In the treatment of most medical conditions, there are many choices. A critical question for practicing physicians is: “Are all drugs within a class interchangeable?” In the past decade, the market has seen a proliferation of drugs within popular drug classes. The original drugs within a class typically have better scientific documentation than the newer ones, which are often referred to as “me-too” drugs. Due to a lesser financial investment, the latter may be available at a lower cost. Good reasons exist for grouping drugs, however, there is no accepted definition of the term “class effect.” Although members of a drug class share main actions, they may have clinically important differences in terms of efficacy and safety. There are many such examples in the literature. This article reviews the class effect concept as it applies to the angiotensin-converting enzyme (ACE) inhibitors. Only half of the 10 ACE inhibitors available in the U.S. have been shown to improve survival and reduce morbidity in patients with heart failure or myocardial infarction. It is unknown whether the other five have the same safety and efficacy profiles or what their optimal doses are. Thus, we do not know whether all ACE inhibitors are fully interchangeable. The practice of medicine ought to be based on solid scientific evidence, not on assumptions or extrapolations. For our patients, such practice is a legitimate expectation. Therefore, it seems prudent to recommend that patients requiring ACE inhibitor therapy be prescribed one that has been proven effective and safe. (J Am Coll Cardiol 2001;37:1456–60) © 2001 by the American College of Cardiology
different clinical actions. While the effects of the “not-in-common” actions may be unimportant, they could also enhance or diminish the overall health effects. There are many examples in the literature of drugs from a class having different favorable and unfavorable health effects (1,2).

Thus, members of a drug class share qualitative mechanisms of action that define the class, but since they are not identical, the assumption that they are clinically interchangeable for every indication requires empirical validation. It seems prudent to assume that untested members of a class are not interchangeable for a specific indication until clinical evidence of interchangeability is available.

**Are all ACE inhibitors equally effective?** They may or they may not be. The answer will depend on what we mean by equal and by effective and in which dose and in which patient population. Effective should be defined as clinical effectiveness for a specific indication. Angiotensin-converting enzyme inhibitors have been shown to improve survival, to decrease the risk of nonfatal complications of
coronary heart disease, congestive heart failure (CHF), left ventricular dysfunction, hypertension and diabetes and to reduce the need for cardiovascular procedures and hospitalizations (3–10). The treatment effects on all-cause mortality observed in the major randomized clinical trials of ACE inhibitors are shown in Figure 2 by type and dose of study drug and kind of study population. The relative reductions in mortality are small for patients with acute myocardial infarction (approximately 10%) compared with the reductions in patients with left ventricular dysfunction postinfarction or CHF (approximately 25%).

Effectiveness should not be confused with a mechanism of action, that is, surrogate efficacy, such as blood pressure reduction. Unfortunately, the demonstration of a blood pressure lowering potential is sufficient for regulatory approval of ACE inhibitors for hypertension and often forms the basis for decisions regarding recommended dosages of other indications. The relative reductions in mortality are small for patients with acute myocardial infarction (approximately 10%) compared with the reductions in patients with left ventricular dysfunction postinfarction or CHF (approximately 25%).

Comparative clinical effectiveness can only be determined by large randomized outcome trials comparing drugs or dosages head-to-head. It is important to know how ACE inhibitors in different dosages compare with each other. For example, ramipril 2.5 mg every day was shown to be ineffective in preventing the progression of carotid atherosclerosis, as assessed by B-mode ultrasonography, while 10 mg every day was effective (14). Patients should have access to the optimal dose of the best ACE inhibitor. In clinical medicine, assumptions or extrapolations regarding clinically effective dosages based on surrogate outcomes like blood pressure are unwarranted. Decisions regarding interchangeability ought to rely on proper dose-dependent evidence. Ideally, they should not be influenced by marketing forces and restricted formularies.

