Pharmacogenetic Advances in Cardiovascular Medicine: Relevance to Personalized Medicine

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Abstract The field of pharmacogenetics aims to more fully delineate the genetic basis of interindividual variation in pharmacokinetics, pharmacodynamics, and adverse drug reactions. Indeed, remarkable progress has been made in the past decade, so that we now have a far greater appreciation for the genetic contribution to observed variation in drug responsiveness. We are now starting to witness the translation of findings observed in pharmacogenetic studies to their implementation for patient care as personalized medicine, where an individual patient's genetic makeup is used to guide drug selection and dosing. Many widely utilized cardiovascular drugs have now been linked to commonly occurring heritable genetic variations referred to as single nucleotide polymorphisms to variation in observed efficacy as well as risk for toxicity. As such, the current report outlines clinically relevant evidence supporting the important role of pharmacogenetics to the treatment of patients with cardiovascular disease.

Keywords Pharmacogenetics · Cardiovascular medicine · Personalized medicine · Interindividual variability · Drug response

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Introduction

Clinical trials have clearly demonstrated the therapeutic benefit for many cardiovascular agents; however, some patients, even on the same dose, exhibit loss of efficacy or higher risk of toxicity. We know that, while an average dose of a medication can benefit a large proportion of the patient population, the one-size-fits-all dosing regimen disregards the importance of identified variation in drug metabolism, transport, and response pathways known to exist in any given population. Not surprisingly, preventable adverse drug reactions (ADRs) often occur in subsets of susceptible patients. Interindividual differences in drug response are multifactorial and may be explained by an array of factors including environmental, genetic, comorbidities, and drug–drug interactions.

Advances in the field of pharmacogenetics over the past decade have dramatically improved our understanding of the impact of genetic variability to observed variation in drug response and toxicity. Accordingly, we now have the capability to use an individual genetic makeup in combination with clinical variables to choose appropriate drug therapy and dosages in an a priori fashion. Therefore, the field of pharmacogenetics has significant implication for optimizing cardiovascular drug therapy, considering the large proportion of patients with cardiovascular disease requiring pharmacotherapy.

Associations of genetic variations with drug response largely fall within two categories (Fig. 1): polymorphisms that affect drug pharmacokinetics by introducing variability in systemic drug exposure; and polymorphisms that affect pharmacodynamics by affecting the drug's ability to act at the target site. Not surprisingly, for the most part, candidate gene approaches have been used to identify single nucleotide polymorphisms (SNPs) in genes suspected to influence

Fig. 1 Pharmacogenetic determinants of interindividual variability in cardiovascular therapy. Genetic variability in drug transporter and metabolizing enzymes expressed at the level of enterocytes and hepatocytes affect pharmacokinetics and overall disposition. Genetic

variability in the gene(s) encoding the drug's pharmacological target affects pharmacodynamics. Identified genetic variants confer altered drug sensitivity, response, and toxicity, allowing classification of patients as responders or nonresponders

Table 1 Summary of current evidence in cardiovascular pharmacogenetics

Drug	Drug class	Description	Gene(s)	Category	Problem	Clinical implementation
Warfarin	Anti-coagulant	Variation in dose requirement for achieving and maintaining INR in therapeutic range	<i>CYP2C9</i> , <i>VKORC1</i>	PK, PD	<i>CYP2C9</i> *2, <i>CYP2C9</i> *3, <i>VKORC1</i> 1639G>A carriers have increased sensitivity to warfarin	Dose reduction for loss-of-function variant carriers
Clopidogrel	Anti-platelet	Variation in antiplatelet response leading to resistance in a subset of patients	<i>CYP2C19</i>	PK	<i>CYP2C19</i> *2 and <i>CYP2C19</i> *3 carriers have insufficient active metabolite formation leading to resistance	Dose increase or consider newer antiplatelet agents for loss-of-function variant carriers
Simvastatin	Statin	Variation in lipid lowering efficacy and increased risk of myopathy	<i>OATP1B1</i>	PK	<i>OATP1B1</i> *5 carriers have increased systemic exposure and risk of myotoxicity	Avoid using high-dose or consider using alternative statins
Metoprolol	β-Blocker	Variation in blood pressure lowering response and reduction in cardiovascular events	<i>CYP2D6</i>	PK	<i>CYP2D6</i> *4 carriers have increased sensitivity to metoprolol	Dose reduction for loss-of-function variant carriers
Perindopril	ACE-inhibitor	Variation in blood pressure lowering response and reduction in cardiovascular events	<i>AGTR1</i> , <i>BDKRB1</i>	PD, PD	Variant carriers have reduced cardiovascular benefit	Requires additional validation

ACE angiotensin converting enzyme, *AGTR1* angiotensin II receptor 1, *BDKRB1* bradykinin B1 receptor, *CYP* cytochrome P450, *OATP* organic anion transporting polypeptide, *PD* pharmacodynamics, *PK* pharmacokinetics, *VKORC1* vitamin K epoxide reductase subunit 1

variation in response. On the other hand, genome-wide association studies (GWAS) for drug response represent an unbiased screen across the entire genome and may inform novel pathways of relevance to ADRs or therapeutic response.

