, propofol, selegiline)	Strong (carbamazepine) Moderate (efavirenz, rifampicin, ritonavir) Weak (nevirapine) Other (artemisinin, phenobarbital, phenytoin)	Weak (**clopidogrel**, tenofovir, **ticlopidine**, voriconazole) Other (thiotepa)
CYP2C8	Sensitive (repaglinide) Moderate sensitive (montelukast, pioglitazone, rosiglitazone) Other (amodiaquine, paclitaxel, **torsemide**)	Moderate (rifampicin)	Strong (**clopidogrel, gemfibrozil**) Moderate (deferasirox, teriflunomide) Weak (telithromycin, trimethoprim) Other (montelukast)
CYP2C9	Sensitive (celecoxib) Moderate sensitive (glimepiride, phenytoin, tolbutamide, **warfarin**) Other (diclofenac, fluvastatin, glibenclamide, glipizide, ibuprofen, **irbesartan, losartan**, naproxen, piroxicam, rosiglitazone, **torsemide**, valproic acid, zafirlukast)	Moderate (aprepitant, carbamazepine, enzalutamide, rifampicin, ritonavir) Other (nevirapine, phenobarbital, St. John's wort)	Moderate (**amiodarone**, felbamate, fluconazole, miconazole, piperine) Weak (diosmin, disulfiram, **fluvastatin**, fluvoxamine, voriconazole) Other (efavirenz, isoniazid, metronidazole, paroxetine, sulfamethoxazole)
CYP2C19	Sensitive (omeprazole, mephenytoin) Moderate sensitive (diazepam, lansoprazole, rabeprazole, voriconazole) Other (amitriptyline, carisoprodol, citalopram, clomipramine, **clopidogrel**, cyclophosphamide, esomeprazole, imipramine, **labetalol**, pantoprazole, phenobarbital, phenytoin, proguanil)	Strong (rifampicin, ritonavir) Moderate (efavirenz, enzalutamide, phenytoin) Other (St. John's Wort)	Strong (esomeprazole, fluconazole, fluoxetine, fluvoxamine, omeprazole, **ticlopidine**) Weak (voriconazole) Other (cimetidine, felbamate, isoniazid, ketoconazole, lansoprazole, oral contraceptives, pantoprazole)

CYP2D6	Sensitive (atomoxetine, desipramine, dextromethorphan, eliglustat, **nebivolol**, nortriptyline, perphenazine, tolterodine, venlafaxine) Moderate sensitive (amitriptyline, **encainide**, imipramine, **metoprolol, propafenone, propranolol**, tramadol, trimipramine) Other (aripiprazole, **carvedilol**, clomipramine, codeine, desipramine, doxepin, duloxetine, **flecainide**, fluoxetine, haloperidol, **mexiletine**, ondansetron, oxycodone, paroxetine, risperidone, tamoxifen, thioridazine, **timolol**)	–	Strong (bupropion, fluoxetine, paroxetine, **quinidine**, terbinafine) Moderate (cinacalcet, duloxetine, fluvoxamine, mirabegron) Weak (abiraterone, **amiodarone**, celecoxib, cimetidine, clobazam, cobicistat, desvenlafaxine, escitalopram, **labetalol**, lorcaserin, ritonavir, sertraline, vemurafenib) Other (aripiprazole, chlorphenamine, clomipramine, diphenhydramine, doxepin, haloperidol, methadone)
Transporters			
ABCB1 (P-gp)	Actinomycin D, **aliskiren, ambrisentan, apixaban, atorvastatin, bepridil**, berberine, **celiprolol**, ciclosporin, cimetidine, ciprofloxacin, **clopidogrel**, colchicine, **dabigatran**, daunorubicin, **digoxin, diltiazem**, domperidone, doxorubicin, **edoxaban**, erythromycin, etoposide, everolimus, fexofenadine, imatinib, irinotecan, ivermectin, **labetalol**, lapatinib, **lidocaine**, loperamide, **losartan, lovastatin**, maraviroc, methotrexate, mitomycin c, **nadolol**, nilotinib, ondansetron, paclitaxel, posaconazole, **propranolol**, quinine sulfate, rifampicin, **rivaroxaban**, saxagliptin, tacrolimus, **talinolol**, taxol, terfenadine, **ticagrelor, timolol**, tolvaptan, topotecan, **verapamil**, vinblastine, vincristine, **warfarin**	Strong (carbamazepine, dexamethasone, doxorubicin, phenytoin, rifampicin, St. John's wort) Others (ciclosporin, tipranavir, venlafaxine)	Strong (**amiodarone, carvedilol, dronedarone**, itraconazole, lopinavir and ritonavir, **quinidine**, ritonavir, saquinavir, **verapamil**) Others (clarithromycin, lapatinib, **propafenone, ranolazine**, telaprevir, tipranavir)
SLCO1B1	Asunaprevir, **atorvastatin, bosentan**, danoprevir, docetaxel, fexofenadine, glibenclamide, nateglinide, paclitaxel, **pitavastatin, pravastatin**, repaglinide, **rosuvastatin, simvastatin**	-	Strong (atazanavir and ritonavir, ciclosporin, lopinavir and ritonavir, rifampicin) Others (clarithromycin, erythromycin, **gemfibrozil**, simeprevir)

Notes: [a]Drugs in bold are cardiovascular medicines. [b]Sensitive and moderate-sensitive substrates are taken from the Food and Drug Administration (FDA) table of substrates, inhibitors and inducers.[44] Sensitive and moderate-sensitive substrates experience areas under the concentration–time curve (AUC) increments of ≥5 and ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway, respectively. The substrates that are not present in the FDA table but are listed in the Indiana Flockhart Table TM[45] are categorized under "Other". [c]Substrates for transporters taken from the FDA tables,[44] and Wessler et al[46] d Strong, moderate and weak inducers, taken from the FDA tables,[44] decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively. "Other" inducers are those not present in the FDA table but are listed in the Indiana Flockhart Table™. [e]P-gp inducers from Wessler et al[46] with the assessment of strength of P-gp inducers from Appendix A of the British Columbia guidelines on Potential NOAC Drug Interactions.[47] Strong, moderate and weak inhibitors increase the AUC of sensitive index substrates of a given metabolic pathway by ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively. They were all taken from the FDA tables,[44] except for (es)omeprazole designated as strong CYP2C19 inhibitors based on the Indiana Flockhart Table TM[45] and Modak et al[48] "Other" inhibitors are those not present in the FDA table but are listed in the Indiana Flockhart Table™, and whose inhibitory strength is not yet confirmed. [g]Transporter inhibitors taken from the FDA tables,[44] with strength assessment taken from Wessler et al[46] and Appendix A of the British Columbia guidelines on Potential NOAC Drug Interactions.[47]

Abbreviations: ABCB1 (P-gp), ATP Binding Cassette Subfamily B Member 1 (P-glycoprotein 1); AUC, area under the concentration–time curve; CYP, Cytochrome P450; SLCO1B1, Solute Carrier Organic Anion Transporter Family Member 1B1.

https://doi.org/10.2147/PGPM.S338601 DovePress

Transcellular Transport

P-glycoprotein and organic anion transporter polypeptides (such as Solute Carrier Organic Anion Transporter Family Member 1B1 [SLCO1B1]) can also mediate DDIs;[27] examples of substrates, inducers and inhibitors for these drug transporters are shown in Table 2. As P-glycoprotein is an efflux transporter, its inhibition and induction usually increase and decrease bioavailability/exposure of the victim drug, respectively.[51] P-glycoprotein is expressed in many tissues and affects several pharmacokinetic attributes, including absorption (expressed in the intestines), distribution (blood–brain barrier and placenta), metabolism (liver) and elimination (kidney).[4,18,51] When two substrates are co-prescribed, DDIs can also occur through competition for the transport protein (similar to competitive CYP inhibition, except that the concentration of the inhibitor or second substrate is also clinically relevant).

