Choosing Between the Scylla of Observational Studies and the Charybdis of Subgroup Analysis

Pardeep Jhund, MB, ChB; John J.V. McMurray, MD

Fourteen years ago, Hall and colleagues1 reported observations that initiated a vigorous debate about a possible interaction between aspirin and angiotensin-converting enzyme (ACE) inhibitors that continues to this day. That debate centers on whether the apparent pharmacological interaction between aspirin and ACE inhibitors might influence clinical outcomes and has been heightened greatly by the provocative suggestion that long-term aspirin use might not be beneficial in patients with chronic coronary heart disease, including those with heart failure.2 Although interesting, the clinical importance of this observation is uncertain. First, whether the effect of aspirin persists in the longer term is unknown. Second, we do not know how an ACE inhibitor exerts its beneficial effect and therefore how important its hemodynamic or other actions are. Third, experience has taught us that however plausible a pharmacological mechanism may seem, it may not lead to the expected effect on clinical outcome. Consequently, studies on the actions of drugs on potentially important biological mechanisms can only be hypothesis generating with respect to clinical outcomes and often have been misleading.3–8 Despite these reservations, such studies remain the foundation of therapeutic drug development.

The report by McAlister and colleagues9 represents a completely different approach in contemporary cardiovascular research, one that is becoming increasingly common with the availability of relatively inexpensive and powerful statistical software and the growing number of large administrative data sets created as a result of the explosion in information technology in healthcare systems. McAlister et al looked for a potential interaction between ACE inhibitors and aspirin in a large observational study of patients discharged from hospital in Ontario with a primary diagnosis of heart failure, recording death and readmission for heart failure over the subsequent year.9 The authors did not find evidence of an interaction between the 2 treatments. Can we be reassured by this? The reader should have both specific and general reservations about the study by McAlister and colleagues. Specifically, the proportion of patients with nonischemic heart failure (44%) was unusually high, even assuming that the recorded origin was reliable, and because it is not indicated in nonischemic heart failure, it is unclear why some of these patients were treated with aspirin. Aspirin is not likely to be of benefit in patients without atherosclerotic disease, which may be one explanation why aspirin treatment was not associated with a reduced risk of death in the analysis. Furthermore, the authors could not tell whether patients identified as not taking aspirin at discharge subsequently received a prescription for this drug or purchased over-the-counter aspirin or other nonsteroidal antiinflammatory drugs. More important, ACE inhibitors are of proven benefit only in patients with a low left ventricular ejection fraction, and this measure was not available in nearly half of the patients (and was not reduced in many others). Because aspirin could not reduce the benefit of an ACE inhibitor in instances when an ACE inhibitor is not known to be of benefit, inclusion of such patients will have reduced the chance of showing the interaction in question.

There are more important general reservations related to the inherent weaknesses of observational studies.10 The intrinsic unreliability of these studies as a means of predicting therapeutic effects has been vividly and repeatedly demonstrated in cardiovascular medicine in recent times. Hormone replacement therapy to prevent coronary heart disease, “antioxidants” and other vitamins to prevent coronary heart disease and cancer, and homocysteine to reduce cardiovascular risk are only a few such false leads.11–13 Plausible biological mechanisms were found to explain each of these relationships. Although observational studies may give valuable information about the natural history of disease, the reasons why they have misled us in relation to therapeutic interventions (and will continue to do so) are well described.
The most important of these is bias. Although 35 types of bias have been described, they have been conveniently categorized as selection bias, information bias, and confounding.10,14

Because the characteristics of the patients treated with the drugs of interest are not given separately by McAlister et al.,9 selection bias can only be guessed at in the present study. It is likely to include less prior renal dysfunction and hypotension and more atherosclerotic disease, hypertension, and systolic dysfunction in those given ACE inhibitors, less peptic ulceration and more atherosclerotic disease (and more statins) in those given aspirin, and potentially extreme differences between those taking neither or both treatments. Whether these differences, each of which is likely to influence outcome, have been or can be adequately adjusted for is uncertain.

The increased risk related to digoxin use shown in the authors’ multivariable analysis (Table 2 in McAlister et al)9 is probably an example of confounding. The Digitalis Investigators Group’s (DIG) prospective, randomized, controlled trial showed that digoxin neither increased nor decreased mortality but reduced the risk of hospitalization for heart failure and the composite outcome of death or hospitalization for heart failure, an outcome also used by the current authors, by 15% (P<0.001).15 Digoxin is indicated for patients with atrial fibrillation and in sinus rhythm when symptoms are severe. The increased risk related to digoxin use in the present observational study probably reflects those attributes and suggests that the authors’ multivariable analysis did not adequately control for all important confounders, a limitation that is not rectified by having a large sample size. It is also important to note that other, albeit smaller, observational studies16,17 have reached a conclusion different from that of McAlister et al.