We now see a number of pharmacogenetic linkages for a number of medications, some of which have resulted in FDA label changes to incorporate guidance on consideration of genetic information during treatment. The present review highlights the genetic determinants of commonly used cardiovascular drugs (Table 1), and how the use of such information may enhance patient care in a clinical setting.

Oral Anticoagulants

Warfarin

The vitamin K antagonist warfarin is a common oral anticoagulant prescribed in North America for stroke prevention in atrial fibrillation (AF) patients and thromboembolism prophylaxis in venous thromboembolism (VTE) [1]. However, warfarin therapy is particularly challenging due to marked and often unpredictable interindividual dosing variation (up to 20-fold) to reach and maintain adequate anticoagulation. Not surprisingly, its clinical use is associated with ADRs, mainly

in the form of bleeding events; in fact, warfarin was recently reported to account for one-third of hospitalizations in the elderly [2]. For most indications, optimal warfarin therapy is achieved by maintaining the international normalized ratio (INR) within a narrow therapeutic range of 2–3. An insufficient warfarin dose leads to a lack of antithrombotic effect while over-anticoagulation is associated with elevated bleeding risk. Aside from demographic (age, gender, weight) and clinical variables (renal or hepatic disease, diet, drug–drug interactions), pharmacogenetics explains a large portion of the observed variability in warfarin dose requirement [3].

CYP2C9

Warfarin is administered as a racemic drug; *S*-warfarin is 3–5 times more potent than *R*-warfarin. The clearance and thus pharmacokinetics of warfarin is largely dependent on the metabolic pathways of each enantiomer. While CYP1A2, CYP3A4, and CYP2C19 are enzymes that convert the *R*-warfarin to its inactive metabolite in varying extents, CYP2C9 is the primary enzyme responsible for metabolism of *S*-warfarin. As such, candidate gene studies have consistently shown that *CYP2C9* polymorphisms significantly affect warfarin sensitivity [4]. In particular, common *CYP2C9**2 and *3 variant alleles result in decreased enzymatic activity (30 and 90 % reduction, respectively) compared to the wild-type allele [5]. The clinical implication for these SNPs is lower therapeutic dose requirement, increased time to stable anticoagulation and increased bleeding risk due to greater rate of over-anticoagulation [6]. A large meta-analysis of 39 studies ($n = 7,907$) demonstrated that maintenance dose for *CYP2C9**2 and *3 homozygous patients were 36 and 78 % lower, respectively, as compared to wild-type patients [7].

VKORC1

S-warfarin inhibits the vitamin K epoxide reductase, encoded by *VKORC1*, the enzyme responsible for recycling oxidized vitamin K to the reduced form, an essential cofactor for γ -glutamyl-carboxylase carboxylation (GGCX) in clotting factor II, VII, IX and X activation [8]. Common genetic variants in *VKORC1* result in altered warfarin sensitivity while rare polymorphisms result in warfarin resistance [9]. Of note, the common promoter SNP (*VKORC1* 1639G>A, rs9923231) is thought to be the causative variation responsible for the greater warfarin sensitivity, resulting in lowered dose requirement [10].

Other SNPs

In addition to *CYP2C9* and *VKORC1* polymorphisms, SNPs in other genes have been studied as potential contributors to

warfarin response. These genes include *GGCX*, calumenin (*CALU*), apolipoprotein E (*ApoE*) as well as multidrug resistance protein (*ABCB1*) [11]. However, the impact of these polymorphisms on warfarin response has generally been minimal or none at all. An exception to this is the growing importance of the *CYP4F2* 1297C>T genotype, whereby several retrospective studies have demonstrated that variant T carriers (rs2108622) require 1 mg more than wild-type C carriers [12]. Moreover, CYP4F2 is the metabolizing enzyme of vitamin K accounting for the pharmacological basis of the dose difference [13]. However, the *CYP4F2* genotype only accounts for a small portion of the observed maintenance dose variability (0–4 %) [14]. These findings were confirmed by recent GWASs, where polymorphisms in *CYP2C9* and *VKORC1* were the only genetic markers identified to influence warfarin dosing, while the *CYP4F2* genotype was only significant after adjusting for *CYP2C9* and *VKORC1* [15].

Clinical Applicability of SNPs

*CYP2C9**2, *CYP2C9**3 and *VKORC1* 1639G>A variant carriers are at an increased risk of over anticoagulation (INR > 4) and bleeding as well as delayed time to therapeutic efficacy. Based on these findings, the FDA approved a new label for warfarin in 2007 advising physicians to consider pharmacogenetic testing for patients requiring warfarin. Many dosing algorithms have been developed to predict warfarin dose requirement using *CYP2C9*, *VKORC1*, and *CYP4F2* SNPs and clinical parameters [16]. The majority of these studies have focused on the effect of genetic variation on warfarin dose during maintenance phase of anticoagulation. However, warfarin initiation is arguably the most challenging therapeutic phase where risk of hemorrhage and recurrent VTE are greatest [17]. Moreover, we and others demonstrated that *CYP2C9* and *VKORC1* modulate warfarin response even during early anticoagulation [18]. Accordingly, our group recently demonstrated that initiation with the novel pharmacogenetics-based protocol (WRAPID) incorporating loading and maintenance dosing produces a safe, effective, and consistent anticoagulation in AF and VTE patients irrespective of genotype [19].