Pharmacodynamic DDIs

Pharmacodynamic DDIs occur when a perpetrator drug modulates the pharmacological effects of a victim drug in the body.[52] Modulation of effects can be synergistic or additive (similar pharmacological actions) or antagonistic (opposing pharmacological actions) and is usually the case when drugs share the same target (eg, enzyme) or physiological system (eg, blood coagulation).[18,51] If one drug has greater efficacy than another interacting drug (eg, the full opioid agonist morphine vs the partial agonist buprenorphine), its actions will be antagonized even when the two drugs have similar pharmacological actions.[18] Pharmacodynamic DDIs can be beneficial (eg, when different antihypertensives are used for their synergistic effects) or harmful. Examples of synergistic pharmacodynamic DDIs that are harmful and involve different targets but the same physiological system are many in cardiovascular disease and include anticoagulants with NSAIDs (increase the risk of gastrointestinal haemorrhage), anticoagulants with antiplatelets (bleeding), calcium channel blockers with benign prostatic hyperplasia alpha-adrenergic antagonists (orthostatic hypotension and falls), angiotensin-converting enzyme (ACE) inhibitors with potassium-sparing diuretics (hyperkalaemia), diuretics with digoxin (digoxin toxicity), and a pair of QT-interval prolonging drugs (torsade de pointes).[18] On the other hand, examples of antagonistic DDIs include ACE inhibitors and NSAIDs (decreased blood pressure lowering effect) and vitamin K oral anticoagulants and vitamin K supplements (decreased anticoagulation effect).[51]

Clinical Relevance, DDI Prevalence and Implicated Cardiovascular Medicines

For an interaction to be clinically relevant, plasma concentrations of the victim drug should either be increased above (toxicity) or decreased below (lack of efficacy) the therapeutic window, with the likelihood of clinical relevance ie out-of-therapeutic range doses, depending on the steepness of the substrate's dose–response curve, the perpetrator's dosage, and the perpetrator's induction/inhibition strength.[18] The strength of inducers/inhibitors is obtained from pharmacokinetic/mechanistic studies, with the Food and Drug Administration considering strong, moderate and weak inducers to be those that, respectively, decrease the area under the plasma concentration–time curve of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, as stated in Table 2.[44]

It is difficult to recruit and monitor many patients to evaluate the prevalence and clinical impact of DDIs in large populations, which means that most mechanistic DDI studies are small-sized.[15] Additionally, the large number of drug combinations and the potentially multiple pharmacokinetic and pharmacodynamic pathways for each drug make it an insurmountable task to cover all DDIs in clinical trials.[15] Consequently, most DDI literature reports potential DDIs, which are predicted based on an individual's medication list and the known interacting drug pairs within that list. Prediction may also be undertaken through simulation using methods such as pharmacokinetic-pharmacodynamic (PK-PD) and physiologically based pharmacokinetic (PB-PK) modelling. As Hahn and Roll discuss, inducer/inhibitor strength can be used to distinguish between clinically relevant DDIs (ie, those involving strong/moderate inducers/inhibitors) and those that are not (ie, those involving weak inducers/inhibitors), although this might be misleading due to a phenomenon called "phenoconversion" that is discussed in the next sections.[4] DDIs can also be classified by severity into major ("life-threatening or involving permanent damage"), moderate ("requiring additional treatment"), and minor ("unnoticeable or not sufficient to affect therapeutic outcome").[18]

Several DDI prevalence studies have been previously reported. For example, of 20,534 patients who were referred for pharmacogenetic testing and drug interaction screening in a US pharmacogenetic testing laboratory, 69.1% patients had at least one reported interaction (DDI/DGI/DDGI), with metoprolol (1484 patients), clopidogrel (1415 patients), and warfarin (1234 patients) being the first, second and fourth most implicated medications, respectively.[53] Of the total number of interactions (n = 33,665), 16,924 were rated as severe (ie, rated at a level of "change medication" or "consider changing medication or adjusting dose" by study clinicians) and of these 53.0% were DDIs.[53] In another US study of 1143 individuals with known *CYP2D6, CYP2C19* and *CYP2C9* genotypes, 357 (31.2%) of the individuals had a DDI with the top four interacting medications being metoprolol, clopidogrel, simvastatin, and aspirin.[52] A total of 1053 potential major or substantial interactions (including DGIs and DDGIs) were identified in 501 (43.8%) individuals, with potential DDIs accounting for 696 (66.1%) of these interactions.[52] As a third example, data mining of a spontaneous reporting database in Italy to identify adverse drug reactions associated with DDIs revealed that of 17,700 reports with at least two drugs, there were 5345 (30.2%) potential DDIs, and 1159 (21.7%) of these reports had a related adverse drug reaction.[54] Additionally, digoxin and diuretics (95 reports) was the most frequently reported DDI, while the combination of anticoagulants and antiplatelets (50 reports) had the greatest number of serious reactions (100% of the 50 reports) and deaths (14% of the 50 reports).[54] A French study that included more than 6.9 million outpatient dispensed medicines estimated the prevalence of dispensing drugs contraindicated or cautioned because of DDIs further highlights the importance of cardiovascular drugs in DDI literature.[55] Specifically, the most frequently contraindicated drug pair was bisoprolol and flecainide (n = 5036, 37.9%), with eight of the ten most represented pairs involving cardiovascular drugs. For the cautioned category, ramipril and spironolactone (n = 4741, 5.0%) was the most frequent pair, with nine of the ten most represented pairs involving cardiovascular drugs.[55] The prevalence and/or impacts of DDIs in other clinical settings have been reported in multiple other studies.[56–63]

The above studies were not restricted to CVD cohorts. Some, however, like Turner et al[27] who investigate DDIs in hospital-discharged patients following a non-ST elevation acute coronary syndrome (NSTE-ACS) have. DDIs were based on drug inhibition and/or induction of the metabolizing enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) and drug transporters (P-gp and SLCO1B1), with a DDI being present if a patient was given both a victim drug and a perpetrator drug that influenced the latter through at least one of the above enzymes/transporters, without consideration of autoinhibition and autoinduction. Of 652 patients with drug use and actionable genotype information available (the "interaction" cohort), 342 (52.5%) patients had at least one DDI of which 186 (28.5%) patients had at least one substantial interaction (defined as DDIs due to strong inhibitors/inducers, with the assessment of the strength of transporter inhibitors/inducers being based on relevant literature).[44–48,64] In a Moroccan study conducted in 138 hospitalized cardiac patients, DDI prevalence was 68.1% (94 patients) with the most common DDIs including aspirin and clopidogrel (12.2% prevalence), aspirin and heparin (8.3%) and furosemide and spironolactone (5.8%).[65] In this study, there were 726 prescribed drugs with drugs of the cardiovascular system (n = 372, 51.2%) and the blood and hematopoietic organs (n = 288, 39.7%) being the most common. Lastly, out of a total of 360 interactions, there were 40 (11.1%) and 134 (37.2%) DDIs classified as major and moderate severity, respectively.[65] Another study investigated potential DDIs in 2343 hospitalized cardiac Pakistani patients and found that 91.6% patients had at least one potential DDI, with 86.3% and 84.5% having at least one major and moderate potential DDI, respectively.[66] Of 5109 identified potential DDIs, 45% and 55% were or major and moderate severity, respectively, and all the top 10 most common potential DDIs included at least one cardiovascular drug (aspirin and clopidogrel combination [n = 489] being the most common).[66] The prevalence and/or impacts of DDIs in CVD patients have been reported in other studies.[67–69]

Due to high prevalence, cardiovascular medicines are the most included drug category in DDI-related guidance. For example, the Society for Post-Acute and Long-Term Care Medicine, based on a survey of physicians and pharmacists and three criteria (clinical significance and potential to cause harm, frequency of occurrence, and frequency of being prescribed in nursing homes), compiled a list of the top 10 particularly dangerous drug interactions in post-acute and long-term care medicine.[70] Out of the 10 pairs (ACE inhibitors + potassium supplements, ACE inhibitors + spironolactone, digoxin + amiodarone, digoxin + verapamil, theophylline + quinolones, warfarin + macrolides, warfarin + NSAIDs, warfarin + phenytoin, warfarin + quinolones, and warfarin + sulfa drugs), nine involved at least one cardiovascular drug, with warfarin appearing in five pairs.[70] Another study that aimed to establish an international

consensus list of potentially clinically significant DDIs in people aged ≥65 years and that included 29 experts (geriatricians and clinical pharmacists among these) from 8 European countries came up with 66 potentially clinically significant DDIs, of which about two thirds of the DDIs included at least one cardiovascular drug (ACE inhibitors/ARBs, anti-arrhythmics, anticoagulants, antiplatelets, calcium channel blockers, digoxin, diuretics, and lipid-modifying agents).[71]

Drug–Gene Interactions

Drug–gene interactions (DGIs) occur when an individual's genotype affects the pharmacokinetics (pharmacokinetic DGIs, Figure 1C) and/or pharmacodynamics (pharmacodynamic DGIs) of a victim drug.[4] For example, polymorphisms in the cytochrome P450 metabolizing enzymes (or drug transporters) can lead to five different phenotypes: poor, intermediate, extensive/normal, rapid, and ultra-rapid metabolizers (or transporters).[52,72] Normal metabolizers/transporters respond as expected to standard drug doses as they do not have genetic variants that alter drug metabolism/transport. Poor metabolizers or poor function transporters usually have two copies of loss-of-function (LoF) genetic variants, while intermediate metabolizers usually have one or two copies of reduction-of-function (RoF) genetic variants or one copy of a LoF genetic variant. If metabolism is reduced, drug concentrations increase, which might increase efficacy (patients respond to lower doses) and/or lead to adverse effects. By contrast, decreased metabolism for prodrugs means decreased concentration of the active metabolites, which might decrease efficacy and/or adverse effects. On the other hand, ultra-rapid (usually two or more copies of a gain-of-function [GoF] genetic variant on the same chromosome) and rapid (usually one or two copies of a GoF genetic variant) metabolizers/transporters have increased drug metabolism/transport, with increased drug metabolism resulting in decreased drug exposure and decreased efficacy/adverse effects.[52,72] Of note is that non-genetic factors including age, sex, comedications (DDIs), smoking, kidney and liver function can also alter the capacity to metabolize/transport drugs, which might lead to a mismatch between the individual's genotype-based prediction of drug metabolism/transport and the actual/observed metabolism/transport, a phenomenon termed as phenoconversion.[4,73]

