Cytochrome P450 Genetic Polymorphisms and the Response to Prasugrel
Relationship to Pharmacokinetic, Pharmacodynamic, and Clinical Outcomes

Jessica L. Mega, MD, MPH; Sandra L. Close, PhD; Stephen D. Wiviott, MD; Lei Shen, PhD; Richard D. Hockett, MD; John T. Brandt, MD; Joseph R. Walker, PharmD; Elliott M. Antman, MD; William L. Macias, MD, PhD; Eugene Braunwald, MD; Marc S. Sabatine, MD, MPH

Background—Both clopidogrel and prasugrel require biotransformation to active metabolites by cytochrome P450 (CYP) enzymes. Among persons treated with clopidogrel, carriers of reduced-function CYP2C19 alleles have significantly lower levels of active metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events. The effect of CYP polymorphisms on the clinical outcomes in patients treated with prasugrel remains unknown.

Methods and Results—The associations between functional variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to prasugrel were tested in 238 healthy subjects. We then examined the association of these genetic variants with cardiovascular outcomes in a cohort of 1466 patients with acute coronary syndromes allocated to treatment with prasugrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 trial. Among the healthy subjects, no significant attenuation of the pharmacokinetic or the pharmacodynamic response to prasugrel was observed in carriers versus noncarriers of at least 1 reduced-function allele for any of the CYP genes tested (CYP2C19, CYP2C9, CYP2B6, CYP3A5, and CYP1A2). Consistent with these findings, in subjects with acute coronary syndromes treated with prasugrel, no significant associations were found between any of the tested CYP genotypes and risk of cardiovascular death, myocardial infarction, or stroke.

Conclusions—Common functional CYP genetic variants do not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovascular event rates in persons treated with prasugrel. These pharmacogenetic findings are in contrast to observations with clopidogrel, which may explain, in part, the different pharmacological and clinical responses to the 2 medications. (Circulation. 2009;119:2553-2560.)

Key Words: cardiovascular diseases • drugs • genetics

Treatment with the thienopyridine clopidogrel reduces cardiovascular death and ischemic complications in patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI) with stenting and has been widely adopted in clinical practice.1–3 However, the interpatient variability in the pharmacodynamic response to clopidogrel is well recognized,4–6 and patients with coronary artery disease with lesser degrees of platelet inhibition in response to clopidogrel have been shown to be at increased risk of cardiovascular events.7–9 Prasugrel is a third-generation thienopyridine that achieves greater platelet inhibition than does clopidogrel with less variability.10 The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38) trial demonstrated that, compared with clopidogrel, treatment with prasugrel resulted in a significantly lower rate of ischemic events and more bleeding among patients presenting with ACS with planned PCI.11

Clinical Perspective on p 2560

Both clopidogrel and prasugrel are prodrugs that require biotransformation to active metabolites by cytochrome P450 (CYP) enzymes. Although the active metabolites of both drugs have similar affinity for the P2Y12 receptor in vitro, the in vivo difference in response appears to be mediated predominantly by differences in the metabolic pathways leading
to the formation of the active metabolites. Esterases shunt the majority of clopidogrel to a dead-end inactive pathway, with the remaining prodrug requiring 2 separate CYP-dependent oxidative steps. In contrast, esterases are part of the activation pathway with prasugrel, and prasugrel is oxidized to its active metabolite in a single CYP-dependent step, without an apparent dead-end inactive pathway (Figure 1).

The genes that encode the CYP enzymes are polymorphic, with certain alleles demonstrated to confer reduced enzymatic function, thereby interfering with production of the drug metabolites. These reduced-function alleles, particularly in CYP2C19, have been shown to affect the pharmacokinetic and pharmacodynamic responses to clopidogrel. Moreover, in the setting of treatment with clopidogrel, patients carrying reduced-function CYP2C19 alleles compared with noncarriers have substantially higher rates of major adverse cardiovascular events, including stent thrombosis.

