Published in final edited form as:
Curr Opin Cardiol. 2013 May ; 28(3): 305–314. doi:10.1097/HCO.0b013e32835f0bbc.

Clopidogrel and warfarin pharmacogenetic tests: what is the evidence for use in clinical practice?

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Abstract

Purpose of review—To review the most promising genetic markers associated with the variability in the safety or efficacy of warfarin and clopidogrel and highlight the verification and validation initiatives for translating clopidogrel and warfarin pharmacogenetic tests to clinical practice.

Recent findings—Rapid advances in pharmacogenetics, continuous decrease in genotyping cost, development of point-of-care devices and the newly established clinical genotyping programs at several institutions hold the promise of individualizing clopidogrel and warfarin based on genotype. Guidelines have been established to assist clinicians in prescribing clopidogrel or warfarin dose based on genotype. However, the clinical utility of clopidogrel and warfarin is still limited. Accordingly, large randomized clinical trials are underway to define the role of clopidogrel and warfarin pharmacogenetics in clinical practice.

Summary—Pharmacogenetics has offered compelling evidence toward the individualization of clopidogrel and warfarin therapies. The rapid advances in technology make the clinical implementation of clopidogrel and warfarin pharmacogenetics possible. The clinical genotyping programs and the ongoing clinical trials will help in overcoming some of the barriers facing the clinical implementation of clopidogrel and warfarin pharmacogenetics.

Keywords

clinical implementation; clopidogrel; personalized medicine; pharmacogenetics; warfarin

INTRODUCTION

Cardiovascular disease (CVD) remains the primary cause of death in the United States and worldwide. In 2008, CVD deaths represented 30% of all deaths globally [1,2]. Despite the presence of numerous highly efficacious drugs for the management of CVD, however, many of these drugs exhibit large interpatient variability in their efficacy or side-effects risk. Warfarin and clopidogrel are excellent examples of widely prescribed cardiovascular medications that are highly efficacious in the treatment and prevention of CVDs and their thrombotic complications. Warfarin and clopidogrel are also considered excellent examples of medications with wide interpatient variability in the efficacy, safety or dose requirements. The variability in warfarin dosing makes it extremely challenging in the clinical setting, and

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Conflicts of interest
There are no conflicts of interest.

influences the risk of both bleeding and thrombotic complications [3–7]. Similarly, clopidogrel exhibits wide interpatient variability in its antiplatelet effect, which affects its ability to limit cardiovascular events in some.

The completion of the Human Genome Project in 2001 led to promises of improving care through genomic medicine [8,9]. The rapid growth in pharmacogenetics research and the better understanding of the impact of genetic variation on drug response for certain drugs prompted the Food and Drug Administration (FDA) to relabel more than 100 medications with genetic information in the last decade [10]. As was projected at the time of completion of the Human Genome project, pharmacogenetics represents the first major use of genomic medicine to improve the safety and effectiveness of a variety of drugs, with the goal of delivering better, individualized medical care [11–13].

Cardiovascular medications like warfarin and clopidogrel illustrate well the role of inheritance in variability of drug safety and efficacy [3,7,14]. Candidate gene approaches and genome-wide association studies (GWASs) have shown important genetic markers significantly linked with the safety or the efficacy of warfarin and clopidogrel [14–18].

Herein we review the most promising genetic markers associated with the variability in the safety or efficacy of warfarin and clopidogrel and highlight the verification and validation initiatives for translating clopidogrel and warfarin pharmacogenetic tests to clinical practice.

CLOPIDOGREL

Clopidogrel is a thienopyridine antiplatelet agent widely prescribed for the prevention of ischemic events in patients with acute coronary syndrome (ACS), percutaneous coronary intervention (PCI) and myocardial infarction (MI) [19]. Despite the importance of clopidogrel in reducing the risk of adverse cardiovascular outcomes, including stent thrombosis, platelet function in response to clopidogrel varies [17,20–22]. Studies showed that about 30% of the patients taking clopidogrel do not respond effectively [17,20,21,23]. Clopidogrel is a prodrug that is rapidly absorbed from the intestine and extensively metabolized in the liver through two pathways [24–26] (Fig. 1). Several cytochrome P-450 (CYP) enzymes, including CYP2C19, work on activating clopidogrel to give an active metabolite, which irreversibly binds to the $P2Y_{12}$ receptor, resulting in the inhibition of platelet aggregation [27–29].