Pharmacogenomic Studies and Clinical Implementation Guidelines

Thousands of pharmacogenomic studies (aka DGI studies) have explored how genetic/genomic factors influence drug response variability.[74] As of 5 July 2022, the "Variant, Gene and Drug Relationship Data" that contains relationships summarized from the Pharmacogenomics Knowledge Base (PharmGKB) annotations contained 9695 unique gene-chemical/gene-drug response relationships ("associated", "not associated", and "ambiguous"), reporting the influence of 1933 genes on 1307 drugs.[75] The US FDA Table of Pharmacogenetic Associations (last updated 24 May 2022) describes 121 DGIs (influence of 21 genes on 111 drugs) in three sections: Section 1 ("Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations", n = 60 DGIs), Section 2 ("Pharmacogenetic Associations for which the Data Indicate a Potential Impact on Safety or Response", n = 21 DGIs), and Section 3 ('Pharmacogenetic Associations for which the Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only', n = 40 DGIs).[72] Of the 121 DGIs, 12 (9.9%) involve cardiovascular drugs including five in Section 1 (clopidogrel:CYP2C19, propafenone:CYP2D6, warfarin:CYP2C9, warfarin: CYP4F2, and warfarin:VKORC1), two in Section 2 (carvedilol:CYP2D6 and simvastatin:SLCO1B1), and five in Section 3 (atorvastatin:SLCO1B1, metoprolol: CYP2D6, nebivolol:CYP2D6, propranolol: CYP2D6, and rosuvastatin:SLCO1B1). It should be noted that although cardiovascular drugs represent less than 10% of the FDA Pharmacogenetic Associations, they are among the most highly ranked drugs in terms of prescription volume, which increases their impact. For example, of the 111 unique drugs mentioned in the US FDA Table of Pharmacogenetic Associations, 41 (36.9%) featured in the 2019 list of the top 300 most prescribed drugs in the US (Figure 2),[40] representing a total of 658 million prescriptions and 155 million patients. Only 9 (22.0%) of the 41 drugs were cardiovascular medicines; however, they represented 48.2% (318 million) and 44.5% (69 million) of the total prescriptions and number of patients, respectively.

Based on a summation of available evidence that ranges from case reports, retrospective cohorts, mechanistic and pharmacokinetic studies to prospective cohorts and randomized control trials,[76] several pharmacogenomic clinical implementation guidelines including the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian

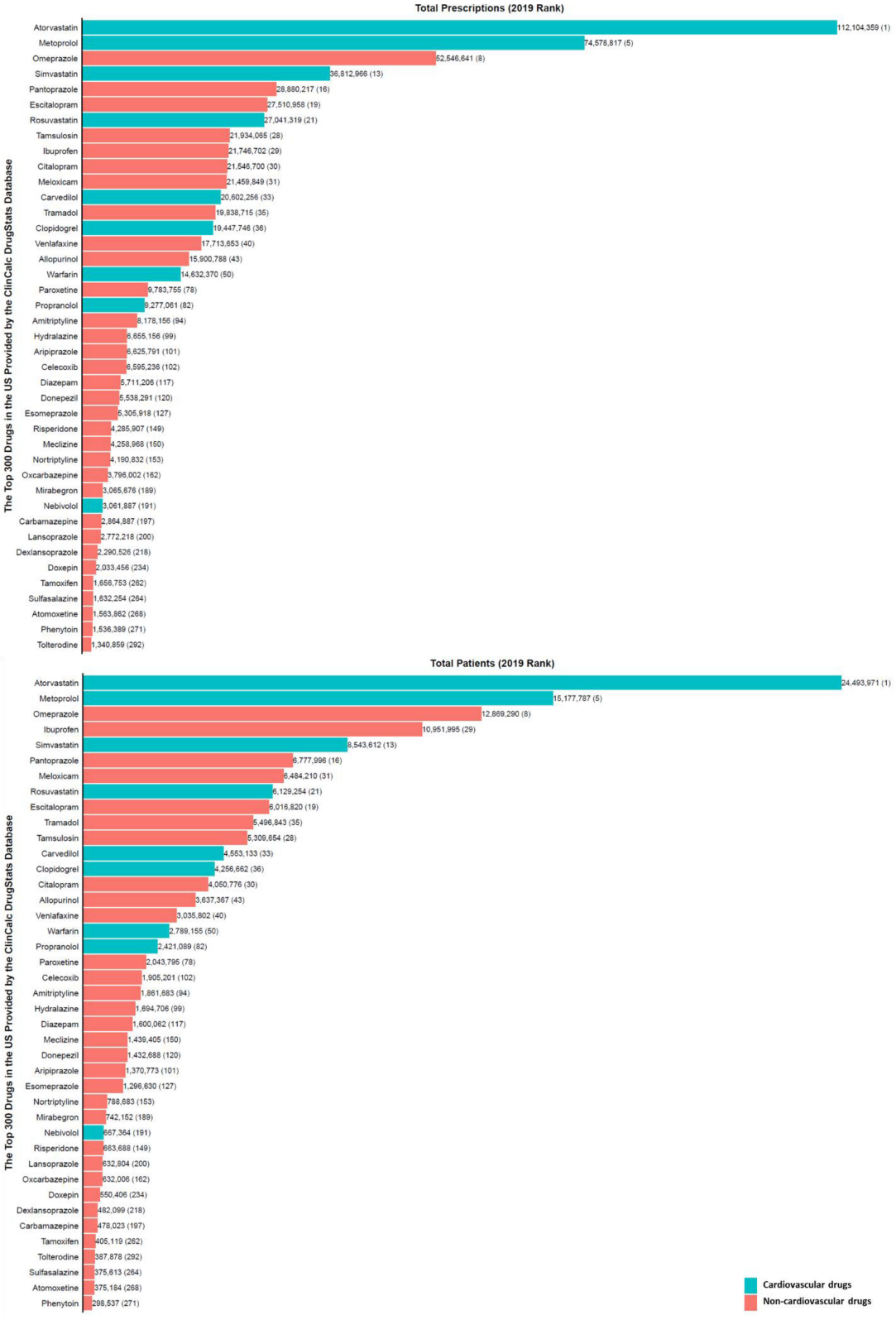

Figure 2 Commonly used medications influenced by pharmacogenes. The bar chart shows the total number of prescriptions (top panel) or patients receiving the prescriptions (bottom panel) in 2019 in the United States. Corresponding ranks are shown in parentheses. Data from the ClinCalc DrugStats Database[40] that used the Medical Expenditure Panel Survey 2013–2019 (Agency for Healthcare Research and Quality) as a prescription data source.

Pharmacogenomics Network for Drug Safety (CPNDS), the Dutch Pharmacogenetics Working Group (DPWG), and the French National Network (Réseau) of Pharmacogenetics (RNPGx) have been developed.[30] For example, as of 28 Jul 2022, CPIC (https://cpicpgx.org/genes-drugs/) reported 442 DGIs between 119 genes and 271 drugs. Only the clinically actionable DGIs have corresponding guidelines and as of 26 Mar 2021, there were 26 CPIC guidelines (https://cpicpgx.org/guidelines/)[77] that documented the influence of 23 genes on 95 drugs, with three guidelines[78–80] documenting the influence of six genes on nine cardiovascular medicines. Abdullah-Koolmees et al have previously summarized DGIs from the above four clinical implementation guidelines and about a sixth of the listed drugs were cardiovascular medicines, which are shown in Table 3.

DGI Prevalence and Implicated Cardiovascular Medicines

In terms of the prevalence of DGIs in the general population, one retrospective US study of 1143 individuals with known *CYP2D6, CYP2C19* and *CYP2C9* genotypes reported that 138 (12%) of the individuals had a DGI, with DGIs (n = 155) accounting for 14.7% of all potential major or substantial interactions.[52] Another US pharmacogenetic testing and drug interaction screening study of 20,534 patients reported that of 16,924 severe interactions (with a guidance of "change medication" or "consider changing medication/adjusting dose"), 24.6% were DGIs,[53] while DGI prevalence in 316 (es)citalopram-treated patients from the Northern part of the Netherlands has been estimated to be 47%.[81] In another personalized medicine program that recruited 705 US patients, clinically significant (moderate, major or contraindicated) DGIs were identified in 514 (72.9%) of patients and the most common actionable DGIs were for opioid, psychotropic and cardiovascular medications.[63] A total of 1295 drugs were prescribed to patients with a detected DGI for that drug, with the majority being psychotropics (34%), cardiovascular medicines (21%) and analgesics (21%). The top cardiovascular medications included clopidogrel, warfarin, beta-blockers (including metoprolol, carvedilol and nebivolol), losartan and statins (simvastatin or atorvastatin) with 69.2% (36/52), 45.3% (24/53), 50.0% (73/146), 38.1% (16/42) and 26.0% (39/150) of those taking these medications having clinically significant DGIs.[63] In a Dutch study of 9.7 million patients with 51.3 million drug exposures, a quarter of exposures (12.4 million, 24.1%) were risky DGIs ie had clinical significance that could result in decreased drug efficacy and/or adverse drug reactions.[28] About 60%, 22% and 12.4% of the risky exposures were attributable to *CYP2D6, SLCO1B1* and *CYP2C19* actionable genotypes, while cardiovascular medications (eg, simvastatin and atorvastatin), gastroenterology (eg, omeprazole and pantoprazole), psychiatry/neurology and analgesic/anaesthetic medications were the most prescribed comprising 43%, 29%, 15% and 7% of the prescribed drugs, respectively. Individually, the most issued drugs were metoprolol (16% of the prescriptions), simvastatin (15%), omeprazole (14%) and pantoprazole (10%).[28] Lastly, to determine the prevalence of potential DGIs in CVD patients, Turner et al conducted a UK study and of 652 post-NSTE-ACS patients, 384 (58.9%) patients had at least one DGI mediated by the genes *CYP2C9* (8 patients), *CYP2C19* (275 patients), *CYP2D6* (19 patients), *CYP3A5* (1 patient), *SLCO1B1* (175 patients), and *VKORC1* (7 patients).[27] Fifty (7.7%) patients experienced at least one substantial interaction, defined as DGIs due to drugs with pharmacogenomic clinical recommendations and variant homozygous/compound heterozygous actionable genotypes.