The effect of CYP polymorphisms on the clinical outcomes in patients treated with prasugrel remains unknown. To address this question, we examined the association of functional polymorphisms in CYP genes with plasma exposure to prasugrel active metabolite levels and platelet inhibition in 238 healthy individuals. We then determined whether reduced-function CYP alleles were associated with adverse cardiovascular outcomes in a separate cohort of 1466 ACS patients allocated to treatment with prasugrel in TRITON–TIMI 38.

Methods

Pharmacokinetics and Pharmacodynamics

Healthy subjects in 6 studies (n=238) involving prasugrel were included in the pharmacokinetic and pharmacodynamic analyses (Table I in the online-only Data Supplement). Plasma concentrations of prasugrel active metabolites were measured by liquid chromatography with mass spectrometry. The area under the plasma concentration-time curve from time of dose to last measurable concentration (AUC$_{0-t}$) of prasugrel active metabolite was computed by noncompartmental methods of analysis with the log-linear trapezoidal method. The pharmacodynamic response, assessed with the use of light transmission aggregometry in response to 20 μmol/L ADP, was expressed as absolute reduction in maximal platelet aggregation from baseline (ΔMPA).

Clinical Outcomes

In the TRITON–TIMI 38 trial, patients with ACS with planned PCI who were randomly allocated to treatment with prasugrel received a 60-mg loading dose followed by 10 mg daily for up to 15 months. The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, or stroke. A key prespecified secondary end point was definite or probable stent thrombosis as defined by the Academic Research Consortium. Safety end points included non–coronary artery bypass graft-related TIMI major or minor bleeding. All outcomes were adjudicated by a blinded clinical events committee.

The prasugrel pharmacogenetic analysis included 1466 patients who provided a DNA sample (Table II in the online-only Data Supplement). All studies were approved by institutional review boards, and written informed consent was obtained from subjects.

Genotyping Methodology

Genotyping was performed with the use of the Affymetrix Targeted Human DMET (drug-metabolizing enzymes and transporters) 1.0 Assay (Affymetrix, Santa Clara, Calif; 98% of genotypes) and bidirectional sequencing or exon-specific polymerase chain reaction amplification followed by restriction fragment length polymorphism gel electrophoresis in the case of CYP2C19*17 or a no-call on the DMET chip (2% of genotypes). A total of 54 alleles, comprising the known major functional variants, were determined with the use of clinically validated assays for CYP2C19, CYP2C9, CYP2B6, CYP3A5, CYP3A4, and CYP1A2 (Table III in the online-only Data Supplement). Of note, the tested alleles in CYP3A4 were not polymorphic, leaving 5 genes for analysis. Genotypes were presumed to be in Hardy-Weinberg equilibrium if the P value was >0.001 (0.05/50 alleles=0.001).

CYP Genotype Classifications

Each allele of the CYP genes was classified a priori by its known effect on enzymatic function according to the literature and with the use of the established common-consensus star allele nomenclature. For each CYP gene, subjects were dichotomized a priori into 2 groups on the basis of whether or not they possessed at least 1 significantly reduced-function allele. Table IV in the online-only Data Supplement describes the measured alleles, observed genotypes, and their classification.
Statistical Analysis
The associations between genetic variation and pharmacokinetic and pharmacodynamic parameters were tested with the use of likelihood ratio tests based on linear mixed-effects models, with the primary outcomes being exposure to active drug metabolite [$\log(\text{AUC}_{0-t})$] and platelet inhibition ($\Delta\text{MPA}$). The models contained subject as a random effect, reduced-function allele carrier status as the predictor of main interest, and other fixed effects including study, dose, and ethnicity and, for pharmacodynamics, time, dose-by-time interaction, and baseline MPA. To account for other potential baseline differences, additional demographic variables including age, sex, weight, and smoking were included as determined by forward selection for each model. Two-sided $P$ values were calculated, and a significance threshold of $P<0.01$ was used to correct for multiple hypotheses testing for the 5 CYP genes.