Clinical Implementation

There is a strong association between *CYP2C9* and *VKORC1* SNPs with warfarin response and dose. However, the widespread use of pharmacogenetics-based warfarin dosing remains has not yet been achieved, in part related to concerns regarding costs associated with pharmacogenetic testing and additional clinical evidence to support superiority of a pharmacogenetics-based approach. Recently, the

COUMAGEN-II trial showed clear superiority of pharmacogenetics-based warfarin dosing over standard care with respect to time spent in therapeutic range and reduced occurrence of ADRs [20•]. Additionally, a recent large scale community-based study found that genotyping during warfarin therapy reduced the hospitalization rate for bleeding or thromboembolic event by 30 % compared to a historical control group [21]. A number of RCTs (www.clinicaltrials.gov; COAG, GIFT, EU-PACT) involving larger sample sizes are currently underway to more fully confirm such findings focusing on safety and efficacy of pharmacogenetics-based dosing compared to standard dosing. Given the extent of supportive evidence to date for warfarin, pharmacogenetics-based warfarin dosing is likely to be widely implemented, particularly given the rapid improvement in genotyping technologies that has resulted in greater accuracy, turnaround time, and lower cost.

New Oral Anticoagulants: Dabigatran and Rivaroxaban

Dabigatran, a direct thrombin inhibitor, and rivaroxaban, a factor 10a inhibitor, are new oral anticoagulants recently approved for AF and VTE. Dabigatran etexilate is a pro-drug, requiring bioactivation to active dabigatran by esterases while rivaroxaban undergoes metabolism predominantly by CYP2J2 and CYP3A4 [22]. Interestingly, both agents are substrates of P-glycoprotein (ABCB1) while rivaroxaban is also a substrate of breast cancer resistance protein (BCRP) [23]. Very recently, a genome-wide subanalysis of the RE-LY trial demonstrated that a common variant in the carboxylesterase 1 (*CES1*) gene (rs2244613) was associated with dabigatran-related bleeding events (unpublished data). The polymorphism is thought to attenuate dabigatran formation resulting in lowered systemic exposure and reduced bleeding risk, indicating the potential for pharmacogenetics-based dosing. Further studies are needed to confirm these findings in addition to identification of additional genetic variations in candidate genes such as *ABCB1* and *BCRP* to determine SNPs capable of modulating their efficacy and toxicity.

Antiplatelets

Aspirin

Aspirin is commonly prescribed for prevention of cardiovascular events. Aspirin irreversibly binds and inactivates cyclooxygenase (COX) 1 and 2 in platelets, and thereby reduce platelet aggregation [24]. The term of aspirin resistance has been coined to note the occurrence of cardiovascular events, presumably related to suboptimal antiplatelet inhibitory effect in patients prescribed with

therapeutic doses of aspirin. However, classification of aspirin resistance has been highly controversial with prevalence of 5–60 % depending on the population and ex vivo response measurement used; a patient defined as a non-responder in one test would be normal in another [25]. Therefore, it has been challenging to interpret the relevance of genetic markers associated with aspirin response.

PTGS1

Since COX1 is the direct pharmacological target of aspirin, considerable amount of focus has been on the COX1 encoding gene, *PTGS1*. However, results of such studies have been variable. Although genetic polymorphisms in this gene have been linked to greater platelet aggregation in some studies, many others failed to replicate such an effect or find an association with cardiovascular events such as myocardial infarction (MI) [26].

Other SNPs

Several other genes encoding platelet activation pathway proteins have been linked to aspirin antiplatelet response. The *ITGB3* gene encodes GPIIb protein and carriers of the risk allele (rs5918) appear to confer elevated risk of MI, arterial and venous thrombosis. However, other studies in this regard have been conflicting [26]. A recent study found carriers of an intronic SNP in the *PEAR1* gene (rs12041331) corresponded to higher aspirin response [27]. Additionally, a SNP in the *LPA* gene (rs3798220) determined plasma levels of apolipoprotein A and associated with differential aspirin efficacy in a large placebo-controlled trial [28].

Clinical Implementation

The extent of clinically relevant genetic markers and their role to aspirin response remain to be defined. The lack of consistent associations indicates it may be premature to include genetic testing for aspirin therapy, at least based on currently published genetic markers. In addition, a key impediment has been the lack of a standardized antiplatelet response measurement assay for aspirin prescribed patients.