Drug–Drug–Gene Interactions

Drug–drug–gene interactions (DDGIs) occur when the individual's genotype and another drug affect the pharmacokinetics and/or pharmacodynamics of a victim drug ie are a cumulative effect of DDIs and DGIs (Figure 1D).[4,52] Like DDIs/DGIs, it is possible to divide DDGIs into pharmacokinetic and pharmacodynamic categories, with a possibility of a third category that involves both pharmacokinetic and pharmacodynamic effects. Malki and Pearson separate the DDGIs into inhibitory, induction and phenoconversion interactions,[15] while Bruckmueller and Cascorbi report a slightly different classification in which DDGIs that boost clinically relevant interactions (either inhibition or induction) on the same pathway are classified under category 1, those that boost clinically relevant interactions on different pathways as category 2 and those whose constituent DDIs and DGIs lead to opposing effects as category 3.[13] The latter classification is discussed further below.

Table 3 A Summary of Clinical Implementation Pharmacogenetic Guidelines for Cardiovascular Drugs (Data from Abdullah-Koolmees[a] et al)[30]

Drug Class	Drug	Guidelines	Genes/Genetic Variants	Recommendation (Evidence Classification[b])
Anticoagulants	Acenocoumarol	DPWG	*VKORC1 −1639G>A*	AA: reduce dose by 50% and check INR more frequently. Initial and maintenance doses can be calculated using an algorithm (4F). AG: no action required (4C).
	Phenprocoumon	DPWG	*VKORC1 −1639G>A*	AA: reduce dose by 50% and check INR more frequently. For patients younger than 75 years, initial and maintenance doses can be calculated using an algorithm, as done by EUPACT (4D). AG: no action required (4D).
	Warfarin	CPIC	Non-Africans: *CYP2C9*2, CYP2C9*3, VKORC1 −1639G>A*	Use Gage and IWPC dosing algorithms (Strong/Moderate).
			African: *CYP2C9*2, CYP2C9*3, VKORC1 −1639G>A*	
			African carriers of *CYP2C9*5, *6, *8* or **11*	Decrease calculated dose by 15–30%; 20–40% in variant homozygotes (Moderate).
			African carriers of the *CYP2C* rs12777823 A allele	Decrease calculated dose by 10–25% (Moderate).
			*CYP4F2*3*	Increase calculated dose by 5–10% (Optional).
		CPNDS	*CYP2C9*2, CYP2C9*3, VKORC1 −1639G>A*	Calculate dose based on www.warfarindosing.org (++++, Moderate).
		DPWG	*CYP2C9*	**1*3, *2*2, *2*3, *3*3*: use 20–65% of the standard initial dose. Initial and maintenance doses can be calculated using an algorithm, as done by EUPACT (4A-D).
			VKORC1 −1639G>A	AA: use 60% of the standard initial dose. Initial and maintenance doses can be calculated using an algorithm, as done by EUPACT (4A). AG: no action required (4A).
		RNPGx	*CYP2C9*2, CYP2C9*3, VKORC1 −1639G>A*	As per dosing table (Advisable).

(*Continued*)

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Table 3 (Continued).

Drug Class	Drug	Guidelines	Genes/Genetic Variants	Recommendation (Evidence Classification[b])
Antiplatelets	Clopidogrel	CPIC	*CYP2C19*	PM/IM: Use alternative antiplatelet non-contraindicated drug such as prasugrel or ticagrelor (Strong/Moderate). UM: Dosage and administration as per drug label (Strong).
		DPWG	*CYP2C19*	PM: for PCI, stroke or TIA, avoid clopidogrel and consider alternatives such as prasugrel, ticagrelor and aspirin/dipyridamole while for other indications, determine the level of inhibition of platelet aggregation and consider alternatives in poor responders (4F). IM: for PCI, stroke or TIA, choose an alternative or double the dose to 150 mg/day (600 mg loading dose) while for other indications, no action required (4F). UM: no action required (4A).
		RNPGx	*CYP2C19*	PM/IM: Use alternative drug, not metabolized by CYP2C19 (Essential). UM: Use as per standard of care ie 75mg/day (Essential).
Anti-arrhythmics (class I, membrane stabilizing drugs)	Flecainide	DPWG	*CYP2D6*	PM: reduce dose by 50%, record ECG, and monitor plasma concentrations (4F). IM: for the diagnosis of Brugada syndrome, no action required; otherwise reduce dose by 25%, record ECG, and monitor plasma concentrations (3A). UM: record ECG and monitor plasma concentration or select alternative drug eg, amiodarone, disopyramide, quinidine, and sotalol (not available).
	Propafenone	DPWG	*CYP2D6*	PM: reduce dose by 70%, record ECG, and monitor plasma concentrations (4C). IM/UM: adjust dose based on plasma concentrations and record ECG or select alternative drug eg, amiodarone, disopyramide, quinidine, sotalol (3A/3D).
Beta-blockers	Metoprolol	DPWG	*CYP2D6*	PM: if a gradual heart rate reduction is required or if there is symptomatic bradycardia, gradually increase dose up to 25% of the standard dose (4C). IM: if a gradual heart rate reduction is required or if there is symptomatic bradycardia, gradually increase dose up to 50% of the standard dose (4A). UM: use the maximum dose for the relevant indication or titrate dose up to 250% of normal dose or use alternative drugs eg bisoprolol or carvedilol for heart failure, and atenolol or bisoprolol for other indications (4D).

HMG-CoA reductase inhibitors (statins)	Eg atorvastatin, simvastatin	CPIC	*SLCO1B1*	Low/intermediate function: for simvastatin, prescribe a lower dose, consider an alternative statin like pravastatin/rosuvastatin and consider routine creatine kinase surveillance (Strong).
		DPWG	*SLCO1B1*	*1*5, *5*5 (atorvastatin): If patient has additional risk factors for statin-induced myopathy, choose alternative drugs fluvastatin. If patient has no additional risk factors or an alternative is not an option, then advise the patient to contact their doctor when muscle symptoms occur (4C). *1*5, *5*5 (simvastatin): consider additional risk factors for statin-induced myopathy to choose an alternative. If an alternative is not an option, avoid doses exceeding 40mg/day and advise the patient to contact their doctor when muscle symptoms occur (4D).
		RNPGx	*SLCO1B1*	*1*5: High dose statins and OATP1B1/CYP3A4 inhibitors should be avoided (Possibly helpful). *5*5: High dose statins and OATP1B1/CYP3A4 inhibitors should be avoided. Lower simvastatin dose to 20 mg/day with creatine phosphokinase assay or use another statin (Possibly helpful).

Notes: [a]These guidelines were accurate as of 1 July 2020, and some may have been updated. For instance, the CPIC Clopidogrel[78] guideline now considers additional phenotypes such as CYP2C19 likely intermediate metabolizer and CYP2C19 likely poor metabolizer while the statin guideline[80] now considers *ABCG2* and *CYP2C9* genotypes. [b]CPIC has three recommendation levels for genotype/phenotype-drug pairs (strong, moderate, and optional); CPNDS has four levels of evidence (+ to ++++), and three levels for genotyping recommendations (strong, moderate, and optional); DPWG has five (0–4) levels of evidence and eight for clinical relevance (AA to F); and RNPGx has three levels for genotyping recommendations (essential, advisable, and possibly helpful).