Clopidogrel pharmacogenetics discovery

Among genetic polymorphisms studied to date, the *CYP2C19* polymorphisms show the strongest evidence for association with variability in the efficacy and safety of clopidogrel [30–35]. *CYP2C19**2 (c.681G>A; rs4244285) creates a cryptic splice site and eventual premature stop codon. This polymorphism is the most common loss-of-function (LOF) polymorphism (Table 1) and carriers of this polymorphism have lower levels of clopidogrel active metabolite, reduced platelet inhibition, and increased risk of cardiovascular events [17,23,30, 35,36]. Conversely, the *CYP2C 19**17 (c.806C>T; rs12248560) is a common gain of function polymorphism (Table 1) in which its carriers have higher levels of active metabolite, increased platelet inhibition, and increased bleeding risk [30,35,38,39]. Other variants (*CYP2C19**3, *CYP2C19**4, *CYP2C19**5, *CYP2C19**6, *CYP2C19**7, and *CYP2C19**8) have reduced function or LOF, but most are rare [30,40–43,44■■].

Clopidogrel pharmacogenetics and cardiovascular outcomes

Recently, there was an extensive focus on defining the clinical importance of *CYP2C19* genotypes for clopidogrel response. Many studies verified the association between *CYP2C19* genotype and its clinical impact on the efficacy and safety in patients with

coronary artery disease (CAD) taking clopidogrel [17,36,38,39,45–55]. Studies consistently showed that the presence of the *CYP2C19**2 allele, especially in those patients on clopidogrel post-PCI, is associated with a significantly higher risk of adverse cardiovascular events, particularly stent thrombosis [17,32,47,51,52,55,56].

A recent meta-analysis of aggressively managed CAD patients, over 90% with a PCI, addressed the association between *CYP2C19**2 genotype and cardiovascular outcomes in 9685 patients from nine independent studies [30]. *CYP2C19**2 hetero-zygotes and homozygotes had 55 and 76% higher risk, respectively, of a composite endpoint of cardiovascular death, MI, or stroke, compared with non-carriers. This meta-analysis found carriers of the *CYP2C19**2 LOF allele had a significantly higher risk of stent thrombosis [heterozygous *CYP2C19**2: hazard ratio = 2.67, 95% confidence interval (CI) 1.69–4.22, $P < 0.0001$; homozygous *CYP2C19**2: hazard ratio = 3.97, 95% CI 1.75–9.02, $P = 0.001$], compared with noncarriers [30].

In contrast, meta-analyses focused on lower risk populations (e.g. those without PCI) showed a less profound effect of genotype, with only modest effect sizes and borderline statistical significance [48,50,57,58]. The most likely explanation for the differential impact of the association observed is that the magnitude of benefit from clopidogrel is smaller in the non-PCI patient populations, and thus it is more difficult to observe the effects of the LOF *CYP2C19* alleles [59–63].

The *CYP2C19**17 gain of function polymorphism has also been extensively studied and some studies showed a significant association between *CYP2C19**17 polymorphism and higher antiplatelet response or adverse cardiovascular events [17,38,39, 47,48,58,64–66], whereas others showed no association [17,36,67]. A recent meta-analysis found that *CYP2C19**17 carriers have a lower risk of cardiovascular events (hazard ratio = 0.75; 95% CI 0.66– 0.87; $P < 0.001$) and a higher risk of major bleeding (hazard ratio = 1.26; 95% CI 1.05–1.50; $P = 0.011$) compared with noncarriers [58].

Based on the early literature on this topic, in March 2010, the FDA added a boxed warning to the clopidogrel label. The warning stated the relationship between *CYP2C19* genotypes and drug response and recommended an alternative therapy for clopidogrel-poor metabolizer patients, meaning those homozygous for LOF alleles. Studies have shown that prasugrel and ticagrelor are good alternatives to clopidogrel in carriers with the *CYP2C19* reduced function allele [49,50], as these drugs are not impacted by *CYP2C19* genotypes [67–70].

Clinical implementation of clopidogrel pharmacogenetics testing

In 2010, the American College of Cardiology (ACC) and American Heart Association (AHA) issued a consensus statement that, in the absence of prospective randomized clinical trials, ‘the evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time’ [71]. There are mixed opinions in the clinical cardiology community on clopidogrel pharmacogenetics testing, with arguments both for [72] and against [73]. Collectively, a series of consensus statements, including the original ACC/AHA statement, suggest it might be reasonable to consider pharmacogenetics testing in high-risk PCI patients [30,61,73].