For clinical outcomes, rates of the end points were expressed as Kaplan–Meier estimates at 15 months and were compared between carriers and noncarriers of at least 1 reduced-function CYP allele. Consistent with the primary trial analyses, the Gehan–Wilcoxon test was used for the primary efficacy end point, and the log-rank test was used for other end points.\(^{11}\) Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated on the basis of Cox proportional hazards regression models with clinical syndrome (non–ST-segment ACS versus ST-elevation myocardial infarction) as a stratification factor. If a statistically significant relationship was found between genotype and prasugrel pharmacokinetics and pharmacodynamics, then this genotype was to be carried forward as the primary hypothesis with a $P$ value threshold of $<0.05$. Because none was found, the associations between CYP genes and clinical outcomes were conducted in an exploratory manner, with 2-sided $P$ values calculated and a significance threshold of $P<0.01$ used to correct for multiple hypotheses testing for the 5 genes.

To assess whether statistically significant heterogeneity exists in the effect of $CYP2C19$ genetic variation on pharmacokinetic and pharmacodynamic parameters in prasugrel-treated subjects versus our previous observations in these same study populations for clopidogrel-treated subjects,\(^{23}\) formal interaction terms were tested in linear mixed-effects models containing data from the healthy subject studies involving treatment with both clopidogrel and prasugrel (N=346). In an analogous fashion, a formal interaction term was tested in a Cox proportional hazards model in the entire TRITON–TIMI 38 genetic data set (N=2943).

In keeping with the informed consent and privacy policies, all genetic data reside with the sponsor in a deidentified database behind a firewall and were analyzed by statisticians distinct from those with access to the clinical database. The genetic studies were designed and performed as a collaboration between the TIMI Study Group and the sponsors, Eli Lilly and Daiichi Sankyo. Academic authors directed and had access to all the analyses as well as the full clinical database, wrote all drafts of the manuscript, decided to publish the results, and vouch for the accuracy and completeness of the data.

Results
Pharmacokinetics and Pharmacodynamics
DNA samples were available for 238 healthy subjects for the pharmacokinetic and pharmacodynamic analyses. Their average age was 33.9±14.6 years, and 26.9% were women. After 4 hours, treatment with a 60-mg dose of prasugrel resulted in an absolute reduction of MPA of 70.6±11.1 percentage points.

The association between being a carrier of a reduced-function CYP allele and plasma exposure to the prasugrel active metabolite and platelet inhibition is presented in Figure 2. Carrier status for a reduced-function allele was not associated with an attenuation of either the pharmacokinetic or pharmacodynamic response to prasugrel for any of the CYP genes evaluated. Moreover, even when an extended $CYP2C19$ genotypic classification was used (ultrarapid, extensive, intermediate, and poor metabolizer genotypes; Table IV in the online-only Data Supplement), no association was found between $CYP2C19$ genotype and pharmacokinetic or pharmacodynamic response (Figure in the online-only Data Supplement). In an analysis of the healthy subjects studies involving treatment with both clopidogrel and prasugrel, the interaction between $CYP2C19$ and thienopyridine treatment group was significant for both the pharmacokinetic effect ($P<0.0001$) and the pharmacodynamic effect ($P=0.015$), demonstrating heterogeneity in the pharmacological impact of $CYP2C19$ reduced-function alleles between subjects treated with clopidogrel and those treated with prasugrel.

Clinical Outcomes
DNA samples were available in 1466 subjects allocated to treatment with prasugrel in the TRITON–TIMI 38 trial. Their average age was 60.3±10.7 years, 27.3% were female, 69.8% presented with non–ST-segment elevation ACS, and 30.2% presented with ST-segment elevation myocardial infarction.

Consistent with the pharmacokinetic and pharmacodynamic results, no significant associations between any of the tested CYP genotypes and the TRITON–TIMI 38 primary efficacy end point (cardiovascular death, myocardial infarction, or stroke) were observed (Table 1). Notably, prasugrel-treated patients exhibited no association between $CYP2C19$ genotype and the primary efficacy end point (8.5% for carriers versus 9.8% for noncarriers; HR, 0.89; 95% CI, 0.60 to 1.31; $P=0.27$; Figure 3). In an analysis of the entire TRITON–TIMI 38 genetic data set, the interaction between $CYP2C19$ and thienopyridine treatment group was significant ($P=0.046$), demonstrating heterogeneity in the clinical impact of $CYP2C19$ reduced-function alleles between subjects treated with clopidogrel and those treated with prasugrel.