Abbreviations: ABCB1 (P-gp), ATP Binding Cassette Subfamily B Member 1 (P-glycoprotein 1); CPIC, Clinical Pharmacogenetics Implementation Consortium; CPNDS, Canadian Pharmacogenomics Network for Drug Safety; CYP, Cytochrome P450; DPWG, Dutch Pharmacogenetics Working Group; EU-PACT, European Pharmacogenetics of Anticoagulant Therapy; HMG-CoA, β-Hydroxy β-methylglutaryl-Coenzyme A; IM, intermediate metabolizer; IWPC, International Warfarin Pharmacogenetics Consortium; PCI, percutaneous coronary intervention; PM, poor metabolizer; RM, rapid metabolizer; RNPGx, French National Network (Réseau) of Pharmacogenetics; SLCO1B1, Solute Carrier Organic Anion Transporter Family Member 1B1; TIA, Transient Ischaemic Attack; UM, ultra-rapid metabolizer; VKORC1, Vitamin K epOxide Reductase Complex 1.

https://doi.org/10.2147/PGPM.S338601

Category 1 DDGIs

In this category, DDIs and DGIs that share the same pathway and have similar effects produce a DDGI (Figure 1D). For example, in 115 Swiss patients starting acenocoumarol, 35 (30.4%) had DDIs mediated by CYP2C9 inhibitors (amiodarone, clopidogrel, fluconazole, fluoxetine, fluvastatin, irbesartan, losartan, metronidazole, and pantoprazole). This resulted in an age and sex adjusted hazard ratio of 2.50 (95% confidence intervals [CI] 1.38 to 4.53) for the time to first International Normalized Ratio [INR] ≥ 4 (which represents an increased risk of over-anticoagulation). Forty-one (35.7%) patients had *CYP2C9* RoF mutations (**2* and **3*) with this DGI resulting in an age and sex adjusted hazard ratio of 1.68 (95% CI 1.12 to 2.45) for the time to first INR ≥ 4.[82] The cumulative effect of the DDI and DGI in 14 patients who were given a CYP2C9 inhibitor and who also had the *CYP2C9*2/*3* alleles tripled the over-anticoagulation risk (age and sex adjusted hazard ratio = 3.04, 95% CI 1.29 to 7.15). Of note is that the cumulative effects are not always additive (ie, DDGI effects do not always equal the sum of the independent effects of the DDI and DGI). For instance, if the maximum reduction of enzyme activity has already been reached as is the case for patients carrying two LoF variants, then a perpetrating inhibitor cannot decrease the activity any further, with the converse being true (the role of genetic variants may be limited in patients given very strong inhibitors).[13] Other category 1 DDGIs that include at least one cardiovascular medicine are shown in Table 4. These DDGIs also apply to prodrugs, with the clopidogrel (CYP2C19 substrate) + proton pump inhibitors (CYP2C19 inhibitors) + *CYP2C19*2/*3* (*CYP2C19* LoF/RoF mutations) DDGI increasing the likelihood of clopidogrel resistance.[15,94] Although metabolizing enzymes are the most-frequently studied/reported, transporter-mediated DDGIs also exist. For instance, the *SLCO1B1 c.521 T>C* RoF mutation significantly increases the magnitude of the interaction between pravastatin (SLCO1B1 substrate) + cyclosporine (SLCO1B1 inhibitor), with the TT genotype increasing susceptibility to the inhibitory effects of cyclosporine compared to C allele carriers.[130]

Category 2 DDGIs

In this category, the constituent DDIs and DGIs have similar effects but different pathways, which can happen when a substrate drug is metabolized by two or more enzymes (Figure 1D). For example, in a pharmacokinetic study, 32 healthy participants were administered the broad-spectrum triazole antifungal voriconazole that is metabolized by CYP2C19 and to a lesser extent by CYP3A4.[135] Co-administration with ritonavir-boosted atazanavir that strongly inhibits CYP3A4 (a DDI) in eight *CYP2C19* poor metabolizers increased the voriconazole area under the curve and maximum plasma concentration by 5.6-fold (90% CI 4.5-fold to 7.0-fold) and 4.4-fold (90% CI 3.6-fold to 5.4-fold), respectively. Examples of CVD category 2 DDGIs are shown in Table 4.

Category 3 DDGIs

In this category, constituent DDIs and DGIs lead to opposing effects, which can diminish the clinical relevance of the interaction or lead to phenoconversion in which the individual's DDI-based or DGI-based prediction of drug metabolism/transport differs from the observed metabolism/transport (Figure 1D).[4,13] An example is provided by a pharmacokinetic study of five ultra-rapid metabolizers with a *CYP2D6* gene duplication or triplication.[136] Due to the *CYP2D6* ultra-rapid metabolizer phenotype, the five participants had subtherapeutic concentrations of nortriptyline (dosed at 25 mg twice a day for a week). In the second and third weeks, the CYP2D6 inhibitor paroxetine (10 mg or 20 mg twice a day) was co-administered, which normalized the CYP2D6 metabolic status (increase of nortriptyline plasma concentrations). Three CVD examples are provided in Table 4, with one (a phenoconversion example) being that of a patient taking clopidogrel (CYP2C19 substrate) who has the GoF polymorphism *CYP2C19*17*, where the administration of a proton pump inhibitor which inhibits CYP2C19 can change the metaboliser status from ultra-rapid to poor, resulting in decreased clopidogrel efficacy.[15,95]

DDGI Prevalence and Implicated Cardiovascular Medicines

Few studies have explored potential or actual DDGIs. Some have been mentioned above including a US study (n = 1143 individuals, of whom 137 [12.0%] had a potential DDGI, with DDGIs [n = 202] accounting for 19.2% of all potential major or substantial interactions),[52] another US study (n = 20,534 patients who had 16,924 severe interactions, of which 22.4% were DDGIs),[53] and a study in the Netherlands (n = 316 participants, of whom 8.5% were exposed to DDGIs).[81]

Table 4 Examples of Drug–Drug–Gene Interactions Involving Cardiovascular medicines[15,31,83]

Victim Drugs/Substrates	Perpetrator Drugs (Inhibitors[a]/ Inducers)	Relevant Genotype	Effects	References
Category 1 (similar effects, same pathway eg CYP2C9 inhibitor with CYP2C9 RoF/LoF mutation)				
CYP2C9-mediated				
Fluvastatin	Telmisartan	*CYP2C9*1/*3*	Myotoxicity.	[84]
Losartan	Phenytoin, valproic acid	*CYP2C9*2/*3*	Inhibition of the conversion of losartan to its active metabolite E3174.	[85,86]
Vitamin-k antagonists (eg acenocoumarol, warfarin)	Amiodarone, clopidogrel, pantoprazole, losartan, fluconazole, fluoxetine, irbesartan, fluvastatin, metronidazole, NSAIDs, simvastatin	*CYP2C9*2/*3*	Over-anticoagulation, decreased dose requirements, increased bleeding risks.	[82,87–92]
CYP2C19-mediated				
Clopidogrel	Proton-pump inhibitors	*CYP2C19*2/*3*	Reduction of antiplatelet effect/increased clopidogrel resistance in poor metabolizers.	[93–95]
Omeprazole	Antiplatelets (clopidogrel, ticlopidine)	*CYP2C19*2/*3*	Increased AUC, especially for *1*1[b].	[96,97]
Warfarin	Proton-pump inhibitors (lansoprazole, omeprazole)	*CYP2C19*2/*3*	Warfarin potentiation and increased bleeding risks, increased AUC (especially for *1*1)[b] for R- but not S-warfarin.	[98,99]
CYP2D6-mediated[c]				
Brofaromine, dextromethorphan, encainide, methoxyphenamine, mexiletine, procainamide, propafenone, R-flecainide, venlafaxine	Quinidine	*CYP2D6* poor and/or intermediate metabolizers	Increased AUC and/or decreased clearance, especially for normal metabolizers[b].	[100–112]
Flecainide	Amiodarone, paroxetine	*CYP2D6* poor and/or intermediate metabolizers	Increased AUC, increased QT interval corrected using the Fridericia formula, or increased flecainide-induced QRS prolongation, especially for normal metabolizers[b].	[113–115]
Lidocaine, mexiletine	Propafenone	*CYP2D6* poor and/or intermediate metabolizers	Increased AUC and/or decreased clearance, especially for normal metabolizers[b].	[116,117]
Metoprolol	Amiodarone, celecoxib, diphenhydramine, dronedarone, hydroxychloroquine, imatinib, propafenone, terbinafine.	*CYP2D6* poor and/or intermediate metabolizers	Increased AUC and/or decreased clearance, especially for normal metabolizers[b] and/or increased clinical and adverse effects (eg sinus bradycardia, confusion, falls, tiredness and dyspnea on exertion).	[118–127]

(*Continued*)

https://doi.org/10.2147/PGPM.S338601 DovePress

Table 4 (Continued).