Clopidogrel

Antiplatelet therapy with thienopyridine is an important therapeutic intervention for the prevention of ischemic events in patients with high-risk cardiovascular disease, particularly for those undergoing percutaneous coronary intervention (PCI) [29]. Clopidogrel is the most widely prescribed thienopyridine known to exert its pharmacological effect by irreversibly binding to P2Y₁₂ receptors on platelets, thereby diminishing platelet aggregation [30]. Although benefits from

clopidogrel has been widely documented in large clinical trials, marked interpatient variation in platelet responsiveness has meant that 21 % of patients (termed nonresponders) remain at risk for coronary artery and stent thrombosis [31].

CYP2C19

Clopidogrel is a prodrug and its clinical efficacy is a function of the amount of enzymatically derived active thiol metabolite formed (H4) [32]. While most of the prodrug undergoes hydrolysis to an inactive metabolite, clopidogrel bioactivation is a two-step process catalyzed by several CYP isozymes [33]. Both metabolic steps leading to H4 formation have been shown to be predominantly dependent on CYP2C19, and to a lesser extent CYP3A4 [33].

A number of studies have examined the influence of genetic variation in CYP enzymes on clopidogrel antiplatelet response. The most consistent finding is that *CYP2C19**2 (rs4244285) and *CYP2C19**3 (rs4986893) loss-of-function SNPs results in lower platelet inhibition, high on-treatment platelet reactivity and, consequently, an increased risk of major cardiovascular events, particularly stent thrombosis in PCI patients [34]. A meta-analysis including nine studies ($n = 9,685$) reported a gene-dose effect for variant carriers; one reduced function allele carrier had a hazard ratio of 1.57 (95 % confidence interval 1.13–2.16) for a composite of cardiovascular endpoints while carriers of two reduced function alleles had an even greater risk (hazard ratio 1.76, 1.24–2.5) [34]. Another common *CYP2C19* polymorphism (*17, rs3758581) results in increased enzyme activity, greater efficacy, and better cardiovascular outcomes at the expense of increased bleeding risk [35]. These findings prompted the FDA to update the clopidogrel label with a boxed warning for cautious use amongst *CYP2C19* reduced function carriers.

PON1

Bouman et al. [36] recently demonstrated that a non-CYP enzyme, paraoxonase-1 (PON1) was the key determinant of clopidogrel active metabolite formation. They showed plasma PON1 activity as well as the Q192R SNP (rs662) in *PON1*, but not *CYP2C19* SNPs was predictive of antiplatelet response and risk for stent thrombosis in clopidogrel-treated patients. However, several subsequently published studies of large sample sizes refuted the role *PON1* in clopidogrel response and cardiovascular outcomes [37]. Mechanistically, we and Dansette et al. [38, 39] demonstrated that PON1, unlike CYP2C19, is incapable of generating H4 active metabolite. Our study demonstrated that *CYP2C19* loss-of-function genotype was a major determinant of H4 exposure corresponding to lowered ADP-induced antiplatelet response, while *PON1* failed to play any role.

ABCB1

Clopidogrel has been demonstrated to be a substrate of P-glycoprotein, which limits the extent of its bioavailability. Not surprisingly, the *ABCB1* 3435C>T SNP (rs1045642) has been shown to result in lower peak concentrations of clopidogrel and its active metabolite [40]. However, the definitive role of this SNP on clopidogrel antiplatelet response remains controversial. While Mega et al. [41] reported that the elevated cardiovascular risk of *CYP2C19* variant allele carriers was accentuated in presence of homozygous 3435C>T genotype, other studies could not replicate this finding [42].

P2Y₁₂

Clopidogrel exerts its pharmacodynamics effects by inhibition of P2Y₁₂ receptor on platelets. Recently, Ziegler et al. [43] reported a fourfold increase in cerebrovascular events in patients possessing the 34C>T (rs6809699) variant while another variant, 52G>T (rs6785930), confers clopidogrel resistance following PCI. However, other studies have failed to show the same trend for antiplatelet response and cardiovascular events [44].

Other SNPs

CYP2C19 undoubtedly predicts cardiovascular outcomes in patients treated with clopidogrel following PCI, yet it is thought to represent only a portion of the observed variation in antiplatelet response. A GWAS demonstrated that clopidogrel platelet aggregation was highly heritable ($r^2 = 0.73$) in an Amish population [45]. However, the *CYP2C19**2 SNP only accounted for 12 % of the interindividual variation, indicating that other genetic markers affecting efficacy remain to be identified to explain the large heritable component of clopidogrel response. More recently, the Scripps Clinic conducted whole genome sequencing in 392 patients on clopidogrel and found two novel genes *ATP2B2* and *TIAM2* to predict poor platelet response (unpublished data).