When we examined each component of the primary efficacy end point, no difference in hazard was observed among...
Discussion

Treatment with the thienopyridine clopidogrel is frequently used after an ACS or PCI with stenting to reduce ischemic complications. However, there has been a growing appreciation of the variability in the pharmacological as well as the clinical response to clopidogrel, with genetic polymorphisms in CYP genes explaining some of this variation. In contrast, prasugrel has been found to display less pharmacological variability than clopidogrel. We now show that common functional CYP genetic variants do not affect active metabolite levels, platelet inhibition, or clinical cardiovascular events among individuals treated with prasugrel.

Clopidogrel and prasugrel are both prodrugs and require oxidation by similar CYP enzymes (Figure 1). However, CYP genetic variants may have different influences on the pharmacological and clinical responses to clopidogrel and prasugrel because of the differences in the metabolic pathways of the 2 thienopyridines. Approximately 85% of clopidogrel is shunted into an inactive metabolite by esterases. As such, genetic variants that slow the first CYP-oxidative step involved in clopidogrel metabolism may divert the prodrug preferentially into a dead-end pathway. In contrast, esterases are part of the activation pathway for prasugrel, and even in the setting of delayed CYP oxidation, no inactivation pathway is involved in prasugrel metabolism. Additionally, clopidogrel requires 2 CYP-oxidative steps, whereas prasugrel requires only 1.

Genetic variants in CYP2C19 have been shown to alter the pharmacokinetics and pharmacodynamics of clopidogrel. The most influential of these appears to be the CYP2C19*2 allele, a loss-of-function polymorphism that encodes a cryptic splice variant that leads to loss of enzymatic activity.31 In several platelet aggregation studies, platelet inhibition in response to clopidogrel was significantly less in carriers compared with noncarriers of a CYP2C19 reduced function allele compared with noncarriers for cardiovascular death (0.99% versus 1.58%; HR, 0.80; 95% CI, 0.26 to 2.47; \( P = 0.70 \)), nonfatal myocardial infarction (6.6% versus 8.1%; HR, 0.82; 95% CI, 0.53 to 1.27; \( P = 0.37 \)), or nonfatal stroke (1.0% versus 0.82%; HR, 1.30; 95% CI, 0.39 to 4.31; \( P = 0.67 \)). Likewise, no significant relationship between CYP2C19 genotype and stent thrombosis was observed (0.5% for carriers versus 1.0% for noncarriers; HR, 0.58; 95% CI, 0.13 to 2.69; \( P = 0.48 \); Figure 4) among patients allocated to treatment with prasugrel.

Rates of non–coronary artery bypass graft–related TIMI major or minor bleeding did not differ statistically by CYP genotype among prasugrel-treated subjects (Table 2).
noncarriers of this variant.\textsuperscript{16,17,20–22} We have recently shown not only that genetic variants in \textit{CYP2C19}, particularly \textit{CYP2C19*2}, significantly diminish both the pharmacokinetic and pharmacodynamic responses to clopidogrel by approximately one quarter to one third but also that the same variants are associated with a \textit{H11022}50\% higher rate of cardiovascular death, myocardial infarction, or stroke and a 3-fold higher rate of stent thrombosis in patients treated with clopidogrel in the TRITON–TIMI 38 trial.\textsuperscript{23} In another study, only homozygotes for a \textit{CYP2C19} reduced-function allele variant were found to be at risk of increased cardiovascular events.\textsuperscript{24} However, 3 additional studies demonstrate that individuals who carry at least 1 copy of \textit{CYP2C19*2} have worse clinical outcomes than noncarriers in the setting of treatment with clopidogrel.\textsuperscript{25,32,32a} Thus, the totality of the pharmacokinetic, pharmacodynamic, and clinical outcomes data suggests that both heterozygotes and homozygotes for the \textit{CYP2C19*2} allele are at increased risk of adverse events in the setting of treatment with clopidogrel.