Victim Drugs/Substrates	Perpetrator Drugs (Inhibitors[a]/ Inducers)	Relevant Genotype	Effects	References
CYP3A-mediated				
Simvastatin	Cyclosporine, diltiazem	*CYP3A5*3/*3* and *CYP3AP1*3/*3*	Myopathy.	[128,129]
SLCO1B1-mediated				
Pravastatin	Cyclosporine	*SLCO1B1 c.521 T>C*	Increased AUC, especially for the TT genotype[b].	[130]
Category 2 (similar effects, multiple pathways eg CYP3A4 inhibitor with CYP2C19 LoF mutation)				
Atorvastatin	Pantoprazole (CYP2C19 and CYP3A4/5 inhibitor)	*CYP2C19*2*2*	Rhabdomyolysis and acute renal failure.	[131]
Diazepam	Diltiazem (CYP3A4 inhibitor)	*CYP2C19*2/*3*	Increased AUC and prolonged elimination diazepam half-life in all genotypes.	[132]
Caffeine	Propafenone (CYP2D6 and CYP1A2 inhibitor)	*CYP2D6* poor metabolizers	Decreased clearance (increase in caffeine plasma concentrations) especially in poor metabolizers.	[133]
Category 3 (opposing effects)				
Clopidogrel	Proton-pump inhibitors (CYP2C19 inhibitors)	*CYP2C19*17* (GoF)	Higher rates of cardiac rehospitalization due to decreased clopidogrel efficacy (in this case, the effects of the inhibitors were stronger than the genetic influence).	[95]
Propafenone	Rifampicin (CYP3A4/1A2 inducer)	*CYP2D6* poor metabolizers (LoF)	Decreased AUC for all genotypes (effects of the inducer stronger than those of the genetic mutation), with the percentage decrease more pronounced in normal metabolizers (no genetic mutation to offset some of the effects of the inducer).	[134]
Warfarin	Rifampicin (*CYP2C9* inducer)	*CYP2C9*2/*3* (RoF)	Higher changes in S-warfarin clearance for *2*3 and *3*3 subjects (effects of the inducer more pronounced in poor metabolizers).	[92]

Notes: Data from references[15,31,83]. [a]Inhibitors include other substrates (competitive inhibitors). [b]Mutant-type genotypes or poor/intermediate metabolizers have high drug exposure (high AUC or low clearance) to start with, so the effect of adding inhibitors (increase in AUC or decrease in clearance) is less pronounced compared to wild-type genotypes or normal/extensive metabolizers. In terms of the absolute effects, poor/intermediate metabolizers have the highest drug exposures, with or without the inhibitors. When normal/extensive metabolizers are given strong inhibitors, the actual/observed phenotype is that of a poor/intermediate metabolizer resulting into phenocopies or phenoconversion. [c]For *CYP2D6*, normal metabolizers included two normal function alleles (eg *CYP2D6*1/*1, CYP2D6*1/*2, CYP2D6*2/*2*), or a normal function allele combined with a decreased function allele (eg *CYP2D6*1/*10, CYP2D6*1/*41, CYP2D6*2/*10, CYP2D6*2/*41*); intermediate metabolizers consisted of one normal function allele combined with no function allele (eg *CYP2D6*1/*3, CYP2D6*1/*4, CYP2D6*1/*5, CYP2D6*1/*6, CYP2D6*1/*21, CYP2D6*2/*3, CYP2D6*2/*4, CYP2D6*2/*5*), or two decreased function alleles (eg *CYP2D6*10/*41, CYP2D6*10/*10*) or one decreased function allele combined with no function allele (eg *CYP2D6*3/*41, CYP2D6*4/*41, CYP2D6*5/*10, CYP2D6*6/*10, CYP2D6*6/*41, CYP2D6*10/*21, CYP2D6*10/*30*); poor metabolizers consisted of two no function alleles (eg *CYP2D6*3/*4, CYP2D6*4/*4, CYP2D6*4/*5, CYP2D6*4/*6, CYP2D6*5/*5, CYP2D6*5/*16, CYP2D6*7/*7*); while ultra-rapid metabolizers consisted of two increased function alleles or more than two normal function alleles (eg *CYP2D6*1/*1xN, CYP2D6*1/*2xN, CYP2D6*1/*4xN, CYP2D6*1/*41xN, CYP2D6*2/*2xN*).

Abbreviations: AUC, area under the concentration–time curve; GoF, Gain-of-Function; CYP, Cytochrome P450; LoF, Loss-of-Function; RoF, Reduction-of-Function; SLCO1B1, Solute Carrier Organic Anion Transporter Family Member 1B1.

The Turner study that included only CVD patients reported that 106 (16.3%) patients had at least one DDGI mediated by the genes *CYP2C9* (1 patient), *CYP2C19* (74 patients), *CYP2D6* (3 patients), and *SLCO1B1* (34 patients).[27] Eighty-eight (13.5%) of these patients experienced at least one substantial interaction, defined as DDGIs in which the constituent interactions acted in the same direction eg the constituent DDIs and DGIs did not lead to opposing effects as is seen with category 3 DDGIs.

The cardiovascular drugs that have been previously implicated in DDGIs are shown in Table 4 and these were mainly obtained from two systematic reviews. The first reviewed DDGI case reports and out of 34 cases, 7 (20.6%) involved at least one cardiovascular medicine.[83] The second review included clinical, observational and case studies involving CYP2D6, CYP2C9, and CYP2C19-mediated drug interactions with 66 and 39 studies, respectively, reporting the impact of pharmacogenetics on DDIs and DDGIs, of which 38 (57.6%) and 5 (13.9%) included at least one cardiovascular medicine.[31]

Other Interactions

There are other kinds of interactions such as drug–gene–gene interactions (DGGIs) that involve the influence of more than one genetic factor on the pharmacokinetics and/or pharmacodynamics of a victim drug.[4] For instance, inhibition of one of several drug metabolism pathways by a genetic polymorphism might have minimal effect due to redundancy, but the interaction can become clinically significant when the alternative pathway enzyme is also affected by a -polymorphism.[4] Some drugs such as warfarin have genes affecting both pharmacokinetics (eg, *CYP2C9*) and pharmacodynamics (eg, *VKORC1*) leading to a DGGI.[27] These two DGGI scenarios were reported in Turner et al's study in which 10 (1.5%) patients had at least one substantial DGGI (defined as DGGIs in which the constituent interactions were synergistic) and included six amitriptyline/CYP2D6/CYP2C19 and four warfarin/CYP2C9/VKORC1 DGGIs.[27]

More complex interactions can involve more than one DDI/DGI. For example, in a randomized three-way crossover study of 27 healthy subjects, the additive antiplatelet effect of cilostazol and clopidogrel was maximized in participants with both the *CYP2C19* poor metabolizer and *CYP3A5*3/*3* genotypes, which represented a drug–drug–gene–gene interaction (DDGGI, two drugs and two genetic factors).[137] A drug–drug–drug–gene interaction (DDDGI) arises when clopidogrel (CYP2C19/CYP3A4 substrate) is prescribed with proton pump inhibitors (CYP2C19 inhibitors) and calcium channel blockers (CYP3A4 inhibitors) in *CYP2C19*2* carriers, which increases the risk of adverse cardiovascular events.[138]

Interactions can also involve disease status (most commonly kidney or hepatic impairment), with a systematic review of case reports reporting 25 cases of drug-drug-disease interactions of which 12 (48%) interactions included at least one cardiovascular medicine.[83] In this review, four cases of drug-drug-gene-disease interactions were reported with one (dextromethorphan 30 mg + metoprolol 40 mg/day + *CYP2D6*1/*10* + chronic renal failure leading to myoclonus) including a cardiovascular medicine.[83,139]

As stated earlier, non-genetic factors such as age and sex can alter the capacity to metabolize/transport drugs, and these could lead to more complex interactions. For instance, in a large-scale analysis of Brazilian electronic health records (1,025,754 distinct drug pair co-administrations), women had a 60% increased risk of DDIs as compared to men, and a 90% increased risk when only DDIs known to lead to major adverse drug reactions were considered. DDI risk also increased substantially with age.[140]

Challenges in Clinical Practice

Drug Information Compendia, Interaction Databases and Clinical Implementation Guidelines

Several organisations have used existing literature to develop interaction databases and other resources that help to predict and/or detect DDIs (eg, the British National Formulary, Micromedex, Stockley's Interactions Checker, etc.) and DGIs (eg, PharmGKB annotations, the FDA Table of Pharmacogenetic Associations, the Drug-Gene Interaction database,[141] the CPIC, CPNDS, DPWG and RNPGx clinical implementation guidelines, etc.).[15,30] However, most have considered DDIs or DGIs separately, which might lead to the underestimation of the impact or clinical relevance of a DDI or DGI when it is boosted by another interaction, as in the case of category 1 and 2 DDGIs, or the prediction of

a wrong phenotype as can happen with DDGIs that lead to phenoconversion. Missing or underestimating clinically relevant interactions and phenotype misclassification can also lead to incorrect study findings including the failure to replicate previous associations, poor translation of study findings to the clinic, potentially damaging clinical recommendations and/or implementation guidelines that contradict each other, which compromises the potential to advance personalized medicine.[4,27]