Clinical Implementation

Clopidogrel resistance and the lack of adequate therapeutic efficacy is a major concern, thus identification of resistant patients prior to treatment is of great value for favorable outcomes. Although there is ample evidence linking *CYP2C19* with cardiovascular outcomes in PCI patients, RCTs assessing the benefit of genotyping for *CYP2C19* over standard care has yet to be conducted. One recent RCT using point-of-care *CYP2C19**2 genotyping showed that such genetic information led to better prediction of

antiplatelet response in a real world setting, indicating that personalized clopidogrel therapy may be effective in improving efficacy [46]. Accordingly, a number of institutions (Vanderbilt University Medical Centre, Scripps Clinic) adopted routine *CYP2C19* genotyping for patients undergoing PCI [47•]. Conversely, although several small prospective trials have restored diminished H4 exposure and poor antiplatelet response in *CYP2C19* variant carriers by increasing clopidogrel loading and maintenance dose [48], recent larger studies failed to overcome the reduced antiplatelet response in individuals harboring *CYP2C19**2 variant alleles [49]. This indicates that clopidogrel potency at the P2Y₁₂ receptor is likely inadequate for *CYP2C19* variant carriers. Accordingly, the Clinical Pharmacogenetics Implementation Consortium suggested that newer antiplatelet agents with greater affinity and potency (prasugrel and ticagrelor) should be considered for carriers of one or two loss-of-function variant alleles [50]. Indeed, *CYP2C19**2 carriers were more likely to switch to prasugrel due to high on-treatment platelet reactivity [51]. Current ongoing studies include the GIANT trial which will assess the clinical efficacy of using high-dose clopidogrel for *CYP2C19**2 carriers and the RAPID-STEMI trial that will evaluate efficacy of either high-dose clopidogrel or switching to prasugrel for *CYP2C19**2 and *ABCB1* 3435TT carriers.

New Antiplatelets: Prasugrel and Ticagrelor

Neither agent requires extensive bioactivation by *CYP2C19*. Thus, *CYP2C19* genetic variation has not been demonstrated to affect cardiovascular outcomes in subanalysis of the TRITON-TIMI (prasugrel) or the PLATO (ticagrelor) trial [52]. However, we note that *CYP3A4* and *CYP2B6* are responsible for bioactivation of prasugrel to its active form, and the influence of polymorphisms in these enzymes to prasugrel platelet efficacy remains to be delineated. An important consideration of prasugrel use over clopidogrel is that, although it proved more efficacious than clopidogrel, this is at the price of increased bleeding risk. Similarly, ticagrelor use over clopidogrel is complicated by the finding that ticagrelor was as effective as clopidogrel across all international centres of PLATO trial except for North America.

Lipid-Lowering Drugs

Statins

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) is the rate-limiting step for cholesterol biosynthesis in the liver. The cholesterol lowering class of statin drugs exerts its pharmacological effect by inhibiting

HMGCR, reducing circulating cholesterol and low-density lipoprotein (LDL). Accordingly, statins are widely prescribed for primary and secondary prevention of cardiovascular disease. Although clinical effectiveness of statins has been proven in large RCTs, substantial interindividual variability has meant that a subset of patients fail to attain sufficient cholesterol reduction and prevention of cardiovascular events [53]. Thus, pharmacogenomic studies have been conducted to gain insight into genetic basis of response and tolerability.

SLCO1B1

Statins are known to be substrates of the solute carrier organic anion transporting polypeptides 1B1 (OATP1B1), encoded by the *SLCO1B1* gene, expressed on the basolateral membrane of hepatocyte facilitating the hepatocellular uptake of statins from the portal circulation [54]. In 2001, our group was the first to identify and create the nomenclature (from *1a to *14, which has since been widely adopted) for *SLCO1B1*, which at that time was known as OATP-C (also known as SLC21A6, OATP2, and LST1) as well as deduce their functional relevance [55]. In particular, the *SLCO1B1**5 variant conferred reduced membrane localization of OATP1B1, and clinical studies have consistently linked this SNP to altered statin disposition, in terms of decreased hepatocellular uptake which then results in enhanced systemic exposure. On the other hand, the *SLCO1B1**1b genotype has been associated with lower plasma statin exposure. However, controversy exists for the relevance of *SLCO1B1* variants in predicting LDL-lowering efficacy and requires further assessment in a large patient cohort [56, 57].

It should be noted that statin-use may result in unexpected muscle toxicity ranging from mild myalgia to the life-threatening rhabdomyolysis. Indeed, the most convincing data to date comes from a recent GWAS that identified *SLCO1B1**5 allele as the single most important predictor of simvastatin-induced myopathy [58]. In that study, the odds ratio for myopathy-risk owing to *SLCO1B1**5 was found to be 4.5 for heterozygous carriers and 16.9 for homozygous carriers [58]. Subsequently, the *SLCO1B1**5 SNP has been shown to predict statin-related ADRs (discontinuation, creatine kinase elevation and myalgia) and statin intolerance (dose adjustment, statin switching) in patients prescribed with atorvastatin, simvastatin, or pravastatin [59, 60]. Overall, these data provide sufficient evidence to indicate that SNPs in *SLCO1B1* alter pharmacokinetics and pharmacodynamics and contribute to statin-induced ADRs. It is noteworthy that myopathy risk is statin-dependent, the greatest risk was observed with simvastatin followed by atorvastatin, pravastatin, rosuvastatin, and fluvastatin [61]. Genotyping for *SLCO1B1*

polymorphisms may contribute to delivering optimal cholesterol lowering effects while reducing the risk of statin-induced myopathy.

