

Cardiovascular Events and COX-2 Inhibitors

To the Editor: In their meta-analysis, Dr Mukherjee and colleagues¹ found that cyclooxygenase 2 (COX-2) inhibitors might cause an increase in cardiovascular (CV) events. This may lead clinicians to avoid COX-2 inhibitors for their patients with arthritis. I believe that this conclusion is ill advised.

Other nonsteroidal anti-inflammatory drugs (NSAIDs) have been estimated to have a 1% to 4% annual rate of significant adverse events.² The 2 large trials of COX-2 inhibitors, VIGOR (Vioxx Gastrointestinal Outcomes Research Study³) and CLASS (Celecoxib Arthritis Safety Study⁴), both found a 1% to 2% decline in serious gastrointestinal (GI) complications with the use of COX-2 inhibitors compared with other NSAIDs. In contrast, Mukherjee et al found a 0.24% and 0.3% increase in cardiovascular events for rofecoxib and celecoxib, respectively. Preventing about 3 CV events per thousand while increasing GI complications 10 to 20 per thousand may not be the most equitable trade.

It is also possible that COX-2 inhibitors may be detrimental because they eliminate the cardioprotective effect mediated by upregulation of COX-2 during the late phase of ischemic preconditioning. However, this would occur whether an anti-inflammatory agent is COX-2 specific or not. Both COX-1 and COX-2 are inhibited, albeit to varying degrees, at therapeutic doses of all common NSAIDs, including aspirin.⁵

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1. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954-959.
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To the Editor: Dr Mukherjee and colleagues¹ warned of the possibility of increased CV events associated with selective COX-2 inhibitors, based on the results of 2 long-term (6-9 months) safety studies in rheumatoid arthritis (RA) patients with celecoxib 800 mg (CLASS) and rofecoxib 50 mg (VIGOR).^{2,3}

RxIntelligence (which is sponsored by Blue Cross and Blue Shield of Illinois) recently compared the efficacy and safety of the 2 COX-2 inhibitors.⁴ Most of the studies we included in our analysis were short term (up to 6 months) and did not re-

port long-term events such as myocardial infarction (MI). However, they did include hypertension, which is commonly accepted as a risk factor for MI.

We found the highest hypertension rate with rofecoxib (25 mg). The rate with rofecoxib (12.5 mg) was not significantly different than with placebo or nonselective NSAIDs. We found no differences between celecoxib (200 mg) and placebo or nonselective NSAID controls in the rates of hypertension.

Our results suggest a dose-dependent effect of rofecoxib on hypertension. This conclusion is consistent with the concerns of Mukherjee et al related to increased CV events when selective COX-2 inhibitors are used over the long term. Since few head-to-head studies are available, we performed metaregression to compare hypertension risks within the selective COX-2 inhibitor class. This analysis included multiple doses of each drug from 14 randomized controlled trials in a total of 18439 patients, and was controlled for length of study, the specific NSAID comparator, and the event rate in the comparator group. We found that the difference in hypertension rates between rofecoxib and placebo was larger than the difference between celecoxib and placebo. The same was true when comparing each COX-2 inhibitor to NSAID control groups. However, due to differences in dosing levels, patient populations (specifically RA vs osteoarthritis [OA]), and inconsistency in adverse event reporting (eg, hypertension not defined or not reported), we cannot state conclusively whether the finding represents true differences between the 2 drugs.

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1. Mukherjee D, Nissen ST, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954-959.
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GUIDELINES FOR LETTERS. Letters discussing a recent *JAMA* article should be received within 4 weeks of the article's publication and should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 500 words and 6 references. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors as space permits and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Letters will not be returned unless specifically requested. Also see Instructions for Authors (July 4, 2001). Letters may be submitted by surface mail: Letters Editor, *JAMA*, 515 N State St, Chicago, IL 60610; e-mail: JAMA-letters@ama-assn.org; or fax (please also send a hard copy via surface mail): (312) 464-5225.

Letters Section Editors: Stephen J. Lurie, MD, PhD, Senior Editor; Jody W. Zylke, MD, Contributing Editor.

To the Editor: Dr Mukherjee and colleagues¹ concluded that COX-2 inhibitors may be associated with an increased risk of CV events. We believe that the analysis provides no substantive support for their conclusion.

