The efficacy of various antiplatelet agents in preventing cardiovascular and thrombotic complications has been established in large-scale clinical trials. Composite data from such studies tend to mask individual variability in responsiveness to the drugs being investigated. In fact, antiplatelet drugs that are effective and safe in one individual may be ineffective or harmful in another.1

Individual heterogeneity in responsiveness to antiplatelet agents may be due to either inherited or acquired factors. These potential variables include genetic polymorphisms in platelet proteins targeted by the drugs, differences in their pharmacokinetics, drug or other environmental interactions, and the baseline state of platelet function before initiation of treatment. With regard to the latter factor, just as underlying platelet dysfunction increases the risk of bleeding with antiplatelet therapy, it could be predicted that intrinsic platelet hyperaggregability should cause resistance to antiplatelet agents. Indeed, recent studies have demonstrated that pretreatment platelet hyperreactivity is an important determinant of resistance to antiplatelet therapy.2,3 Although intrinsic platelet hyperreactivity may be due to acquired factors, such as accelerated vascular disease (eg, acute coronary syndrome), hypertension, diabetes, or smoking, it can also be caused by genetic factors. A study of sibships drawn from a large, population-based sample without overt cardiovascular disease demonstrated that hereditary factors play an important role in the marked interindividual differences in ex vivo platelet aggregability.4

Failure of aspirin to produce expected inhibition of platelet function can be due to genetic determinants or to interference with its antiplatelet action by other drugs. A substantial proportion of individuals treated with aspirin do not achieve the inhibitory response anticipated on laboratory measures of platelet activation and aggregation, a phenomenon termed “aspirin resistance.”5,6 The clinical relevance of aspirin resistance was recently demonstrated in a study of stable patients with cardiovascular disease who were found to have a greater than threefold increase in the risk of major adverse events during long-term follow-up compared with those on aspirin who exhibited normal inhibition of platelet aggregation.7 Aspirin resistance has been associated with the PI42 genotype, a common polymorphism of the platelet glycoprotein (GP) IIIa gene, a component of the GP Ib/IIa complex that forms the platelet fibrinogen receptor.1,8 Other platelet polymorphisms that could theoretically confer genetic resistance to aspirin include those for the cyclooxygenase isoforms directly targeted by aspirin, other arachidonic acid–mobilizing and –metabolizing enzymes (phospholipases, thromboxane synthase), and other membrane GP receptors involved in initiation of platelet activation. The antiplatelet actions of aspirin can also be antagonized by interactions with certain drugs used concurrently. In particular, nonsteroidal antiinflammatory drugs (NSAIDs), but not selective cyclooxygenase-2 inhibitors, competitively block the ability of low-dose aspirin to cause inhibition of platelet function. Concomitant administration of NSAIDs may thus potentially compromise the cardioprotective effects of aspirin.9 The clinical impact of this drug–drug interaction has yet to be demonstrated.

Clinical trials of the different classes of GP IIb/IIia antagonists have likewise revealed interindividual variability in platelet aggregation inhibition and protective clinical response. The reasons some patients have a subtherapeutic response to GP IIb/IIia inhibitors are unknown, but polymorphisms in the GP IIb/IIia complex could potentially contribute to relative resistance to these drugs.10 The thienopyridines ticlopidine and clopidogrel inhibit platelet function by irreversibly blocking he binding of adenosine diphosphate (ADP) to its P2Y12 (P2Y12c) platelet receptor. Both of these drugs are inactive and require conversion to their active platelet-inhibitory metabolites by the hepatic cytochrome P450 system in vivo. Clopidogrel has a more favorable side effect profile and a more rapid onset of action than does ticlopidine.11,12 Interindividual variability in platelet inhibition by clopidogrel and the occurrence of “clopidogrel resistance” has been recently documented by several groups.2,3,13,14 Although not conclusively demonstrated, one study suggested that clopidogrel resistance increases the risk of coronary stent thrombosis.14 The reasons for variability in response to clopidogrel are unknown, and as yet no genetic determinants (eg, polymorphisms in the platelet ADP receptors) have been identified.

Interactions with other drugs that compete with clopidogrel for metabolism to its active form by its predominant cytochrome P450 isoenzyme could significantly reduce clopidogrel’s antiplatelet effect. Lau et al15 have reported that coadministration of atorvastatin, an HMG-CoA reductase

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inhibitor that may share with clopidogrel the cytochrome P450 3A4 (CYP3A4) route of metabolism, reduces the ability of clopidogrel to inhibit platelet aggregation. Because statins are not uncommonly used in patients who require clopidogrel, the clinical relevance of this drug–drug interaction is important to establish. In the present issue of Circulation, Saw et al16 found that the benefit of clopidogrel after percutaneous coronary intervention was similar with the concurrent use of different statins, irrespective of their route of metabolism. The study does provide a degree of reassurance that CYP3A4-metabolized statins do not interfere with clopidogrel’s antiplatelet action. However, the results should be interpreted with caution. They are derived from a post hoc efficacy analysis of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial, and as such, they are subject to the pitfalls and biases inherent in such an analysis. Because the data were derived from only a subset of patients selected post hoc on the basis of features observed after randomization into the trial, the results may not apply to a more general population of patients treated prospectively. The results also do not exclude the possibility of drug–drug interactions because the beneficial antiplatelet and antithrombotic properties of statins, unrelated to their direct lipid-lowering actions,17 may have offset any attenuating effects on the antiplatelet action of clopidogrel.

Not only can some drugs interfere with the efficacy of antiplatelet agents, but the converse may also occur. For example, the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure may be attenuated by concomitant administration of aspirin.18 A price we must pay for the dramatic expansion of our armamentarium of cardiovascular and antithrombotic drugs is the need for increased vigilance for drug interactions that can mitigate the efficacy of one or another in frequently used combinations. It is also becoming increasingly clear that there is considerable intrinsic variability in the responsiveness of individuals to antiplatelet agents, much of which is genetically determined. Point-of-care platelet function testing in acute settings and rational pharmacogenomic approaches will permit more individualized treatment, in some cases requiring dosing changes or the use of alternate drugs to optimize antiplatelet therapy.

References


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Genetic and Acquired Determinants of Individual Variability of Response to Antiplatelet Drugs
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