HMGCR and APOE

The pharmacodynamic response to statins in terms of LDL reduction appears to be affected genetic variations in *HMGCR* and *APOE*. Carriers of the *HMGCR* H7 haplotype, defined by three intronic SNPs (rs17244841, rs3826662, and rs17238540) experienced 11–19 % lower statin sensitivity, as measured by LDL reduction [62]. However, these findings were not replicated in a GWAS with atorvastatin response [63•]. The effect of *APOE* haplotypes (rs429358 and rs7412 define 3 haplotypes) on statin response is controversial. The first GWAS study on statin response showed that *APOE* polymorphisms related to LDL lowering response, where the response was greatest for the ϵ 2 haplotype and variant carriers had attenuated efficacy [63•]. However, a recent meta-analysis failed to confirm these associations [64]. Thus, the impact of *HMGCR* and *APOE* genetic variations on lipid-lowering statin response remains to be further evaluated.

KIF6

The kinesin-like family 6 (KIF6) gene was identified to predict incidence of coronary artery disease (CAD) and may represent a novel pathway underlying cardiovascular disease [65]. Indeed, carriers of the rs20455 SNP attained greater cardiovascular benefit than noncarriers in some studies [66]. However, a subsequent meta-analysis of large statin trials showed no association of this SNP with risk of CAD [67]. Similarly, no differential relationship was found with statin efficacy in carriers and noncarriers. Additional studies are needed to explore the impact of KIF6.

Other SNPs

Rosuvastatin has been shown to be a substrate of the efflux transporter BCRP (encoded by *ABCG2*), expressed on the apical membrane of hepatocytes. Indeed, the *ABCG2* 421C>A polymorphism was associated with rosuvastatin pharmacokinetics and greater reduction in LDL [68]. The greater LDL reduction would be equivalent to doubling of the rosuvastatin dose. Atorvastatin and simvastatin are both metabolized by CYP3A4 and common polymorphisms in *CYP3A4* may affect statin exposure and response. Statin use leads to subsequent upregulation of LDL receptor (LDLR) [69]. In a population of African ancestry, *LDLR* haplotype was associated with reduced statin efficacy. Carriers of the rs8014194 polymorphism in the *CLMN*

gene, encoding the calpain protein of unknown function, had 3 % greater reduction in total cholesterol compared to noncarriers in a combined GWAS analysis of three trials [70].

Clinical Implementation

The most supportive evidence for clinically relevant statin pharmacogenetics relates to drug transporter polymorphisms. Robust evidence for other genetic markers relating to statin response and myopathy risk is lacking and requires additional evaluation. For this reason, several groups have suggested for the use of genetic variations in transporters to guide statin dosing [58]. Although the association between *SLCO1B1**5 genotype and simvastatin-induced myopathy has been replicated in subsequent clinical studies, the same association for other statins is less compelling. As such, FDA recently changed the label for simvastatin to incorporate *SLCO1B1*-defined guidelines. It was recommended that prescribers should avoid 80 mg simvastatin in homozygous *SLCO1B1**5 carriers in addition to consideration of an alternative statin.

Beta Blockers

β -Blockers are β -adrenergic receptor antagonists and important cardiovascular medicines for the management and treatment of hypertension, post-MI, heart failure (HF) and CAD. Therapeutic response to β -blockers has been measured using alterations in heart rate (HR), blood pressure (BP), and left ventricular ejection fraction (LVEF) and cardiovascular outcomes include rate of MI, death or HF [71]. As with many drugs discussed thus far, β -blockers have substantial interindividual variation in response and efficacy.

CYP2D6

CYP2D6 is responsible for the metabolism of various β -blockers; CYP2D6 extensively metabolizes metoprolol (70–80 %), while to a lesser extent for carvedilol, propranolol, and alprenolol [72]. Not surprisingly, the influence of *CYP2D6* genetic variations on metoprolol pharmacokinetics has been the most extensively studied. *CYP2D6* is extremely polymorphic with many alleles of decreased or complete loss-of-function. In 5–10 % of Caucasians, CYP2D6 enzyme activity is lacking due to possession of two copies of nonfunctional alleles (poor metabolizers, PMs) [73]. Homozygous carriers of *CYP2D6**4 (rs3892087) account for 75 % of CYP2D6 PMs. Individuals with two functional alleles are classified as extensive metabolizers (EMs) while ultra-rapid

metabolizers (UMs) possess carrying more than two functional copies of *CYP2D6* gene.