Recently, the clinical pharmacogenetics implementation consortium (CPIC) recommended guidelines for the use of *CYP2C19* genetic information to guide clopidogrel therapy in ACS/PCI patients if *CYP2C19* genetic testing results are available [44■■]. Alternative therapy is recommended in those carrying a *CYP2C19**2 allele, as shown in Fig. 2. For those carrying the *CYP2C19**1/*CYP2C19**2 genotype, increased clopidogrel dose may be an option. Studies have shown that doubling the clopidogrel maintenance dose to 150 mg per day is not

sufficient to overcome the resistance in those patients carrying the *CYP2C19**2 LOF allele [75,76]. However, a recent study by Mega *et al.* [74■] has shown that giving a clopidogrel dose of 225mg per day to *CYP2C19**2 heterozygotes provides similar levels of platelet reactivity to those achieved by non-carriers taking 75 mg per day of clopidogrel. Doses as high as 300mg per day were not sufficient to achieve similar degrees of platelet inhibition in the homozygous carriers. Although there are no data on cardiovascular outcomes for the higher dose in heterozygotes, some would argue that the platelet reactivity data support 225 mg daily as an option for the *CYP2C19**1/*CYP2C19**2 genotype.

Despite the concrete evidence of the association between *CYP2C19**2 genotype and variability in clopidogrel response, the clinical implementation of clopidogrel genetic testing is still challenging. Several institutions have established preemptive genotyping programs and tried to overcome the barriers that hinder the implementation of pharmacogenetic tests through practice [77–79]. Schildcrout *et al.* [80■] suggested an improvement in the safety and efficacy of six drugs, including clopidogrel, based on this preemptive genotyping approach.

In an attempt to overcome some of the barriers facing the implementation of clopidogrel pharmacogenetics, a novel bedside *CYP2C19**2 genetic test with a buccal swab has recently been developed (Spartan RX CYP2C19, Spartan Biosciences, Ottawa, Ontario, Canada) [81]. The rapidity of this test (results are obtained within an hour) facilitated the use of pharmacogenetics for guiding clopidogrel therapy after PCI. The verification of this test was done in a prospective, randomized proof of concept (POC) study that included 200 patients undergoing PCI [82■■]. Patients were randomized to either *CYP2C19**2 rapid point-of-care genotyping or to standard treatment. Patients in the rapid genotyping arm were screened for the *CYP2C19**2 allele. *CYP2C19**2 carriers were given 10mg per day of prasugrel, whereas noncarriers and patients in the standard treatment group were given 75 mg per day of clopidogrel. After randomization and a week of follow-up, higher risk of stent thrombosis and cardiovascular events was present in patients in the standard treatment arm than the rapid genotyping arm. This study is considered a valuable step toward clopidogrel individualization based on genetics and provides insight into the potential clinical benefits of genotype-guided clopidogrel therapy [83].

In summary, there is a solid literature suggesting the risk of reduced clopidogrel efficacy in the presence of a *CYP2C19* LOF allele. Furthermore, the recent technical advances in genotyping have made the individualization of clopidogrel based on genotype possible. Large prospective randomized trials (NCT01742117, NCT01761786 and NCT01452152) are underway to further evaluate the safety, efficacy and cost-effectiveness of *CYP2C19**2 genetic testing and its clinical utility in PCI patients. However, the data suggest the potential benefit to guide clopidogrel therapy now for those patients undergoing PCI, particularly those at high risk for adverse outcomes. Increasing numbers of centers are implementing this approach, and it may become increasingly common in clinical practice.

WARFARIN

Warfarin is a highly effective therapy, and the cheapest and the most prescribed oral anticoagulant worldwide [5,84,85]. However, warfarin's narrow therapeutic index and wide interindividual variability present challenges in its clinical utilization [3,86–88]. Many studies have shown the important role of both genetic and nongenetic factors in explaining the wide interindividual variability in warfarin dose [16,89–92]. Warfarin is a racemic mixture of *R*-warfarin and S-warfarin, in which the latter is three to five times more potent in its pharmacodynamic effect than *R*-warfarin [93]. *S*-warfarin is mainly metabolized by the CYP2C9 enzyme, whereas the R-warfarin is metabolized by other CYP-450 enzymes

[94–97]. Warfarin works by inhibiting the vitamin K epoxide reductase complex 1 (VKORC1) [98,99]. This inhibition antagonizes the conversion of oxidized vitamin K to functional reduced vitamin K, hindering the conversion of premature clotting factors to active clotting factors, causing an anticoagulation effect [100] (Supplementary Fig. 1, http://links.lww.com/HCO/A16).