Although reduced-function polymorphisms in \textit{CYP2C19} have been linked to lesser pharmacological responses and worse clinical outcomes among individuals treated with clopidogrel, no other clinical studies have been able to examine a group of subjects that could be considered a control group: those with the same \textit{CYP} genetic variants treated with an alternative thienopyridine. It is possible that variants in \textit{CYP2C19} would alter the pharmacological response to all thienopyridines. Moreover, \textit{CYP2C19} variants themselves could be associated with an increase in adverse cardiovascular events in patients after an ACS, regardless of treatment with clopidogrel.

However, our data show that a significant impact of reduced-function \textit{CYP2C19} alleles appears to be confined to patients taking clopidogrel, as \textit{CYP2C19} variants do not significantly affect pharmacological or clinical outcomes in patients treated with prasugrel (Figure 5). Specifically, among persons treated with prasugrel, carriers of a \textit{CYP2C19} reduced-function allele did not have lower prasugrel active metabolite levels or lesser degrees of platelet inhibition compared with noncarriers. Furthermore, carriers and noncarriers of such alleles treated with prasugrel experienced similar rates of cardiovascular death, myocardial infarction, or stroke. Notably, the 95\% CI in this study for the risk of cardiovascular death, myocardial infarction, or stroke in \textit{CYP2C19} carriers versus noncarriers treated with prasugrel excludes a HR down to 1.31, well below what was seen in the 3 aforementioned associations evaluating \textit{CYP2C19} genetic variants and clinical outcomes among patients treated with clopidogrel.\textsuperscript{23–25,32,32a} Additionally, significant interactions

\begin{table}[h]
\centering
\caption{Safety End Point by Genotype Status at 15 Months in Patients Treated With Prasugrel}
\begin{tabular}{llllllll}
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Gene & Carriers of Reduced-Function Allele & & Noncarriers & & HR (95\% CI) & & \(P\) \\
\hline
\textit{CYP2C19} & 4.5 17/405 & 3.8 & 38/1047 & 1.17 (0.66–2.07) & & 0.60 \\
\textit{CYP2C9} & 5.5 12/233 & 3.7 & 42/1211 & 1.48 (0.78–2.82) & & 0.23 \\
\textit{CYP2B6} & 2.3 7/329 & 4.2 & 31/795 & 0.55 (0.24–1.25) & & 0.15 \\
\textit{CYP3A5} & 3.7 39/1092 & 5.5 & 8/157 & 0.71 (0.33–1.52) & & 0.38 \\
\textit{CYP1A2} & 2.7 2/75 & 3.8 & 39/1090 & 0.77 (0.19–3.19) & & 0.72 \\
\hline
\end{tabular}
\end{table}

Rates are expressed as Kaplan–Meier cumulative incidence estimates over 15 months. Not all alleles for all genes were successfully genotyped, and not all patients could be classified as a carrier or noncarrier.
were found between CYP2C19 and the thienopyridine treatment group, demonstrating that the effect of CYP2C19 reduced-function polymorphisms on pharmacological and clinical outcomes was different in clopidogrel-treated individuals versus in prasugrel-treated individuals. Because reduced-function variants of CYP2C19 are common, occurring in 30% of whites, 40% of blacks, and >55% of East Asians,33–33b the effective use of clopidogrel might involve consideration of CYP2C19 genotyping or pharmacodynamic monitoring. Alternatively, use of prasugrel would avoid this issue, albeit with an increased risk of bleeding.