The authors' conclusion was heavily influenced by the findings of VIGOR,² a randomized, controlled comparison of rofecoxib vs naproxen. This study yielded an unanticipated differential in CV events, favoring naproxen. There are several possible explanations, including a protective effect resulting from the antiplatelet action of naproxen,³ or an adverse effect of rofecoxib. The best way to distinguish these possibilities is to examine data with comparators other than naproxen. Konstam et al⁴ recently reported a pooled analysis of the occurrence of thrombotic events in more than 28000 patients randomized to rofecoxib, placebo, or nonselective NSAIDs. In contrast to the comparison with naproxen, comparisons with placebo (n=9772) and with NSAIDs other than naproxen (n=7304) showed no excess of CV events with rofecoxib. In these analyses, the placebo-controlled data were derived largely from patient populations with substantial cardiovascular risk. These findings support a protective effect of naproxen as the most likely explanation for the unexpected findings in VIGOR.

We are particularly dismayed by the authors' comparisons of raw CV event rates for rofecoxib and celecoxib with that of a control group constructed from a primary prevention meta-analysis of aspirin therapy.⁵ Comparison of raw event rates across multiple studies is hazardous. The patients in this meta-analysis are generally at low risk for CV events, while those with RA are at significantly increased cardiovascular risk.⁶ The reported annualized event rates for rofecoxib (0.74%) and for celecoxib (0.80%) fall well within the range of event rates (0.36%-1.33%) for the trials used to construct the placebo group in the meta-analysis of Mukherjee et al.⁵

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Financial Disclosure: Dr Konstam has served as a consultant for Merck and Co, Pfizer, and Pharmacia.

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To the Editor: A significant part of the meta-analysis by Dr Mukherjee and colleagues¹ involves data from the CLASS study.²

However, the 800 mg per day dose of celecoxib used in CLASS is not recommended for either OA or RA.³ Few practitioners actually use celecoxib at that dosage, so the "real world" significance of this meta-analysis is dubious.

The authors excluded 10 recent COX-2 studies in their analysis. They conclude that the investigators for the excluded articles "most likely" were unaware of any CV effects, although they do not substantiate this claim. It is possible that severe CV events were not disregarded but simply did not occur.

Finally, although the authors included data from adverse event reporting systems for rofecoxib and celecoxib, they made no mention of the pitfalls of interpreting such data. For example, when traditional NSAIDs were first released in the United States and Europe, adverse event reporting was highest during the first 2 years and then declined.⁴ Mukherjee et al should have applied statistical adjustments to these adverse event data.

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Financial Disclosure: Dr Grant serves as a consultant to Pfizer and Pharmacia.

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To the Editor: Dr Mukherjee and colleagues¹ did not include all selective COX-2 agents in their meta-analysis. Meloxicam is a COX-2 selective inhibitor² that has been used by more than 45 million patients in more than 100 countries worldwide. The National Institute for Clinical Excellence of the United Kingdom included meloxicam with celecoxib and rofecoxib in their review of the selective COX-2 inhibitors.³

A pooled analysis of 35 clinical trials with 27039 patients presented at the 16th Congress of the European League Against Rheumatism in June 2001 found that rates of adverse CV events and renal toxicity were low and similar for meloxicam and 3 other commonly prescribed NSAIDs (ie, diclofenac, piroxicam, and naproxen).⁴ This analysis included more than 15000 patients who received meloxicam at daily doses ranging from 7.5 mg up to twice the maximum therapeutic dose (30 mg). Moreover, meloxicam at doses higher than 30 mg had no acute or chronic effects on bleeding time and no effects on the arachidonic acid- or adenosine diphosphate-induced platelet aggregation in healthy subjects.⁵

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To the Editor: The meta-analysis by Dr Mukherjee and colleagues¹ compared the risk of MI of the selective COX-2 inhibitors rofecoxib and celecoxib from data^{2,3} reported to the US Food and Drug Administration with that of placebo from a meta-analysis of aspirin for primary prevention.⁴ The results of this analysis showed that the annualized MI rate was higher with both rofecoxib and celecoxib compared with placebo (0.74%, 0.80%, and 0.52%, respectively; $P = .04$ and $P = .02$ for rofecoxib and celecoxib vs placebo, respectively).¹ However, Mukherjee et al did not present the results for the 3 nonselective COX-2 inhibitors relative to placebo. The VIGOR⁵ and CLASS⁶ studies found the annualized MI rates for naproxen, ibuprofen, and diclofenac to be 0.15%, 0.80%, and 0.40%, respectively. Did the authors determine the level of statistical significance between the rates for these medications and placebo?