Warfarin pharmacogenetics discovery

Over the last decade, many of the several hundred publications on warfarin pharmacogenetics have shown that both clinical and demographic factors explain part of the interindividual variability in warfarin dose [14,16,18,101–104]. Countless studies have consistently documented that *CYP2C9**2 (rs1799853) and *CYP2C9**3 (rs1057910) carriers require lower warfarin dose as they have 40–70% reduction in *S*-warfarin clearance, respectively [105–108], which increases bleeding risk, particularly early in the course of therapy [88,105,106]. In 2004, the gene encoding the VKORC1 enzyme was identified [98,99] and numerous studies have since documented the impact of *VKORC1* polymorphisms, particularly −1639 G>A (rs9923231), on warfarin dose requirements [14,16,18,90,92,109– 120]. Other polymorphisms in *VKORC1, CYP2C9, CYP4F2*, gamma glutamyl carboxylase (*GGCX*), epoxide hydrolase 1 (*EPHX1*), and apolipoprotein E (*APOE*) were identified, but their associations with warfarin dose requirements among African-Americans, whites and Asians were inconsistent [16,109,111,113,120–143].

Verifying the clinical utility of genotype-guided warfarin dosing

In 2007, and again in 2010, the FDA updated the warfarin label with genetic information [144]. The 2010 label includes a table to facilitate the dosing of warfarin based on *CYP2C9**2, *CYP2C9**3 and *VKORC1* (−1639 G>A) genotypes (Supplementary Table 1, http://links.lww.com/HCO/A16). Furthermore, several dosing algorithms were published to assist clinicians with genotype-guided dosing [14,18,92,104,145,146]. Among those, the Gage algorithm [18] and the International Warfarin Pharmacogenetics Consortium (IWPC) algorithm, which included more than 5000 patients from four continents, were considered the best validated and most accurate [14,147]. Furthermore, studies have shown a better prediction of warfarin dose requirements by using the IWPC algorithm compared with a clinical algorithm, and with the FDA genotype dosing table [14,144].

In an attempt to investigate the clinical utility and the accuracy of pharmacogenetic-guided dose prediction algorithms, several case–control studies and prospective randomized clinical trials have been conducted [117,118,145,148,149]. Most of those studies provided some evidence for the clinical utility of a pharmacogenetics-based approach in determining loading and maintenance doses. Nevertheless, the results from those trials were limited by small sample size, limitations in design and using surrogate outcomes [5,150]. In 2010, a prospective study compared the incidence of hospitalization during 6 months in 896 patients receiving warfarin genotyping for *CYP2C9**2, *CYP2C9**3, and *VKORC1* (−1693 G>A) versus 2688 in a matched historical control group with standard care [151]. The results of this study showed a one-third reduction in the incidence of hospitalization due to bleeding or thromboembolism in the genotyping-guided approach group compared with the standard care group (hazard ratio = 0.72). However, the results of this nonrandomized trial have been criticized because of flaws in study design, susceptibility to physician treatment bias and lack of temporal plausibility [85,152].

Most recently, CoumaGen-II, a well-powered clinical trial, provided additional support for the potential benefits of warfarin therapy initiation using warfarin pharmacogenetics-based algorithms versus warfarin standard care [153■■]. The first part of this study was a randomized double-blind trial comparing a one-step pharmacogenetics algorithm, derived

from a modified IWPC algorithm, with a three-step algorithm. The three-step pharmacogenetics algorithm was neither superior nor inferior to the one-step algorithm, suggesting the simpler one-step algorithm might be preferable in clinical practice. Furthermore, the second part of this study was a nonrandom trial comparing the clinical effectiveness of patients dosed via the pharmacogenetics algorithm versus standard of care. The pharmacogenetic algorithm arm showed 11% absolute and 26% relative reduction in the percentage of out-of-range international normalized ratio (%OOR INR) at 1 month compared with the standard dosing care. Additionally, a similar difference in %OOR INR was also shown between the two groups after 3 months. Moreover, patients with pharmacogenetic dosing also had a higher percentage of time in the therapeutic range at 1 and 3 months (68 and 71%, respectively) compared with standard dosing (58 and 59%; $P<$ 0.001). Furthermore, there were also statistical differences in clinical outcomes that favored pharmacogenetic dosing. Despite the concern of confounding and bias due to the non-randomization of the standard care management group [5,154], this study provided insight into the promise of pharmacogenetics in controlling warfarin therapy, suggesting the broader use of warfarin pharmacogenetic dosing in clinical practice.

Clinical implementation of warfarin pharmacogenetics testing

The warfarin CPIC guidelines recommended the Gage or the IWPC dosing algorithms as the preferred approaches for estimating the stable warfarin dose [155■■]. They secondarily recommended the FDA dosing table as an alternative approach in case of absence of electronic access to these algorithms. Moreover, they have suggested that inclusion of polymorphisms confined to a particular population, such as *CYP2C9**5, *CYP2C9**6, *CYP2C9**8, and *CYP2C9**11 in African–Americans, might help in better estimating the stable warfarin dose required. On the basis of these findings, more studies are underway to detect other genetic and nongenetic factors associated with warfarin dose variability in underrepresented populations [156,157].