A third type of study also has fueled the debate about the putative interaction between ACE inhibitors and aspirin. Analysis of subgroups of patients treated or not treated with aspirin in the large randomized trials of ACE inhibitors has been carried out.18–21 Although these reports may have given more reliable information because 1 of the 2 treatments of interest was randomized, this type of analysis also has marked limitations, as has been repeatedly illustrated but regularly ignored.22,23 Collectively, however, these analyses suggest that the benefit of adding an ACE inhibitor is somewhat smaller in a patient taking aspirin than in a patient not taking aspirin, although the exact statistical method for testing for this interaction has been debated.24

If aspirin attenuates the benefits of an ACE inhibitor in patients with heart failure, which are unequivocal, we must indeed be certain there is a good reason to give aspirin in the first place. Although the benefits of short-term aspirin use in patients with an acute coronary syndrome are disputed by few, the benefits of long-term aspirin use in patients with chronic stable coronary disease are less definite.25 The reason is that the robustness of clinical trials has improved over time; early aspirin trials were not conducted to the standard expected today. Consequently, the evidence for using long-term aspirin in these patients comes mainly from a meta-analysis of trials that were, individually, not as convincing as a modern trial needs to be.26 We should, however, feel uneasy when the recommendation of any treatment is based just on a meta-analysis and there is no single large, convincing, randomized trial. If accepted uncritically, a meta-analysis can be misleading, as, for example, with magnesium and glucose-insulin potassium as treatments for myocardial infarction.27,28

Thus, it is of potential concern that a meta-analysis can be considered the highest level of evidence by some guideline writing groups.

Therefore, a robust, prospective, randomized, controlled clinical trial remains the most reliable way to answer a therapeutic question, preferably if the results can be replicated, as with, for example, ACE inhibitors, β-blockers, and statins. Testing for an ACE inhibitor–aspirin interaction, however, would require a 2-by-2 factorial design, and such a trial is unlikely ever to be done for many reasons, including size, expense, practicality, and ethics, as McAlister et al correctly emphasize. To test whether aspirin is valuable in patients with coronary heart disease and heart failure (and obviate the former question) is more practical but would raise ethical questions for many. Such a study has already been attempted, but recruitment to the Warfarin or Aspirin Study in Heart Failure Trial (WASH) was poor; only 279 patients were randomized.29 Of note, in that trial, there were trends to worse outcomes and a significantly higher risk of heart failure hospitalization in the aspirin group compared with the placebo or warfarin group. Interestingly, in another study, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure Trial (WATCH), which was also limited in size because of poor recruitment, the risk of heart failure hospitalization was higher in patients treated with aspirin compared with those treated with warfarin or clopidogrel.30 These findings go to the heart of the question at hand: How should we weigh exploratory analyses in small prospective randomized trials with limited numbers of events compared with large observational studies and retrospective subgroup analyses? Unfortunately, none is satisfactory. A further study, the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, is comparing the relative effectiveness of those 2 drugs in preventing death or stroke in patients with heart failure, but it does not have a placebo group.31

Since WASH was initiated, an analogous situation has arisen regarding statins in heart failure. Because most prior statin trials excluded patients with heart failure and because there are theoretical reasons why a statin might not be beneficial in patients with heart failure, it was considered ethical to conduct 2 large placebo-controlled trials that are now at an advanced stage of follow-up.32,33 A similar situation exists in renal failure.34–36 If we can test a statin in placebo-controlled trials in patients with heart failure and coronary heart disease, perhaps we should reconsider doing the same for aspirin.

Disclosures

None.

References


Key Words: Editorials, aspirin, angiotensin-converting enzyme inhibitors, heart failure, pharmacology.
Does Aspirin Reduce the Benefit of an Angiotensin-Converting Enzyme Inhibitor?: Choosing Between the Scylla of Observational Studies and the Charybdis of Subgroup Analysis
Pardeep Jhund and John J.V. McMurray

*Circulation.* 2006;113:2566-2568
doi: 10.1161/CIRCULATIONAHA.106.629212

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/22/2566

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/