Although no consistent effect of genotype was found across pharmacokinetic, pharmacodynamic, and clinical outcomes with any of the tested CYP genes for prasugrel, model-based estimates and 95% CIs for CYP2C19 genetic effects on the pharmacokinetic (percent difference in AUC\textsubscript{0-t}) and pharmacodynamic (\Delta\textsubscript{MPA}) parameters in healthy subjects and clinical outcomes in subjects in TRITON–TIMI 38. Numbers to the right of each graph are the point estimate and corresponding \(P\) value. \(P\) values for the interaction terms between carriage of a reduced-function CYP2C19 allele and thienopyridine treatment group are presented on the far right. Clopidogrel data adapted from Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360:354–362.33

Figure 5. For individuals treated with clopidogrel and for those treated with prasugrel, model-based estimates and 95% CIs for CYP2C19 genetic effects on the pharmacokinetic (percent difference in AUC\textsubscript{0-t}) and pharmacodynamic (\Delta\textsubscript{MPA}) parameters in healthy subjects and clinical outcomes in subjects in TRITON–TIMI 38. Numbers to the right of each graph are the point estimate and corresponding \(P\) value. \(P\) values for the interaction terms between carriage of a reduced-function CYP2C19 allele and thienopyridine treatment group are presented on the far right. Clopidogrel data adapted from Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360:354–362.33

In conclusion, among healthy individuals treated with prasugrel, no CYP genetic variants were found that affected active drug metabolite levels and platelet inhibition. In ACS patients treated with prasugrel who underwent PCI, no CYP genetic variants affected cardiovascular outcomes. These genetic observations explain some of the differences in the DMET 1.0 Assay and therefore were not tested, such as *27 and *5 in CYP2B6, and other non-CYP genes that may be pertinent to the pharmacological response prasugrel and deserve exploration.34 Second, this analysis tested the association between CYP genetic variants and a 60-mg loading dose and 10-mg maintenance dose of prasugrel; other doses were not evaluated. Additionally, the pharmacokinetic and pharmacodynamic sampling was conducted in 6 healthy cohorts of subjects. Because of the need for precise sample handling, these assessments could not be uniformly conducted in the several hundred sites around the world enrolling patients in TRITON–TIMI 38. Finally, the absence of another large prasugrel clinical trial precludes replication of the clinical findings; however, in an independent cohort of healthy subjects, we did not observe any impact of the CYP variants on active metabolite levels and platelet inhibition in response to prasugrel. Given the established association between the degree of platelet inhibition with thienopyridines and clinical outcomes,7–9 the totality of our data supports the notion that these variants do not have a clinical impact.
pharmacological and clinical response to treatment with prasugrel compared with clopidogrel and potentially could be used to help tailor pharmacotherapy in the future.

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**Disclosures**

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**References**


Clopidogrel has been shown to reduce cardiovascular events in acute coronary syndrome patients. However, interpatient variability in the response to clopidogrel is well recognized, and individuals with lesser degrees of platelet inhibition are at increased risk of death and ischemic complications. Prasugrel is a newer, third-generation thienopyridine that achieves greater platelet inhibition than clopidogrel with less variability. Clopidogrel and prasugrel are prodrugs and require biotransformation to an active metabolite by cytochrome P450 (CYP) enzymes, although the exact activation pathways differ between the 2 drugs. Among persons treated with clopidogrel, carriers of reduced-function CYP2C19 genetic variants (~30% of the population) have been shown to have significantly lower levels of active drug metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events. In this study, we examined the associations between functional variants in CYP genes (CYP2C19, CYP2C9, CYP2B6, CYP3A5, and CYP1A2) and the pharmacological response to prasugrel in 238 healthy subjects and the association of these genetic variants with cardiovascular outcomes (cardiovascular death, myocardial infarction, or stroke) in a cohort of 1466 patients with acute coronary syndrome allocated to treatment with prasugrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 trial. No difference was found in the active drug metabolite levels, platelet inhibition, and rates of adverse cardiovascular events in carriers versus noncarriers of at least 1 reduced-function allele for any of the CYP genes tested. These pharmacogenetic findings with prasugrel are in contrast to observations with clopidogrel, which may explain, in part, the different pharmacological and clinical responses to the 2 medications.