Rapid and affordable genotyping is a commonly cited barrier facing the implementation of warfarin pharmacogenetics. In an attempt to facilitate the clinical utilization of warfarin pharmacogenetic testing, a POC warfarin-based genetic test was recently validated. This test provides precise results in less than 2h [158]. Additionally, one of the largest ongoing randomized trials, European Pharmacogenetics of Anticoagulant Therapy, is using a genotyping test that can be done at the bedside or in the clinic using whole blood and provides results within 1.5h [159]. Other scientists are working on designing and evaluating faster and simpler methods for warfarin pharmacogenetic testing [160]. Although the genotyping cost for one patient might range from less than US$ 25 to about US$ 200 for commercial platforms, the rapid advances in genotyping and sequencing technologies promise rapid genotyping with lower cost.

Despite the strong evidence for the clinical and analytical validity of warfarin pharmacogenetic testing, at least for whites, its clinical use is still limited. Accordingly, large randomized controlled trials are underway to assess the use of warfarin pharmacogenetics in clinical practice (Table 2). Furthermore, scientists worldwide are intensifying their efforts to identify other genetic and nongenetic factors that might be associated with warfarin dose variability in nonwhites.

CONCLUSION

Pharmacogenetics holds the promise of giving the right drug to the right patient with the right dose. The rapid advances in pharmacogenetics have offered compelling evidence toward the individualization of clopidogrel and warfarin therapies (Fig. 3). Despite the concrete literature supporting the importance of pharmacogenetics in tailoring both

therapies, several barriers, like turnaround time of genotyping, cost, and lack of large randomized clinical data to confirm beneficial outcomes of pharmacogenetic testing, still limit its clinical implementation. The rapid advances in genotyping and the recent POC devices hold promise to overcome the problem of turnaround time. Furthermore, the approach of preemptive genotyping might also be helpful in overcoming some of those barriers, as, in the future, it is envisioned that large amounts of genetic information will be generated on a person at some point in his life and then stored in his medical record for future use. This would facilitate the clinical implementation of clopidogrel and warfarin pharmacogenetics, where a delay in therapy initiation is not typically possible. Moreover, results from the ongoing large randomized trials will further define the role of clopidogrel and warfarin pharmacogenetics in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by NIH grants U01 HL074492, RO1 NS073346 and UL1 TR000064.

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- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 371).

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KEY POINTS

- A large number of studies have shown important genetic markers significantly associate with the safety or the efficacy of clopidogrel and warfarin.
- The FDA has updated clopidogrel and warfarin label with genetic information and guidelines have been established to assist clinicians in prescribing clopidogrel or warfarin dose based on genotype.
- Despite the strong evidence for the clinical and analytical validity of clopidogrel and warfarin pharmacogenetic testing, however, its clinical utility is still limited.
- Large randomized clinical trials are underway to define the role of clopidogrel and warfarin pharmacogenetics in clinical practice.