It is difficult to know if two ACE inhibitors, shown to confer a similar effect on the risk of CHF, are also equally effective in preventing other clinical outcomes, for example, preservation of renal function or prevention of ischemic
events. A prudent action is the assumption that the benefits of a particular ACE inhibitor apply primarily to the investigated indication, doses and outcomes.

**Can one assume that all ACE inhibitors have the same safety profile?** The purpose of toxicity testing during the development phase is to eliminate candidate molecules with harmful effects. This safeguard is not always effective. A number of individual drugs of established drug classes have been found to cause major harm leading to drug withdrawal after marketing. Large-scale, long-term trials provide opportunities for evaluating long-term safety and for determining risk-benefit ratios. The problem with first-dose hypotension observed when enalaprilat was given intravenously to hypotensive patients on admission for acute myocardial infarction (15) may not apply to all ACE inhibitors. There are also reports of differences among ACE inhibitors regarding the risk of angioedema (16) and cough (17). However, there have been no large-scale comparative trials with adequate statistical power to assess this issue.

Postmarketing surveillance is a crude method for assessing drug safety. An ACE inhibitor that has not been tested in long-term trials lacks the long-term safety documentation of the agents that have been used in trials. Long-term safety data are essential for decisions regarding interchangeability.

**Which ACE inhibitors have adequate documentation of health benefits and long-term safety?** The following ten ACE inhibitors are currently available on the U.S. market (alphabetical order): benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. Five of them—captopril, enalapril, lisinopril, ramipril and trandolapril—have been tested in large-scale trials and have been shown to reduce mortality and morbidity in heart failure and postinfarction (3–10). Only ramipril (10 mg every day) has been shown to reduce mortality in cardiac patients without left ventricular dysfunction and in high-risk patients with diabetes. Another ACE inhibitor, quinapril, 20 mg daily, was tested in one large-scale trial in 1,750 patients after percutaneous coronary intervention and was shown to be no better than placebo for the three-year incidence of cardiac ischemic events. The other four remain untested in large-scale trials and lack the regulatory claim in their labeling of beneficial mortality/morbidity effects. Other ACE inhibitors not mentioned here fall into the category of “yet untested.” Clinicians practicing evidence-based medicine should attempt to achieve the target doses shown effective in the major event trials for specific indications, which were as follows: captopril—50 mg twice a day/three times a day, enalapril—10 to 20 mg twice a day, lisinopril—10 to 35 mg every day, ramipril—10 mg every day and trandolapril—4 mg every day.

**Conclusions.** It is not well understood how clinicians make their decisions regarding selection of drugs and doses within a class. The common use in medical practice of untested “me-too” drugs, of drugs unproven for specific clinical indications, and the widespread underutilization of drugs with documented health benefits and safety suggests that there is room for improvement. The assumption that drugs of the same class, however defined, are clinically interchangeable is a misnomer and should not form the basis for drug selection. Similarly, the assumption that we can achieve equal risk benefits for the same drug at two different doses is untenable.

The promotion of evidence-based practice has undeniable appeal. For our patients, such practice is a legitimate expectation. Applied to the ten ACE inhibitors on the market, one would, today, due to a lack of documentation, dismiss half of them for treatment of patients with CHF until further documentation as to the dose and indication in which they are effective in reducing morbidity/mortality is available. All the others have been shown to be beneficial in patients with CHF or in postinfarction patients with left ventricular dysfunction. In addition, ramipril 10 mg once daily has been shown to be effective in patients with vascular disease and diabetes without impaired ventricular function, giving it the most widely approved indications.

There are many pressures on the clinician to use or substitute a cheaper or formulary-available ACE inhibitor or to use a lower dose than was shown to be effective in the major randomized trials. It would, indeed, be unfortunate if those pressures assuaged our conscience and allowed us to feel as if we were doing something good for our patients. Substituting an unproven alternative for a proven treatment may deny benefit, subject the patient to unnecessary adverse effects and, despite a lower unit cost, may not be cost-effective.

**References**

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