As stated earlier, DDGIs are a subset of DDIs and DGIs, which means that contradictory DDI/DGI information will negatively impact DDGI evidence. Unfortunately, there are several discrepancies in the listing and clinical severity ratings between DDI[142–147] and DGI information sources. For example, out of four DDI compendia (Drug Interaction Facts, Drug Interactions: Analysis and Management, Evaluations of Drug Interactions, and the MicroMedex DRUG-REAX program), only 9 (2.2%) of 406 major DDIs were listed in all four compendia.[142] Another study compared three major online DDI information resources (the British National Formulary [BNF], Thesaurus, and Micromedex), which, respectively, contained 51,481, 38,037 and 65,446 drug pairs involved in DDIs.[147] Only 6970 (13.5% of BNF, 18.3% of Thesaurus and 10.7% of Micromedex) DDIs were common across all three DDI information sources. Of the above DDIs, 12,644 (24.6%), 15,728 (41.3%) and 47,443 (72.5%) had critical severity ratings for the BNF ("severe" rating), Thesaurus ("Contraindicated" and "Not recommended" ratings) and Micromedex ("Contraindicated" and "Major" ratings), respectively. For DGIs, out of a total of 202 drugs for which there is pharmacogenetic guidance from the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), CPIC and DPWG, only one (0.5%) of the drugs (abacavir) is present in all guidance.[148] The CPIC and DPWG are consistent in guidance for the majority of reported actionable DGIs; however, their ranking criteria and methodology are different.[28,149] For example, DPWG rates the metoprolol:*CYP2D6* drug–gene combination as level 4 (the highest rank), whereas CPIC (https://cpicpgx.org/genes-drugs/) rates this drug–gene combination as B/C ("Prescribing actionability based on genetics is not clear without further evidence review"). Some recommendations like for warfarin dosing (Table 3) can result in differences in dosing recommendations of ≥20%.[28,149]

Electronic Decision Support Tools

Due to the high number of possible DDIs, the main strategy for their detection in a clinical setting has been the use of electronic decision support tools with DDIs presented as interruptive alerts.[68,150] However, too many alerts coupled with discrepancies between predicted and observed DDIs can lead to alert fatigue,[4,68] which is likely to be exaggerated when DGIs, DDGIs and other interactions are added to these electronic decision support tools. To deal with alert fatigue, clinicians override these alerts or the number of DDI alerts may be reduced by eliminating minor, moderate and/or low probability DDIs, which carries risks that clinically relevant DDIs may be missed, leading to serious adverse events.[68,150–152]

To incorporate DGIs into electronic decision support tools, several institutions have established pharmacogenomics initiatives. Samwald et al[153] list examples of USA institutions/health systems that have incorporated pharmacogenetic testing into practice. They include Vanderbilt University Medical Center,[154] St. Jude Children's Research Hospital,[155,156] University of Florida and Shands Hospital,[157] University of Illinois at Chicago,[158] Mayo Clinic,[159] University of Maryland,[160] and Mount Sinai Medical Center.[159] Despite these examples, there is a slow pace in translating pharmacogenomics into the clinic, which has been due to challenges that the Royal College of Physicians and British Pharmacological Society have described as being related to the design of the pharmacogenomics clinical service, standardizing the consent process, genotyping and laboratory considerations, clinical decision support, funding, prescriber knowledge and education, patient engagement, perspectives and managing expectations, clinical governance, and research.[161]

Real-World Evidence and "Big Data"

Recruiting and monitoring the extremely large sample sizes needed to evaluate the prevalence and clinical impact of the large number of drug–drug, drug–gene and drug–drug–gene combinations is very difficult.[15] Fortunately, increasing advances in "big data" (including the availability of adverse drug reaction databases, online literature repositories and millions of electronic primary healthcare records that are linked to genetic data eg the UK biobank) as well as novel technology (including data mining strategies that can identify DDI/DGI-related adverse drug reactions), have made it possible to evaluate the real-world impact of these interactions.[15,18,162] However, the use of big-data raises additional

challenges including the need for additional novel computational techniques, validated phenotyping algorithms and technical/clinical expertise. Additionally, routinely collected health data, which is present in most electronic healthcare records, such as the Clinical Practice Research Datalink is obtained for administrative/clinical purposes without pre-specified research goals, and will have several biases (including selection bias, confounding, information bias, missing data and misclassification) that will need to be accounted for.[163,164]

Clinically Relevant Endpoints

Most current evidence comes from extrapolations from case reports and in vitro studies,[165] and uses pharmacokinetic outcomes such the area under the concentration–time curve or clearance (Table 4). These may not necessarily translate into adverse clinical outcomes and is one of the reasons why the number of potential DDIs far outweighs the number of clinically relevant adverse reactions.[18,19] Clinically relevant endpoints that can be used to quantify actual DDI, DGI or DDGI-related harm are well known. For instance, McDonough provides a detailed protocol for designing a cardiovascular pharmacogenomics study and gives examples of both dichotomous and continuous efficacy (eg, blood pressure response to thiazide diuretics in hypertensive patients; [prevention of adverse] cardiovascular outcomes after clopidogrel treatment in patients undergoing percutaneous coronary intervention) and safety/toxicity (eg, bleeding events after warfarin treatment in atrial fibrillation patients; myopathy after simvastatin treatment in patients with hypercholesterolemia) outcomes that can be used.[166] However, whereas collecting these endpoints is easy in well-designed randomized controlled trials, it might not be possible with lower quality, often incomplete, real-world data such as the electronic health care records discussed above. For DDIs/DGIs/DDGIs, clinical endpoints may require expert adjudication (eg, causality-assessed adverse drug reactions), which further makes it harder to use them on a large scale.

Pre-Emptive Genotyping

It is important to genotype multiple genetic factors in order to be able to capture all clinically relevant gene-based interactions, especially in polypharmacy patients, which makes it necessary to use a panel approach rather than test for individual variants.[63] As highlighted in the introduction, there is growing evidence that the majority of patients (some studies reporting more than 99% of the population) have at least one clinically actionable genotype.[4,21–29] This makes pre-emptive genotyping (screening for pharmacogenetic variants before a pharmacological intervention, as opposed to reactive methods in which screening occurs when a high-risk medication is prescribed or after unexplained adverse effects occur) using a test panel that includes all actionable variants a way to maximize clinical impact.[167] However, as pointed out by the Royal College of Physicians and the British Pharmacological Society, genotyping considerations and determining which variants to include on a panel remain a challenge to clinical implementation.[161] Additionally, and although a few small-sized randomized studies have indicated that the clinical utility of pharmacogenetic panel testing is promising, the cost-effectiveness of pre-emptive genotyping needs further study.[167,168]

Ethnic Diversity

Actionability of genotypes is race/ancestry-dependent with minor allele frequencies of a genetic variant determining its actionability in a given population/race.[74] However, most of the existing pharmacogenetic evidence is applicable to Whites and Asians, which means existing databases or guidelines may not be useful for other races.[74,169] As of 8 July 2021, 86% of the genome-wide association studies had been conducted in individuals of European ancestry,[170,171] which demonstrates a lack of ethnic diversity in genomic evidence. Based on the CPIC guidelines, warfarin, clopidogrel and statins are the three cardiovascular medicine drug classes ready for clinical implementation; however, there is also a lack of diversity in these medicine fields. For example, the CPIC,[172] CPNDS,[173] and DPWG[174] clinical implementation guidelines for warfarin DGIs rely on two algorithms (Gage and International Warfarin Pharmacogenetics Consortium)[175,176] that mostly rely on genetic variants discovered in Whites (rs1799853 [*CYP2C9*2*], rs1057910 [*CYP2C9*3*] and rs9923231 [*VKORC1 −1639G>A*]) and miss out important variants such as rs7900194 [*CYP2C9*8*], rs28371685 [*CYP2C9*11*], and *CYP2C* rs12777823 that are likely to be more relevant to Blacks and some Hispanic populations.[169] Like for warfarin, where the key genetic variants have varying MAFs (*CYP2C9*2* African = 0.01, American = 0.10, East Asian ~ 0.00, European = 0.12, South Asian = 0.04; *CYP2C9*3* African ~ 0.00,

American = 0.04, East Asian = 0.03, European = 0.07, South Asian = 0.11; *CYP2C9*8* African = 0.05, Other ~ 0.00; and *CYP2C9*11* African = 0.02, Other ~ 0.00; *VKORC1 −1639G>A* African = 0.05, American = 0.41, East Asian = 0.89, European = 0.39, South Asian = 0.15), the MAFs for the key genetic variants for clopidogrel (rs4244285 [*CYP2C19*2*] African = 0.17, American = 0.11, East Asian = 0.31, European = 0.15, South Asian = 0.36; rs4986893 [*CYP2C19*3*] East Asian = 0.06, South Asian = 0.01, Other ~ 0.00; and rs12248560 [*CYP2C19*17*] African = 0.24, American = 0.12, East Asian = 0.02, European = 0.22, South Asian = 0.14) and statins (rs4149056 [*SLCO1B1*5*] African = 0.01, American = 0.13, East Asian = 0.12, European = 0.16, South Asian = 0.04) also differ,[177] with clinical implications in terms of translating evidence from one population to another. As DGIs are a component of DDGIs, non-representative DGI evidence directly impacts the relevance of existing/future DDGIs in underserved populations.

Recommendations

Managing drug- and gene-based interactions involves managing both existing and future interactions. For existing DDIs, an international panel recommends treatment modification (reduce dose, discontinue and/or substitute drug, add protective drug) for about three-quarters of DDIs with drug therapy monitoring recommended for the rest.[71] For minimizing [future] DDIs, Kennedy, Brewer, and Williams suggest various steps that are outlined in Box 1.[18] These steps/recommendations can be extended to DGIs, DDGIs and other complex interactions and should supplement the proposed solutions (Table 5) to the clinical practice challenges mentioned above.

