Editorial Comment

High-Powered Rifles Versus Shotguns

In the study published in this issue, Guan et al chose to use a mixed population in a trial comparing a prostaglandin (beraprost) with a platelet aggregation inhibitor (ticlopidine) for the treatment of chronic peripheral arterial occlusion. The investigators selected patients on the basis of end-result symptoms (ie, coolness in the limbs, intermittent claudication, limb pain, and ischemic leg ulcers). However, those symptoms were caused by a variety of diseases, including thromboangiitis obliterans, diabetic arterial occlusion, aortitis, and postsurgical intervention in the lower leg. In this study, the investigators took a risk in the response to the treatments they were testing. Different diagnoses may look similar but may differ in the magnitude and even the direction of their responses to treatments. Fortunately for the investigators, the number of patients with diagnoses other than arteriosclerosis was small. Some people might say that, for example, thromboangiitis obliterans is not really that different from other causes of these symptoms. Nonetheless, inflammatory changes in the small and medium-sized arteries and veins, sparing of the coronary arteries, and an etiologic role of cigarette smoking indicate the difference between thromboangiitis obliterans and other diseases that cause the same symptoms.

Many studies include patient populations with a variety of diagnoses, all of which may cause the same end result. Although I remain somewhat of a purist about this subject, I can see how including patients with diabetes mellitus or hyperlipoproteinemia might work in a study of obesity. Unfortunately, there are so many patients with a conglomeration of diagnoses that I am not certain why studies include the whole mixed group instead of focusing on targeted approaches to treating simple obesity, type 2 diabetes mellitus, and hyperlipoproteinemia separately. The investigators in such studies often say that they plan to go back at the end and tease apart the different patient groups. I am certain that such separation can be achieved, but I also believe that it should be done before the start of the study. For example, a study may include patients with many different types of pain, which the investigators may rationalize by saying, "Pain is pain." However, pain is not always the same symptom. Migraine is not just a severe headache. Menstrual cramps are not just a belly ache. Athletic injuries, postoperative pain, pancreatitis, and cancer pain are not the same thing.

Sometimes, the etiology—the starting point—determines patients' response to a medication, even when the resulting signs and symptoms—the end point—look very similar. Often, a medication works very differently depending on the disease state. Thus, a prostaglandin may be more appropriate for one type of leg coolness and intermittent claudication than ticlopidine. There are many examples of differences in response. For example, in neuropathic pain, opioids

simply do not work as well as some neuropsychotropic agents, tricyclic antidepressants, and antiepileptic agents. Imagine what would have happened if the patients with thromboangiitis obliterans had stopped smoking—but only in the ticlopidine group. That might have been enough to throw off the results of this study completely.

In certain cases, investigators would be better off using a high-powered rifle model for selecting a patient population that is homogeneous from the standpoints of both diagnosis and response to therapy. In some diseases, with some drugs, the investigators may be better off choosing a shotgun model, selecting a broad participant population based on a specific sign or symptom. As long as investigators think through these issues and make conscious decisions, they are unlikely to make major mistakes. The readers of *Current Therapeutic Research*® must form their own opinion about whether the investigators of this study erred in using entry criteria based on the end symptoms and signs while neglecting the diagnoses and how patients developed their diseases. We have to ask whether this choice reduced the chance of accomplishing their therapeutic goal.

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