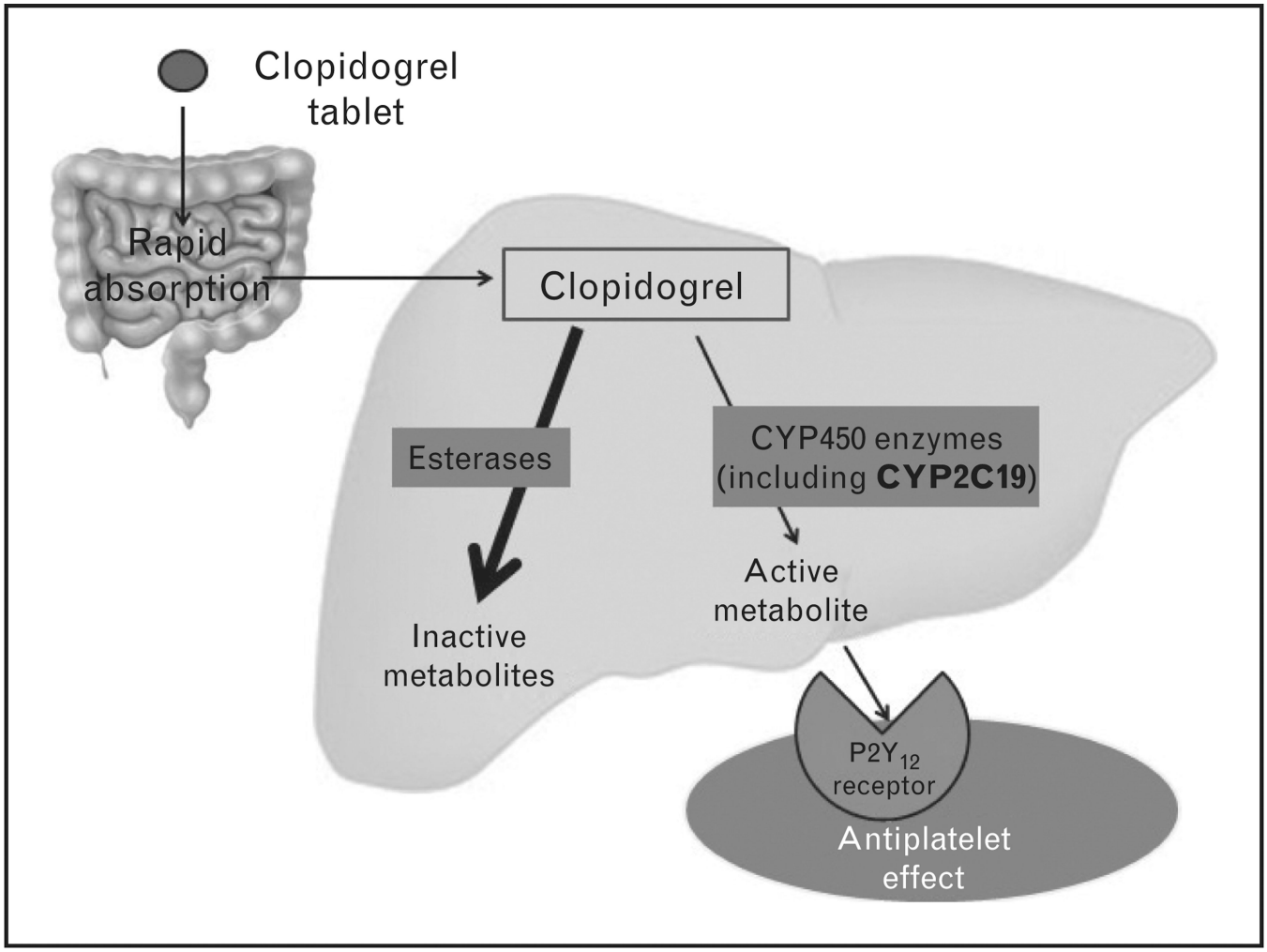

FIGURE 1.
Clopidogrel pharmacokinetics and pharmacodynamics.