Polypills, fixed-dose combinations of cardiovascular medications, are increasingly being recommended for preventing cardiovascular disease as they can improve patient adherence, reduce prescription barriers leading to greater use of guideline-concordant medications, can be availed in numerous formulations to aid dosing flexibility. They have been demonstrated to be safe and effective in reducing the incidence of cardiovascular events in several clinical settings.[188] In the context of this review, the recommendations for polypills are no different to the individual drugs being given separately in that drugs with clinically relevant DDIs should not be included in the same (future) polypills.

Conclusion

Using evidence from pharmacogenomics, this review has illustrated how DDIs and DGIs interact to produce DDGIs, including in the cardiovascular medicine field. Current DDGI evidence is scarce and sometimes contradictory, and electronic decision support tools do not incorporate DDGIs and their management. In addition to direct patient harm when drugs that should be contraindicated due to DDGIs are administered, harm can also result when insufficient evidence on interactions means that a prescriber is less inclined to use a safe and efficacious medicine leading to suboptimal patient outcomes.[165] To improve translation to the clinic, we have provided several recommendations including, expanding the scope of drug information compendia, interaction databases and clinical implementation guidelines (to include clinically relevant DDGIs and other complex interactions) and working towards their harmonization; better use of electronic decision support tools; using big data and novel computational techniques; preemptive genotyping; ensuring ethnic diversity; and upskilling of clinicians in pharmacogenomics and personalized medicine. The cost-effectiveness of incorporating DDGIs should be evaluated, similar to the work done by the Ubiquitous Pharmacogenomics Consortium in

Box 1 Minimizing Drug–Drug Interactions (DDIs)[18]

- Be aware of DDIs and how to detect them, especially those that are clinically relevant.
- Avoid unnecessary polypharmacy with tools such as STOPP/START,[178] ensure an accurate drug history to identify all drugs (including over-the-counter medicines, some dietary elements and herbal therapies)[179] and deprescribe if necessary.
- Use appropriate reference sources (eg the British National Formulary) and available decision support systems.
- Appropriately monitor drug therapy eg conduct therapeutic drug monitoring for high-risk drugs like those with a low therapeutic index.
- Conduct pharmacogenetic testing for clinically actionable variants like those in Table 3.
- Take advice from clinical pharmacists.
- Report DDI-implicated adverse drug reactions to regulatory authorities, since continual surveillance of approved drugs helps to discover safety concerns that may have been missed before marketing approval.

Table 5 Proposed Solutions to Clinical Practice Challenges

Challenges Related to	Proposed Solutions
Drug information compendia, interaction databases and clinical implementation guidelines	• These resources should expand their scope to include DDGIs and other complex interactions. • Existing and future guidance should work towards harmonization to, among other things, reduce clinician fatigue. • Since these resources require a solid evidence-base to be clinically impactful, more studies exploring and quantifying DDGIs and other complex interactions are urgently required.
Electronic decision support tools	• More research should help to identify clinically relevant interactions, which should enable the prioritization of DDIs/DGIs/DDGIs to include in electronic decision support tools and hopefully decrease alert fatigue (irrelevant interactions not included, fewer discrepancies between predicted and actual interactions). • To reduce on the overriding of DDI/DGI/DDGI alerts, clinicians should be educated on the importance and cost-effectiveness of using electronic decision support tools as reduced hospitalizations and substantial savings due to a reduction in interaction-mediated adverse drug events is beneficial to all stakeholders.
DGI (and consequently DDGI) implementation	The Royal College of Physicians and British Pharmacological Society, among others, recommended:[161] • Clinical service designs that consider current healthcare system and staffing challenges, • Establishment of national standardized consenting recommendations/guidelines, • Panel-based pharmacogenetic testing with consideration of point-of-care testing, • Tailored clinical pharmacogenomics guidance, • Centralized funding, • Upskilling of healthcare prescribers in pharmacogenomics and personalized medicine, • Improving clinical governance and oversight, • Involvement of all stakeholders, including patients, and, • Conducting collaborative, inclusive and multidisciplinary research.
Real-world evidence and "big data"	• Follow current guidance with regard to how to best use real-world evidence. For example, the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement can help researchers streamline the design, conduct and reporting of routinely collected real-world data, which should minimize bias and improve the accuracy/validity and completeness of reported findings.[163,164] • Resources such as the HDR UK Phenotype Library (https://phenotypes.healthdatagateway.org/) are providing validated phenotyping algorithms that can be used to more accurately extract data from medical records using clinical codes such as the International Classification of Diseases, while existing techniques such as physiological-based pharmacokinetic modelling and simulation can be employed to predict DDGIs in these studies. For instance, one predictor tool (https://www.ddi-predictor.org/) can incorporate DDIs and DGIs mediated by CYP3A4, CYP2D6, CYP2C9, CYP2C19 and CYP1A2 as well as hepatic function (cirrhosis) to predict DDGIs that can be compared with actual patient outcomes, including adverse drug events.[15,180–182] • For polygenic interactions, where multiple genes contribute to a DGI or DDGI, polygenic risk scores that sum up the influence of several genetic factors on drug-related outcomes into a single score can also be employed.[183] Any signals obtained from such studies will need to be replicated in external cohorts and/or be examined further in clinical trials and/or mechanistic studies.[18]

(*Continued*)

Table 5 (Continued).

Challenges Related to	Proposed Solutions
Clinically-relevant endpoints	• To overcome the issue of incompleteness of electronic health records when it comes to clinically relevant endpoints, validated phenotyping algorithms that extract information from multiple sources can be used. For instance, the CALIBER Bleeding phenotype (https://www.caliberresearch.org/portal/phenotypes/bleeding)[184] uses clinical codes from multiple-sources including primary care (Clinical Practice Research Datalink), secondary care (Hospital Episode Statistics/hospital admission data) and the national death registry to identify patients who suffered a bleeding event. • Where clinically relevant endpoints cannot be used (for example, when a drug is relatively novel and its adverse effect profile is not well known), surrogate/alternative endpoints such as prescribing behaviour or maintenance dose can be used. For example, Malki et al used three Scottish cohorts and the UK Biobank (with linked electronic healthcare records) to identify novel DGIs for 50 most commonly used drugs and 162 variants in 35 genes involved in drug pharmacokinetics.[185] In addition to an efficacy endpoint (systolic blood pressure reduction), they used two phenotypes based on prescribing behaviour (drug-stop and dose-decrease, which are proxies for altered efficacy or tolerability), which enabled them to replicate 11 known DGIs and identify eight novel ones. On the other hand, McInnes and Altman searched the UK Biobank for DGIs among 200 drugs and 9 genes using maintenance dose (the average milligrams of drug per day for the last five prescriptions of each drug) and differential drug response phenotypes (diagnosis codes in primary care data, eg risk of developing a specific side effect).[186]
Pre-emptive genotyping	• It is recommended to use existing pharmacogenetic implementation guidelines and/or prescribing information from regulatory agencies to choose the genetic variants to include on a panel to use for pre-emptive genotyping,[161] as was recently demonstrated.[167] Specifically, Van der Wouden et al based on actionable DPWG guidelines to include 58 genetic variants located within 14 genes (*CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, UGT1A1*, and *VKORC1*) on a panel they called a pharmacogenetics passport. This panel can be used to optimize drug prescribing for 49 commonly prescribed drugs, including nine (18.4%) cardiovascular medicines (namely acenocoumarol, atorvastatin, clopidogrel, flecainide, metoprolol, phenprocoumon, propafenone, simvastatin, and warfarin).[167] • The cost-effectiveness of pre-emptive genotyping for cardiovascular medicines is an area that requires further research.
Ethnic diversity	• Interaction studies should ensure that the different races/ethnicities are adequately represented, which should decrease the discordance in clinical utility studies, improve translation to the clinic and reduce health inequalities.[169] • Underrepresented populations may be exposed to different drugs or DDIs. For instance, some of the underrepresented populations are more reliant on herbal treatment due to easier availability and cheaper cost, which increases the prevalence of herb–drug interactions, including those in the cardiovascular field, in these populations,[187] which further emphasizes the importance of conducting trials in these underserved populations and/or ensuring that they are well represented in future trials.

the Pharmacogenomic testing for prevention of Adverse drug Reactions (PREPARE) study.[189–191] Better evidence (clinical trials, real-world evaluation of drug- and gene-based interactions) and better electronic decision support tools should help reduce DDIs, DGIs, DDGIs and associated adverse drug events, which should improve drug-related outcomes in cardiovascular disease patients, who often experience multimorbidity and polypharmacy. All populations should be well represented in the evidence base to ensure health equity.

Funding

This work was supported by the Medical Research Council [MR/V033867/1; Multimorbidity Mechanism and Therapeutics Research Collaborative].

Disclosure

MP has received partnership funding for the following: MRC Clinical Pharmacology Training Scheme (co-funded by MRC and Roche, UCB, Eli Lilly and Novartis); and a PhD studentship jointly funded by EPSRC and AstraZeneca. He also has unrestricted educational grant support for the UK Pharmacogenetics and Stratified Medicine Network from Bristol-Myers Squibb. He has developed an HLA genotyping panel with MC Diagnostics, but does not benefit financially from this. He is part of the IMI Consortium ARDAT (www.ardat.org). None of the funding MP received is related to the current paper. IGA reports no conflicts of interest in this work.

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