

## VIEWPOINT

# Generic Drugs in Cardiology: Will They Reduce Health Care Costs?

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The introduction of generic drugs should lower health care costs by reducing the price of drugs. The realization of this goal may, however, not be fully achieved: generic drugs may be underused or misused in comparison to prescription drugs because of a lack of ongoing postgraduate physician education. More importantly, there is little incentive to explore new indications for soon-to-be generic drugs and drugs that are already generic. The failure to explore new indications for soon-to-be and existing generic drugs may result in a missed opportunity to further reduce health care costs. Thus, the apparent savings resulting from the introduction of generic drugs may not be fully realized unless the government and other third-party payers take a more active role in postgraduate drug education and investigation. (*J Am Coll Cardiol* 2004;44:10-3) © 2004 by the American College of Cardiology Foundation

Public pressure to increase the availability of low-cost generic drugs and, therefore, lower health care costs is growing. The realization that the cost of prescription drugs makes up an increasingly large percentage of health care costs of the elderly has focused government and other third-party payers on this problem. The ability of generic drug manufacturers to bring generic versions of prescription drugs to market recently has been facilitated, and delaying tactics previously used by prescription drug manufacturers have been severely limited. Pressure to further facilitate the availability of generic drugs is likely to increase during the next several years as some form of prescription drug benefits becomes part of Medicare. Reducing health care costs with generic drugs while maintaining quality of care is an important societal goal. To achieve this objective, however, certain issues must be addressed. First, generic drugs, as described in the following text, are more likely to be underused or misused than their prescription counterparts. Thus, the potential cost savings associated with their use may not be realized, and in some instances health care costs may actually increase. Second, the lack of patent protection may lessen the incentive to compare generic drugs with non-generic members of the same class and with non-generic drugs of another class. There is also little incentive to explore new indications for some soon-to-be generic drugs or drugs that are already generic. This may also have important implications for health care costs because opportunities to reduce morbidity and mortality in a cost-effective manner are missed. The apparent savings resulting from the introduction of generic drugs, therefore, may turn out to be illusory unless the government and other third-party payers

take a more active role in postgraduate drug education and investigation.

## UNDERUSE AND MISUSE OF GENERIC DRUGS

Despite compelling evidence from major randomized studies, guidelines by organizations such as the American College of Cardiology/American Heart Association (ACC/AHA), and local critical care pathways, many major cardiovascular drugs, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers in patients with heart failure (HF) due to systolic left ventricular (LV) dysfunction and statins in patients with known vascular disease, are underused (1,2). This underuse has many causes, which have been reviewed elsewhere (3), and occurs despite journal advertising, postgraduate seminars, and drug detailing.

When a drug, such as the ACE inhibitor enalapril, becomes generic, the interest of the prescription drug manufacturer is reduced because third-party payers reduce reimbursement, limit access, and/or increase co-payments on the non-generic version. Pharmaceutical companies making other non-generic members of the class are forced to increase spending on marketing on ancillary properties of the drug, which may or may not have any major effect on efficacy, safety, or cost effectiveness. The class itself may receive less attention in the market place and may gradually be replaced by newer, more expensive, although not necessarily more effective, drugs of other classes. For example, ACE inhibitors, although effective and widely used in patients with essential hypertension, have decreased their rate of growth in comparison with angiotensin receptor-blocking agents. The potential cost savings from generic ACE inhibitors in patients with essential hypertension, therefore, may not be fully realized as physicians switch to angiotensin receptor blockers and other newer more costly classes of drugs.

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#### Abbreviations and Acronyms

|         |   |
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| ACC/AHA | = American College of Cardiology/<br>American Heart Association |
| ACE     | = angiotensin-converting enzyme                                 |
| HF      | = heart failure   |
| LV      | = left ventricular  |
| RALES   | = Randomized Aldactone Evaluation Study                         |

An example of the misuse of a generic drug is spironolactone. The results of the Randomized Aldactone Evaluation Study (RALES) trial (4) showing a reduction in total mortality and in hospitalization for HF in patients with severe HF due to systolic LV dysfunction randomized to spironolactone has led to its increasing use in patients with severe HF. These results were of particular importance because spironolactone is generic and available in most parts of the world at a cost of only a few cents a day. Although the excess incidence of serious hyperkalemia (serum potassium  $\geq 6.0$  mEq/l) in the RALES trial (4) was only 1% and there were no deaths attributable to hyperkalemia in patients randomized to spironolactone. Since publication, there have been a number of reports of serious hyperkalemia associated with spironolactone use in patients with HF, resulting in renal dysfunction, hospitalization, the need for dialysis, and in some instances, death (5-10). An analysis of these reports, however, reveals that a large percentage of the adverse events occurred with dosages other than those recommended in the RALES trial (25 mg daily) (4), in patients excluded from the trial because of renal dysfunction (creatinine  $< 2.5$  mg/dl or  $K^+ \geq 5$  mEq/l), and/or a failure to monitor serum potassium and to adjust the dose of spironolactone according to the level of serum potassium as recommended in the original report.

Although it is difficult to calculate the exact costs of the adverse effects associated with the use of spironolactone in patients with chronic HF, it would appear that the costs saved by using generic spironolactone compared, for example, with the costs associated with a non-generic angiotensin receptor blocker may have been more than offset by these adverse events. In large part, these adverse events are avoidable and attributable to a lack of physician education involving the indications, dosing, and monitoring of spironolactone. Because spironolactone is generic, there have been no large-scale media advertising or pharmaceutical representative "detailing" efforts focused on the practicing physician and relatively little postgraduate education. Several other cardiovascular drugs are, or will soon be, available in generic form. The risks associated with several of these drug classes are less than with spironolactone; nevertheless, the potential for underuse or misuse of these agents poses an important public health problem. The cost to society regarding underuse of effective drugs such as ACE inhibitors, beta-blockers, and statins may in fact be far greater than that for misuse of drugs such as spironolactone.