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To The Editor: Dr Mukherjee and colleagues¹ reported that COX-2 inhibitors may induce prothrombotic activity. How-

ever, there is an important reason for thinking that COX-2 inhibitors might protect against CV events. Thrombosis is thought to occur when the fibrin coat over plaques is broken down by collagenase released from overactive macrophages.³ Since such macrophages express high levels of COX-2, COX-2 inhibitors should reduce their activity and also should act synergistically with the antiplatelet activity of COX-1 inhibitors.

A clinical trial of a selective COX-2 inhibitor plus aspirin (an irreversible COX-1 inhibitor), compared with aspirin alone, would be of great interest. Furthermore, COX-2 inhibitors may reduce serum levels of C-reactive protein (CRP) in patients at risk of future cardiovascular events. We have reported⁴ that CRP messenger RNA levels were elevated more than 10 fold in the same plaque tissues showing elevated levels of COX-2. C-reactive protein is a secreted protein, and inflamed arteries could be the source of the mildly elevated CRP levels reported to predict CV events.⁵ If COX-2 inhibitors reduce serum CRP levels in those cases, a benefit might be predicted. Unfortunately, current data do not permit conclusions regarding the influence of COX-2 inhibitors on CV events.

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1. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954-959.
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To the Editor: While I concur with Dr Mukherjee and colleagues¹ that further research is warranted given the increased incidence of CV events associated with rofecoxib, there are numerous methodological flaws in their analysis.

First, the authors base their conclusion on 4 studies. However, the odds ratios from these studies shows significant heterogeneity. The heterogeneity is even greater among the CLASS and VIGOR trials, which is probably a reflection of different patient demographics, choice of NSAID or COX-2 comparators, or other differences. Thus, the conclusion about a common "class effect" of COX-2 inhibitors across these studies seems inappropriate.

Second, the authors compare the crude MI rates of COX-2 agents with the nonaspirin rate derived from a meta-analysis by Sanmuganathan et al.² The primary objective of that study was to assess the relative benefit of aspirin use for primary prevention among patients with different levels of CV risk, and

not to determine absolute incidence rate for MI attributable to any exposure type. Sanmuganathan et al state, “[a]ccurate risk estimation requires counting and weighting of major risk factors for coronary heart disease using risk functions derived from epidemiological studies such as Framingham.” These concerns stem from significant heterogeneity in MI rates between studies in their meta-analysis, which Sanmuganathan et al² felt was related to “differences in study design, aspirin dose, patient population, compliance, or other factors.”

Third, in Figure 2, Mukherjee et al show that patients in the CLASS trial who received aspirin had a significantly higher risk of thrombotic complications compared to patients not taking aspirin. Presumably, the use of aspirin was more common among individuals at high risk for coronary disease (confounding by indication). Yet, in Figure 3, the authors compare a pooled group of patients who did not receive aspirin with a combined sample from the CLASS trial, who did or did not receive aspirin. If Mukherjee et al had compared rates from only patients who did receive aspirin, they would actually have found a lower rate of MI (0.3 per 100 patient years) compared with placebo (0.52 per 100 patient years).

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2. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease. *Heart*. 2001;85:265-271.

To The Editor: Dr Mukherjee and colleagues¹ present the CV event data from CLASS study (Figure 2) in an inconsistent fashion. Summary data from the US Food and Drug Administration hearings on the safety of celecoxib during the CLASS trial² are the primary source for this figure. Review of these data reveals that MI and stroke rates are presented as crude event rates while deaths are displayed as annualized incidence rates. Moreover, deaths include all cause deaths, rather than CV deaths. The correct crude event rates for CV deaths in CLASS are 0.57% (aspirin users) and 0.16% (non-aspirin users).²

In Table 2 of the article, simple numbers of CV events were derived from postmarketing data but were unadjusted for exposure and lack estimates of background rates. This type of analysis is insufficient to support meaningful assessments of CV safety. Analyses of postmarketing data from the World Health Organization database suggest in fact that the risk of renal and cardiovascular adverse events associated with the use of rofecoxib are significantly higher than those of celecoxib and NSAIDs (diclofenac and ibuprofen).³ These differences^{3,4} are probably a function of differing structure, pharmacology, and metabolism resulting in distinct renal and cardiovascular safety pro-

files, whose extent needs to be confirmed and clarified in future studies.