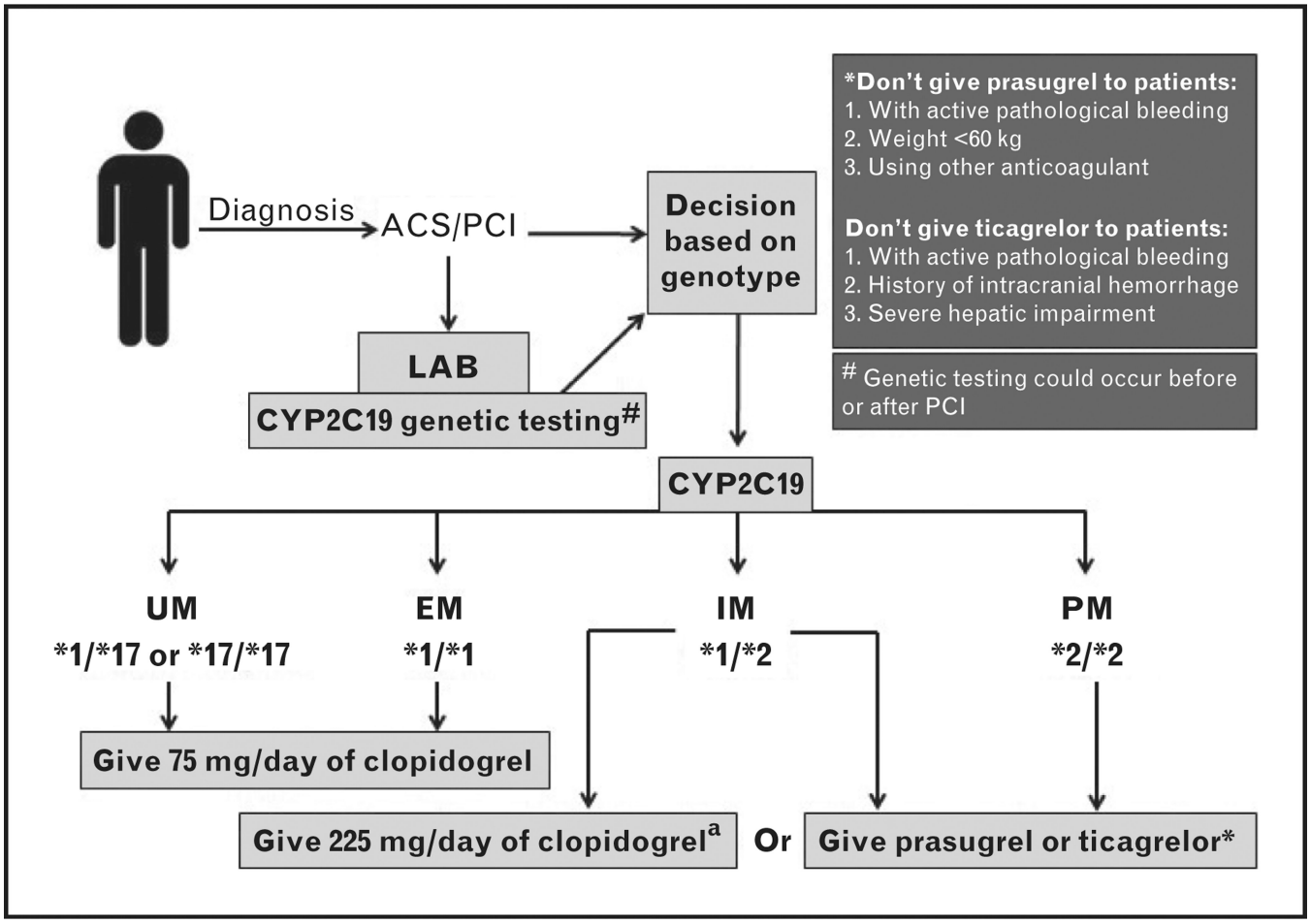

FIGURE 2.

Evidence-based clopidogrel dosing based on CYP2C19 genotype in acute coronary syndrome / percutaneous coronary intervention patients (ACS/PCI), adapted from CPIC guidelines [44■■] with revisions based on more recent literature. UM, ultra metabolizer; EM, extensive metabolizer; IM, intensive metabolizer; PM, poor metabolizer. [a]It is preferable to use the alternative antiplatelet (prasugrel or ticagrelor) as a first option unless there are any contraindications to its use. Giving a clopidogrel dose of 225 mg per day to *CYP2C19**2 heterozygote carriers was reported to be sufficient for getting similar levels of platelet reactivity achieved by noncarriers taking 75 mg per day of clopidogrel [74■]. However, further studies are still needed to confirm this finding.