The *CYP2D6* PM phenotype has been shown to increase metoprolol plasma exposure by sevenfold during short-term and long-term therapy [74]. This also translates to differential pharmacodynamics, where PMs have greater reduction in HR and BP [75]. Moreover, *CYP2D6**4 carriers had an increased risk of ADRs such as bradycardia during metoprolol treatment compared to noncarriers in large studies [76]. Conversely, UMs had significantly lower systemic metoprolol exposure and little therapeutic benefit. The *CYP2D6* UM phenotype was linked to more frequent ventricular rhythm disturbance in acute MI patients. We note that, despite the consistent trend between *CYP2D6* genotype and metoprolol exposure, not all studies demonstrate its association with increased ADR risk [77]. Nevertheless, dose adjustments for metoprolol should be considered for *CYP2D6* PM individuals, particular those at risk for cardiovascular complications.

ADRB1

β -Blockers primarily antagonize the β 1-adrenergic receptor (*ADRB1*). The two common SNPs, Ser49Gly (rs1891252) and Arg389Gly (rs1801253) are in linkage disequilibrium [78]. A meta-analysis of three studies encompassing 504 HF patients supported better LVEF outcome in homozygous Arg389 individuals treated with β -blockers [78]. Furthermore, homozygous Arg389 hypertensive patients treated with metoprolol obtained efficacy in terms of greater reduction in HR and BP, but this trend was not found for other β -blockers [79, 80].

Evaluation of mortality and hospitalization in HF patients with Arg389Gly genotype has yielded variable findings. In the BEST study, a large RCT assessing efficacy of a novel β -blocker bucindolol found that homozygous Arg389 patients had significantly improved survival time and decreased rate of hospitalization [81]. In contrast, no association with Arg389Gly was found in the MERIT-HT trial in patients treated with metoprolol [82]. Similarly, no association was found for mortality in a prospective registry study of HF patients treated with various β -blockers [83]. It is plausible that the association of Arg389Gly with mortality is unique to bucindolol. More recently, AF patients carrying the Gly389 variant had more favorable response to β -blockers than Arg389 carriers [84]. Additional studies are needed to resolve these divergent findings.

The Gly49 genotype has been associated with improved response and favorable survival rates in patients treated with β -blockers [85]. However, these findings should be

interpreted with caution as other studies could not replicate this association [86].

ADRB2

The three polymorphisms in the *ADRB2* encoding β 2-adrenergic receptor are Gly16Arg (rs104213), Gln27Glu (rs1042714), and Thr164Ile (rs1800888). Clinical studies have generally failed to demonstrate an association of response with Gly16Arg genotype [87]. On the other hand, several studies found that Glu27 genotype was associated with better β -blocker response in terms of HR, and LVEF changes [88]. Moreover, possessing *ADRB1* Arg389 and *ADRB2* Gln27 variant genotypes together was associated with twofold increase in mortality compared to other genotype groups in patients treated with carvedilol. In the same study, this association was not found with metoprolol [89]. In a study of HF patients, heterozygous Ile164 carriers treated with β -blockers had a twofold higher mortality rate [90].

ADRA2C

The function of α 2c-adrenergic receptor is autoinhibition of norepinephrine release and therefore may affect β -blocker responsiveness. Individuals carrying the deletion polymorphism, del322–325, have been found to experience greater improvement in LVEF with metoprolol treatment while experiencing reduced efficacy in the BEST trial [81, 91]. The disparate effect of this genotype may be a function of pharmacological differences in bucindolol and metoprolol. In addition, this deletion in combination with the *ADRB1* Arg389Gly genotype has been associated with increased risk of HF in African-Americans [92].

GRK5

The G-protein receptor kinase (GRK5) desensitizes G-protein coupled receptors of β -adrenergic receptors. The Gln41leu variant is a gain-of-function polymorphism commonly found in patients of African descent. In African-Americans, but not European-Americans, individuals homozygous for the Gln41 genotype receiving β -blocker treatment had significantly improved mortality benefit [93]. Additional prospective studies are needed to explain the ethnic differences in mortality associated with this genotype.

KCNQ1

Very recently, a trial of 860 patients demonstrated that those with C-loop mutations in the *KCNQ1* gene attained the greatest therapeutic benefit from β -blocker therapy in terms of lowered risk of cardiac arrest or sudden death [94].

Clinical Implementation

CYP2D6 undoubtedly affects β -blocker metabolisms and PMs have sustained therapeutic effect and greater risk of ADRs due to significant increase in systemic exposure. This is particularly relevant for the widely prescribed β -blocker metoprolol. Very recently, the Pharmacogenetics Working Group advised prescribers to consider alternative β -blocker therapy or dose reduction for *CYP2D6* PMs on metoprolol for HF and vice versa for UMs [95•]. In terms of pharmacodynamic markers, *ADRB1* Arg389Gly genotype gene showed the most evidence for differential HR, BP and survival rates during β -blocker treatment. Thus, dose adjustment may be required for Gly389 carriers, particularly as more data become available supporting this notion.

Angiotensin Converting Enzyme Inhibitors

The clinical role of angiotensin-converting enzyme inhibitors (ACEi) is in the management of hypertension, stable CAD, MI, and HF. Despite the beneficial effects documented in clinical trials, interindividual variability in responses such as BP has been demonstrated [96]. Accordingly, distinguishing patients that will most likely benefit from ACEi therapy may be essential for optimal cardiovascular therapy.