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Financial Disclosure: Dr Whelton serves as a consultant to Pfizer and Pharmacia and has previously served as a consultant to Merck and Co.

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In Reply: Dr Burnakis points out that COX-2 inhibitors decrease GI complications by 1% to 2% while increasing CV events by approximately 0.3%, and suggests that this is a fair trade. We do not want to downplay the morbidity associated with serious GI complications but would like to point out that clinical trials have evaluated COX-2 inhibitors in mostly healthy patients without CV diseases. The low cardiovascular risk of the population studied and the short follow-up in the trials to date may significantly underestimate the CV hazard.

Dr Fleming states that significantly more hypertension is seen with rofecoxib than with celecoxib and might play an important role in CV event rates. In addition to their meta-analysis, 1 small randomized trial showed that systolic blood pressure increased significantly in 17% of rofecoxib-treated patients compared with 11% of those treated with celecoxib.¹ Some of the differential effects on blood pressure may be related to COX-2 selectivity of these agents. The biochemical selectivity of rofecoxib for COX-2/COX-1 inhibition is nearly 9 times that of celecoxib.²

Drs Konstam and Demopoulos refer to the pooled analysis of Konstam et al examining the occurrence of thrombotic event rates in over 28000 patients randomized to rofecoxib, placebo, or nonselective NSAIDs, which suggests that the results of the VIGOR trial are attributable to a beneficial effect of naproxen. We acknowledge the limitations of comparing different populations in different trials in our study but would also like to point out that this pooled analysis has the same limitations, as well as comparing studies with different rofecoxib dosages and without CV end points.

Dr Grant points out that the dosages used in the CLASS trial were higher than those used in clinical practice. He also speculates that there may not have been any CV events in the 10 studies we excluded. This is conceivable but it is difficult to

support that assumption unless some effort was made to collect CV adverse event data. We included only the 4 studies in which some systematic effort was made to collect CV event data.

Mr Haldey and Dr Pappagallo report the international experience regarding cardiovascular safety of meloxicam. However, meloxicam is structurally different from other COX-2 inhibitors and works by exploiting a greater degree of flexibility at the apex of the COX-2 channel.³ Van Hecken et al demonstrated that meloxicam has a significant level of COX-1 inhibition and this may explain the lack of CV adverse effects.⁴

Dr Minic points out that the cardiovascular event rates with the 3 nonselective NSAIDs were significantly different. This is most likely related to the degree of COX-1 inhibition with the agents with 95% inhibition noted with naproxen and lesser degrees of inhibition with ibuprofen and diclofenac.⁴ We did not compare event rates among the 3 nonselective NSAIDs in these trials although we did discuss the fact that NSAIDs differ in their spectrum of activity.

Dr McGeer and colleagues mention a potential beneficial effect of COX-2 inhibition in atherosclerosis. We alluded to their potential anti-inflammatory effect and thus potential benefit of COX-2 inhibitors in atherosclerosis and we agree that a properly designed clinical trial is necessary to evaluate the risk/benefit of these drugs. Surrogate end points such as CRP may, however, be misleading if patients with arthritis are studied, as the inflammatory component of the arthritis may override the inflammatory component of atherosclerosis and confound the results.

Dr Singh points out some of the limitations in our study including the heterogeneity of the population among trials, comparison across trials and other limitations of a post-hoc analysis, which we acknowledged in the article.

Drs White and Whelton point out that we used all-cause death rather than CV death as the end point. We were only able to analyze data that was either published or reported to the US Food and Drug Administration. Since CV death was not separately reported we did not include it. Postmarketing data were included to give a perspective on potential adverse effects.

Since publication of our meta-analysis, several basic research studies have supported the potential thrombotic effects of COX-2 inhibitors. Hennen et al⁶ showed that the observed increase in time to occlusion with aspirin in a canine coronary thrombosis model was abolished with celecoxib. Dowd et al⁷ recently demonstrated that inhibition of COX-2 aggravates doxorubicin-mediated cardiac injury in vivo, suggesting potential salutary effects of COX-2 in the heart. The purpose of our article was to raise concern about the potential risk of COX-2 inhibitors and to spur necessary research to answer this question definitively. We have fulfilled our objective if we have convinced physicians that such a trial is warranted.

