Clarifying Terminology for Adverse Drug Events

TO THE EDITOR: We are currently part of an expert group in the Council of Europe that is establishing a glossary of terms related to medication safety, and we read Nebeker and colleagues’ article on adverse drug events (1) with great attention. We agree with the definitions used throughout the article, which are the result of a comprehensive review of the literature. However, we disagree with Nebeker and colleagues’ figure outlining the relationships of key terms. This figure, which was previously published by the American Society of Health-System Pharmacists (2), differs greatly from the original figure proposed by Bates and associates (3) and creates a hypothetical category of adverse drug events that are due to neither adverse drug reactions nor medication errors.

We believe that adverse drug reactions should not overlap with medication errors. Therefore, we prefer to use a different diagram (Figure) (4), which in our opinion better reflects the definitions and cases presented in Nebeker and colleagues’ article (1). By definition, all medication errors are considered to be preventable and associated with inappropriate drug use, and their prevention results from improvements in the medication use system. Adverse drug reactions are injuries that cannot be prevented and that result not from an error but from the intrinsic properties of the drug itself. Reductions in exposure to drugs and development of less hazardous alternative agents are the only ways to prevent adverse drug reactions. In this sense, adverse drug reactions must be considered nonpreventable adverse drug events. Medication errors that lead to patient injury should be considered preventable adverse drug events, which can be reduced only by building fail-safe medication use systems.

Because medication safety is becoming a priority for many countries, there is a real need to standardize the terminology used to describe drug-related harm. A unified international glossary would allow more accurate research and sharing of information to prevent medication errors and improve patient safety.

IN RESPONSE: We oppose the recommendation of Otero and Schmitt and others to exclude events related to error from the definition of adverse drug reactions. Doing so would significantly alter the meaning of a term used for decades by the pharmacovigilance community, including regulatory agencies worldwide. Adoption of these new definitions would force agencies to revise regulations and would diminish capacity to analyze trends in rates of adverse drug reactions. The additional complexity of classification also risks exacerbating underreporting of adverse drug reactions by clinicians.

The distinction proposed by Otero and Schmitt and others has logical flaws. Regardless of whether an error is judged to be present, harm due to a drug is always caused in part by the drug’s intrinsic properties. Stipulating lack of preventability as central to the definition of adverse drug reactions also tends to increase rather than decrease confusion. One problem with defining error and preventability as exactly equivalent is that not all errors are preventable, given the intrinsic limitations of human-designed systems and behav-

Figure. Relationship between adverse drug events and adverse drug reactions.

The area of each section does not reflect the magnitude of the corresponding incident. Reproduced with permission from reference 4.
Angiotensin-Converting Enzyme Inhibitors after Acute Myocardial Infarction

TO THE EDITOR: Pilote and colleagues (1) presented data suggesting that ramipril was superior to other angiotensin-converting enzyme (ACE) inhibitors after myocardial infarction. Their carefully discussed methods, in concert with the accompanying outstanding editorial (2), should confer the overall message that the study’s design and limitations render its findings no more than hypothesis-generating. The authors rightfully pointed out that the distribution of observed mortality differences among the 7 ACE inhibitors studied is not consistent with any known pharmacologic property of these agents (that is, ACE inhibitors with higher tissue affinity did not consistently fare better than those with low tissue affinity). In addition, the editorial noted that mortality differences among ACE inhibitors in Pilote and colleagues’ analysis were larger than those between ACE inhibitors and placebo in randomized trials (raising significant concerns about the validity of their data). In addition, β-blocker and statin use was substantially higher in patients receiving ramipril. Therefore, the conclusion that “survival benefits . . . seem to differ according to the specific ACE inhibitor prescribed” seems somewhat premature, much like the similar content of the take-home message in the Summary for Patients (3).

My colleagues and I recently completed what is, to our knowledge, the first randomized, double-blind study in patients with congestive heart failure (CHF) comparing effects of long-term therapy with low versus high tissue affinity ACE inhibitors on endothelial function, exercise capacity, and neurohormonal profiles (4). We did not detect any differences. In the absence of positive results from trials performing large-scale head-to-head comparisons of ACE inhibitors, the available evidence, including the recent Valsartan in Acute Myocardial Infarction (VALIANT) trial, strongly suggests that no clinically relevant differences exist among agents blocking the renin–angiotensin system. This is a reassuring message for our patients.

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1. Pilote L, Abrahamowicz M, Rodrigues E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? Ann Intern Med. 2004;141:102-12. [PMID: 15262665]
2. Hennawy S, Kimmel SE. Is improved survival a class effect of angiotensin-converting enzyme inhibitors? [Editorial] Ann Intern Med. 2004;141:157-8. [PMID: 15262673]
3. Summaries for patients. ACE inhibitors after heart attacks: varying effects? Ann Intern Med. 2004;141:134. [PMID: 15262682]
4. Jorde U. AJC. In press.