Most drug information in postgraduate education in the

U.S. comes from the pharmaceutical industry. Therefore, there is little information available on an ongoing basis to the physician concerning generic drugs. If we wish to realize the potential health care savings associated with generic drugs, we need to consider a change in the quality of drug information and the availability of funding for postgraduate education. Society, government, and third-party payers benefit from inexpensive generic drugs. They should therefore insure that these drugs are used effectively and safely. Continuing physician education is important in assuring appropriate use of drugs in eligible individuals.

One approach would be for the government and/or third-party payers to provide direct grant support to universities and/or organizations such as the ACC/AHA to ensure unbiased medical education concerning the indications, dosing, and monitoring of generic drugs. Consideration might also be given to funding an independent force to "detail" generic drugs (academic detailing) to the practicing physician because this approach appears to be one of the most effective means of influencing physician behavior. Academic detailing recently has been shown to be effective in assuring the appropriate use of drugs in patients with essential hypertension (11). Failure of the government and third-party payers to meet this challenge and leave the impetus for postgraduate education to the pharmaceutical industry, which has an incentive to shift physician use of drugs to more expensive, although not necessarily more effective, non-generic drugs, may negate any potential savings from generic drugs and in some instances may actually make generic drug use more expensive than non-generic prescription drugs. Other quality-assurance approaches such as the "check-off" system used to increase the use of beta-blockers and ACE inhibitors in patients postinfarction or in HF due to systolic LV dysfunction also may be effective. The later approach, although addressing the issue of underuse of generic drugs, will not alter the potential for underdosing and misuse, at least until improved information systems are more generally available that allow detailed information on indications and contraindications, dosing, and drug monitoring procedures to be easily collated.

#### IMPACT OF SOON-TO-BE AND GENERIC DRUGS ON DRUG DEVELOPMENT

There are other less apparent costs to society of generic drugs or soon-to-be generic drugs that may be even more costly in the long run than the underuse and the misuse of generic drugs outlined in the preceding text. For example, several ACE inhibitors are generic, and there is relatively little investment in clinical trials to compare their cost effectiveness to other non-generic members of the class, which have been claimed to have special advantages such as "tissue specificity," or to newer agents of another class such as the angiotensin receptor blockers. Increased funding is needed for these comparative cost-effectiveness studies if

physicians are to reach an informed conclusion amidst the many conflicting claims.

There also is relatively little incentive in exploring new indications for generic or soon-to-be generic drugs. For example, there is no incentive to invest in clinical trials of generic ACE inhibitors for new indications whereas angiotensin receptor-blocking agents, which have remaining patent protection, are under active investigation for several new indications. The RALES trial (3,4) demonstrated the effectiveness of aldosterone blockade in patients with severe HF. There has, however, been relatively little use of spironolactone in patients with mild-to-moderate HF, even though there is increasing data to suggest that aldosterone blockade improves ventricular remodeling and endothelial dysfunction and decreases collagen formation and ventricular arrhythmias in patients with mild-to-moderate HF due to systolic LV dysfunction (12–16). The lack of well-designed, large-scale randomized trials of this drug in these individuals precludes its recommendation and inclusion in guidelines and hence its widespread use. Aldosterone blockade may also have an important role in patients with asymptomatic systolic LV dysfunction, HF due to preserved systolic function, hypertension, and a variety of other cardiovascular conditions. The potential health care savings if aldosterone blockade was shown to be effective in reducing morbidity and mortality in these conditions by even a half of that observed in RALES (4) would be enormous. This benefit is unlikely to be realized because there is no incentive for pharmaceutical companies to invest in further trials of a generic agent such as spironolactone.

One potential solution would be to allow pharmaceutical manufacturers who have a prescription drug nearing the end of its patent life to apply to an independent commission with representatives from the Food and Drug Administration, third-party payers, the academic community, and the public to extend patent life based upon the potential savings in health care costs and lives saved from the proposed indication. Although this approach could lead to frivolous requests for patent extension, the potential benefits, likelihood of success, and the effect on public health could be weighed by the commission and assessed prospectively. The pharmaceutical manufacturer would bear the costs of the proposed trial and reap the potential profit should the trial be successful. The extension of a patent for example by a few years for a “blockbuster” drug could result in millions of dollars profit for the manufacturer and justify an investment in a new indication but more importantly could result in an even greater reduction in health care costs and lives. The extension of patent life to promote investment in new potentially cost-effective indications for a soon-to-be generic drug may not be politically obtainable and other solutions may be necessary. However, failure to explore new approaches to this problem may negate much of the potential cost savings to society associated with the introduction of lower cost generic drugs.

For a drug that is already generic, such as spironolactone,

a different solution is necessary. In this instance, funding for further clinical indications should be available through the National Institutes of Health or other third-party payers. Funding is currently available for large-scale drug trials through the National Institutes of Health but is inadequate to address many of the issues we currently have in cardiology. The cost of large-scale randomized trials is large. Therefore, it would be desirable if Congress were to set aside funding for such a program in a special account to avoid the controversy concerning whether these funds would be better spent for basic research. If we are to truly realize further potential health care savings from generic drugs, we will need to adequately fund clinical research into their use. This is not to deny the long-term benefits of basic research for health care costs but rather to emphasize that we need both approaches.

The problems outlined in this report are likely to increase as more cardiovascular drugs become available as generic. Although we should welcome new classes of drugs that provide further health care benefits and cost savings, we should be certain that we do not discard old “generic” drugs and strategies that may be as, or even more, beneficial and possibly more cost effective than newer ones.

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