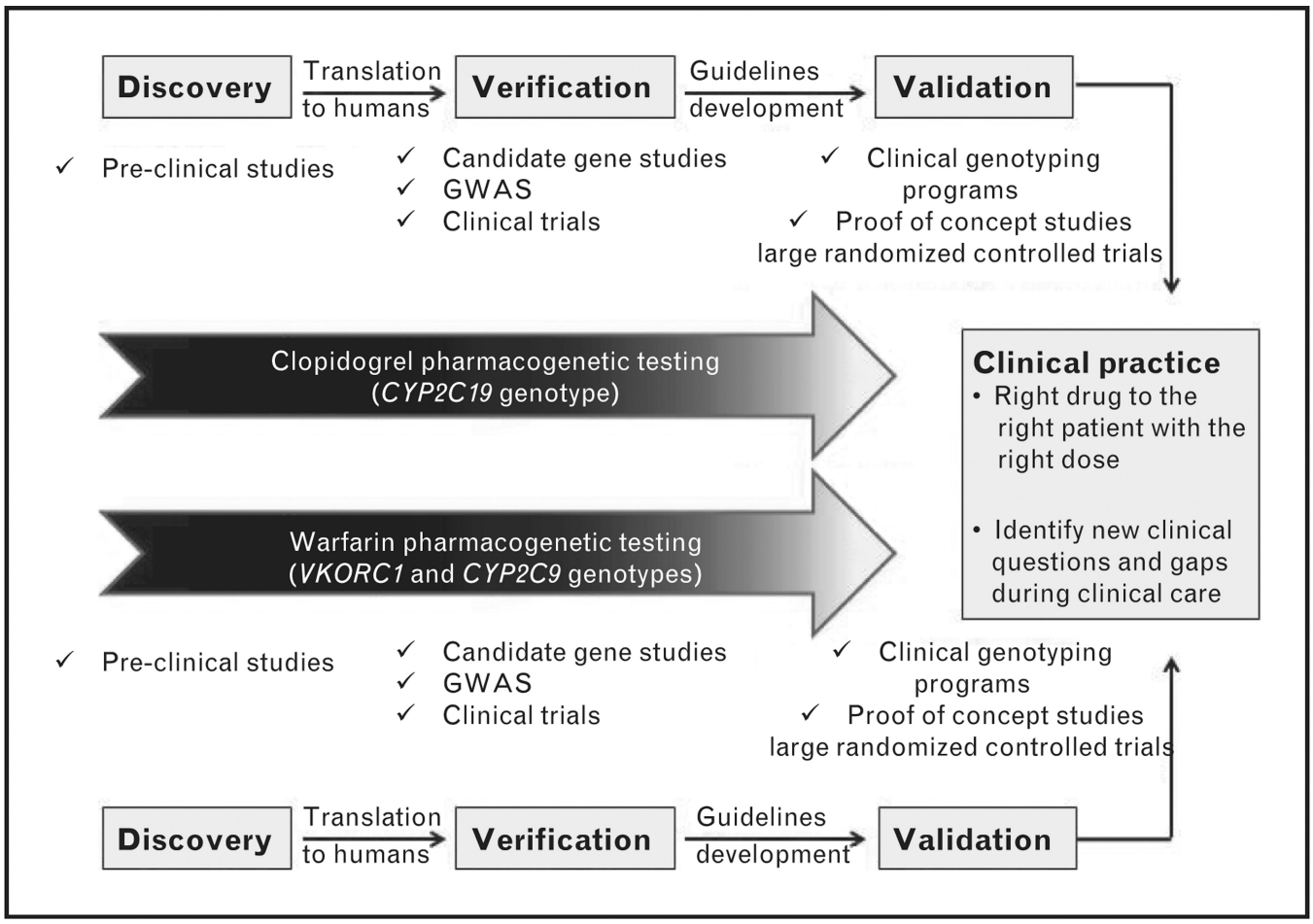

FIGURE 3.
Status of clopidogrel and warfarin pharmacogenetics: from identification toward clinical implementation. GWAS, genome-wide association studies.

Table 1

Population prevalence of CYP2C*2, CYP2C*3, and CYP2C*17 genetic polymorphisms and their effect on clopidogrel response

Genetic polymorphism (rs#)	Asians[a]	Whites[a]	African–Americans[a]	Effect
*CYP2C19**2 (rs4244285)	55%	28%	24%	↓Active metabolite concentration
				↓ Antiplatelet effect
				↑Risk of cardiovascular events
*CYP2C19**3[b] (rs4986893)	17%	<1%	<1%	↓ Active metabolite concentration
				↓ Antiplatelet effect
				↑ Risk of cardiovascular events
*CYP2C19**17 (rs12248560)	4%	41%	23%	↑ Active metabolite concentration
				↑ Antiplatelet effect
				↑ Risk of bleeding

[a] Population prevalence of carrying at least one of the variant alleles in this polymorphism derived from http://hapmap.ncbi.nlm.nih.gov/ and http://browser.1000genomes.org/index.html.

[b] Not sufficiently studied on its own but many studies lumped it together with other loss of function alleles [36,37].

Table 2

Ongoing randomized controlled trials evaluating pharmacogenetic-guided warfarin dosing

Study	Targeted enrolment	Design	Primary endpoint
COAG (NCT00839657)[b] [161]	1238	Multicenter, DB, two arms PGx vs clinical algorithm[a]	PTTR during the first 4 weeks of Therapy
EU-PACT (NCT01119300)[b] [159]	970	Multicenter, SB, two arms PGx vs clinical algorithm	PTTR during the first 12 weeks of therapy
GIFT (NCT01006733)[b] [162]	1600	Multicenter, DB, two arms PGx vs clinical algorithm[a]	Composite of: nonfatal VTE, nonfatal major hemorrhage, death from any cause, and INR ≥4.0
WARFARIN (NCT01305148)[b]	4300	Multicenter, DB, two arms GenoSTAT test (PGx)+clinical factors vs clinical factors alone	Incidence of major hemorrhage and thromboembolic events during the first 30 days of therapy
Pharmacogenetic dosing of warfarin: a controlled randomized trial	600	Three arms study IWPC PGx vs Taiwanese algorithm vs standard care	Time to target INR and PTTR

COAG, Clarification of Optimal Anticoagulation through Genetics; DB, double blind; EU-PACT, European Pharmacogenetics of Anticoagulant Therapy; GIFT, Genetics Informatics Trial; INR, international normalized ratio; IWPC, International Warfarin Pharmacogenetic Consortium; PGx, pharmacogenetics; PTTR, percentage of time within therapeutic range; SB, single blind; VTE, venous thromboembolic event; WARFARIN, Warfarin Adverse Event Reduction For Adults Receiving Genetic Testing at Therapy Initiation.

[a]Each study arm includes a baseline dose initiation algorithm and a dose revision algorithm applied over the first four to five doses of warfarin therapy.

[b]Further information can be found at www.clinicaltrials.gov.