TO THE EDITOR: Although a difference in effect of ACE inhibitors cannot be excluded, the improved survival reported by Pilote and colleagues (1) with ramipril compared with other agents might be alternatively explained by the higher rates of statin and β-blocker use in the ramipril group. The accompanying editorial (2) noted these higher rates, although not as a possible cause of Pilote and colleagues’ results. According to Pilote and colleagues’ data, ACE inhibitors with best to worst survival rates were ramipril, perindopril, lisinopril, enalapril, quinapril, fosinopril, and captopril. Statin use in these groups was 39.2%, 37%, 30.5%, 21.4%, 26.9%, and 14.7%, respectively, and β-blocker use was 70.8%, 70%, 56.7%, 52.6%, 55.4%, 54.3%, and 45.6%, respectively. Given that both statins and β-blockers improve survival after myocardial infarction, it is likely that the differences in survival, which relatively paralleled the differences in both β-blocker and statin use, were due not to differences in the ACE inhibitors but to the concomitant medical therapy.

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References
1. Pilote L, Abrahamowicz M, Rodrigues E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? Ann Intern Med. 2004;141:102-12. [PMID: 15262665]
2. Hennawy S, Kimmel SE. Is improved survival a class effect of angiotensin-converting enzyme inhibitors? [Editorial] Ann Intern Med. 2004;141:157-8. [PMID: 15262673]

IN RESPONSE: We thank Dr. Jorde for his letter, although we take issue with several points. We disagree that our study was “no more than hypothesis-generating” because of its design and limitations. Pharmacoepidemiologic studies allow the assessment of the effect of medications in real-life situations, in contrast to the highly selected samples of clinical trials. However, they are prone to biases because of confounding by indication. State-of-the-art statistical analyses can compensate for these limitations. Since it is unlikely that ACE inhibitors will ever be compared head-to-head in a clinical trial, our findings should alert physicians that all ACE inhibitors do not offer the same level of benefit after myocardial infarction.

Dr. Jorde, and Drs. Hennawy and Kimmel in their editorial (1), mentions that the risk reductions associated with ramipril versus other ACE inhibitors in our study were large compared with those of ramipril versus placebo. Such a comparison is not entirely appropriate because patients across studies have different risks for death and because it completely ignores the 95% CIs. Any value inside a 95% CI should be considered consistent with the data. All of the 95% CIs
for the risk reduction seen with ramipril versus other drugs in our study do overlap with the 95% CIs for ramipril versus placebo in the Heart Outcomes Prevention Evaluation (HOPE) (2) and the Acute Infarction Ramipril Efficacy (AIRE) trial (3). Accordingly, to argue that we reported higher risk reductions between ACE inhibitors than between ramipril and placebo would amount to ignoring the role of sampling error.

The editorial by Drs. Hennessy and Kimmel also suggested that our results might have been confounded by the severity of CHF, even if we did adjust for the presence or absence of any CHF at baseline (1). Fortunately, we were able to empirically test Drs. Hennessy and Kimmel’s conjecture. It posits that by pure logic the impact of CHF on mortality would have to be much weaker in the ramipril group than among users of other ACE inhibitors, implying the CHF-by-drugs interactions. We added 6 such interactions to the multivariable model in our Table 3. All of the interactions were statistically nonsignificant (all $P$ values $> 0.18$), clearly showing that the observed better survival of ramipril users cannot be due to confounding by the unknown severity of CHF.

Dr. Jorde refers to an unpublished study that investigates outcomes such as endothelial function rather than death. This trial, unlike ours, is not a head-to-head comparison of ACE inhibitors. Similarly, the VALIANT trial (4) did not compare different ACE inhibitors but an ACE inhibitor with an angiotensin II blocker. One should be cautious about generalizing results on intermediate outcomes to mortality and about generalizing a similar effect to all agents blocking the renin–angiotensin system.

Drs. Horton, Jorde, Kimmel, and Hennessy are concerned that the higher rate of use of $\beta$-blockers and statins in the ramipril group could explain the apparent survival advantage associated with ramipril. However, all of these authors overlooked the fact that we did adjust for these differences, as can be seen in our Table 3. The results show that the lower mortality rates in the ramipril group are independent of statins and $\beta$-blockers.

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1. Hennessy S, Kimmel SE. Is improved survival a class effect of angiotensin-converting enzyme inhibitors? [Editorial] Ann Intern Med. 2004;141:157-8. [PMID: 15262673]
2. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342:145-53. [PMID: 10639539]
3. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993;342:821-8. [PMID: 8104270]
4. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893-906. [PMID: 14610160]

CORRECTIONS

Correction: Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease

The clinical guideline on primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease (1) contained an error. On page 565, in the first numbered paragraph under the heading “Use of Cardiac Testing during Follow-up,” echocardiogram should be electrocardiogram.

Reference
1. Snow V, Barry P, Fihn SD, Gibbons RJ, Owens DK, Williams SV, et al. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2004;141:562-7. [PMID: 15466774]

Correction: Addressing the Limitations of Structured Abstracts

In a letter on addressing the limitations of structured abstracts (1), the first author’s name should have read “Matthew E. Falagas, MD, MSc.”

Reference
1. Falagas ME, Vergidis PI. Addressing the limitations of structured abstracts [Letter]. Ann Intern Med. 2004;141:576.