ACE

The renin-angiotensin system (RAS) is responsible for blood pressure regulation and electrolyte balance and therefore plays a pivotal role in cardiovascular health. ACEi competitively inhibits the conversion of angiotensin I into angiotensin II, leading to reduced vasoconstriction and water and salt retention. Perhaps the most extensively studied gene affecting ACEi response is *ACE*, particularly the insertion and deletion (I/D) genetic variant in intron 6 (rs4646994). This variant has been associated with significantly higher plasma concentrations of ACE and confers differential reduction of BP [26]. Subsequent sufficiently powered studies have shown no difference in BP reduction among *ACE* I/D genotype groups. In the Rotterdam observational study, individuals of DD genotype had an increased 10-year mortality risk as compared to individuals with II genotype. However, this finding was not validated in the prospective trials GenHAT and PROGRESS [26]. In the PERGENE trial, all five polymorphisms in the *ACE* gene evaluated failed to predict primary cardiovascular outcomes [97]. Currently, there is a lack of convincing evidence for the influence of the *ACE* I/D variant on ACEi response, although there is compelling

evidence for this genotype to higher occurrence of ACEi-induced cough [98].

AGT

Angiotensinogen (AGT) is the precursor to angiotensin I and the variant Met235Thr (rs699) has been linked to modulate plasma concentrations of AGT among hypertensive patients. In a large Rotterdam cohort, *AGT* Thr235 allele carriers were predicted to have an elevated risk of MI and stroke in ACEi-treated patients [99]. In another study, mortality risk was higher for Thr235 allele carriers taking benazepril. Individuals homozygous for the novel variant identified in the 3'-untranslated region of *AGT* (rs7079) was associated with enhanced BP reduction in response to benazepril therapy [100].

AGTR1 and Other SNPs

Haplotype assignment of the angiotensin II receptor 1 (*AGTR1*) gene resulted in a gene-dose effect on BP reduction. Specifically, the recent PERGENE trial in which 8,907 stable CAD patients were evaluated for 52 haplotype tagging SNPs in 12 candidate genes for perindopril response, two polymorphisms in the *AGTR1* gene (rs275651 and rs5182) and one in the bradykinin B1 receptor (*BDKRB1*) (rs12050217) were associated with a reduction in perindopril's cardiovascular benefit. [97]. A pharmacogenetics scoring system developed based on these SNPs successfully predicted the reduction in treatment benefit to perindopril in a stepwise manner as the number of variants increased.

Clinical Implementation

Findings of the PERGENE trial illuminates the usage of pharmacogenetics to guide individualized ACEi therapy. However, additional studies are needed to replicate the findings for perindopril and other ACEis.

Antiarrhythmic Drugs

Antiarrhythmic drugs are an important class of drugs used to manage cardiac arrhythmias, which contribute significantly to morbidity and mortality. Various calcium-channel blockers including verapamil, diltiazem, and digoxin are known *ABCB1* substrates, an efflux drug transporter with broad substrate specificity [101]. Polymorphisms in *ABCB1* have been linked to altered pharmacokinetics of these agents at varying degrees, although no reports have shown differential outcomes or toxicity [101]. *CYP2D6* PMs have an elevated risk of toxicity induced by the sodium-channel blocker flecainide, and the Pharmacogenetics Working

Group recommends dose reduction by 50 % in addition to monitoring response (ECG) [95•]. Similarly, propafenone is also metabolized by CYP2D6 and carriers of the *CYP2D6**4 genotype have enhanced suppression of arrhythmias and toxicity; thus, dose reduction was also suggested for *CYP2D6* PMs [95•].

Conclusions

Interindividual variation in drug exposure and efficacy lead to subsets of patients experiencing drug-related toxicities or inadequate therapeutic benefit. The one-dose-fits-all paradigm for drug therapy is increasingly recognized as inappropriate for many drugs in clinical use. Alternative paradigm for pharmacotherapy pertains to individualized therapies. In the past decade, substantial progress has been made linking commonly occurring genetic variants to cardiovascular treatment response. Despite this, pharmacogenetics-guided care is still in its infancy, as most centres have not implemented this approach to routine clinical practice. However, as the cost of genotyping continues to decline while the extent of clinical evidence supporting pharmacogenetics-based approach rises, there is little doubt that implementation of pharmacogenetics-guided personalized medicine will result in reduced incidence of ADRs, and greater likelihood of therapeutic benefit. Indeed, for drugs where pharmacogenetics-guided care has been shown to be noninferior, and potentially superior to standard care, such an approach should be implemented and further studied in a prospective fashion to show the overall merit of pharmacogenetics to enhancing patient care, reducing ADRs and health care costs in the real-world setting. We also recognize that, for many drugs, clinical decision support algorithms that integrate patient-specific pharmacogenetic data along with environmental and clinical variables will be essential to realizing the promise of personalized medicine.

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