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To the Editor: I am troubled by the letter I received by overnight delivery from Louis Sherwood, MD, Senior Vice President for US Medical and Scientific Affairs at Merck. He sent a "Dear Healthcare Provider" letter in response to the article by Dr Mukherjee and colleagues.¹ Sherwood directly disparages the article as "not new" and offers to supplant its findings with Merck's "confidence" in their product. A full text copy of the package insert was also included.

What disturbs me is the aggressive effort (how much did it cost to send a 5-page mass mailing by overnight delivery?) to "spin" the medical literature. If Merck disagrees with the findings of an article published in a peer-reviewed journal, they should not hesitate to send a letter to the editor, submit an editorial, or contact the authors, just like everyone else.

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- Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA.* 2001;286:954-959.

In Reply: The letter received by Dr Sperber was sent to health care providers following the numerous requests for information Merck & Co received after the publication and ensuing media reports of the article by Mukherjee et al.¹ The letter we sent included selected safety information and the full text copy of the prescribing information for Vioxx (rofecoxib). In addition, Merck did send a letter to the editor (of *JAMA*) to express our views and recently published an article² that provided a pooled analysis of the cardiovascular safety data for rofecoxib.

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Risk Factors for Dating Violence in Adolescents

To the Editor: In their article about dating violence among adolescent girls, Dr Silverman and colleagues¹ state that girls who experience these events have rates of suicidal ideation and attempts that are 6 to 9 times higher than those of girls who do not have these experiences. They also find that these girls are less likely to receive treatment for these mental health issues, perhaps because of pain and humiliation.

Although we agree that clinicians should actively try to identify such individuals, they must also do much more. The age of initiation for sexual activity has decreased and been accompanied by a decline in the health status of adolescent girls. It is important to screen adolescents for associated risk factors such as early sexual behavior and drug and tobacco use, which are markers for multiple health risks.² Historically health care providers have not provided adolescent preventive services effectively—it is estimated that less than a third of adolescents' visits to a clinician resulted in appropriate preventive services.³

We have several additional questions about this study. First, Silverman et al do not mention verbal abuse. Second, because persons engaging in same-sex or bisexual relationships may experience more violence than those in heterosexual relationships,⁴ it would be interesting to know whether Silverman et al have data on these relationships. Third, it would also have been interesting to know what percentage of subjects had been sexually abused as children. Childhood sexual abuse may be a predictor of adult sexual aggression or victimization,⁵ and this may apply during adolescence as well. Finally, the change in ethnic categorization from 1997 to 1999 makes it difficult to compare results or identify the risk or protective factors associated with ethnicity.

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In Reply: We agree with Dr McFee and colleagues that clinicians can play an important role in preventing dating violence

that goes beyond screening. However, we recognize that asking questions about dating or domestic violence remains a major challenge. Barriers likely include lack of training and knowledge of how to respond to disclosure,¹ as well as provision of confidentiality.²

We agree that verbal abuse should be the subject of greater study. We have yet to encounter a case in which some form of verbal abuse did not accompany physical or sexual violence. However, verbal abuse is infrequently included in surveys of behaviors and experiences related to morbidity and mortality.

We strongly agree with McFee et al that violence in same-sex relationships is an important area for investigation. Although this issue has not been well studied for adolescents, recent data on adults suggest that intimate partner violence may be more prevalent among men in same-sex relationships.³ We were not able to conduct such analyses because of the small number of subjects reporting same-sex sexual contact.

Finally, as we have suggested previously, the risk for dating violence victimization associated with race and ethnicity requires greater attention. Different assessments for race and ethnicity across the survey years included in our study and the overall small number of minority subjects limited our ability to examine this issue. However, we found evidence of dating violence in all racial and ethnic groups studied. It should not be assumed that someone is at higher or lower risk of intimate partner violence simply because of his or her race or ethnicity.

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Preventable Deaths From Medical Errors

To the Editor: Drs Hayward and Hofer¹ document the poor reliability of physicians' retrospective judgments of medical errors. They suggest that "previous interpretations of medical error statistics are probably misleading." However, given the methodological problems of their study, we question this interpretation.

First, the sample is small. Although the study started with 4198 deaths, only 111 of them were included in the analysis. The conclusions are based on multiple reviews, but these were conducted for only 62 patients; 59 patients had only 1 review. Second, the problems were not representative. Patients with a small number of fluid, electrolyte, and drug toxicities were oversampled. In addition, the Department of Veterans Affairs hospitals tend to care for sicker patients, but there was no standardization of disease severity. Third, the magnitude of the adverse event problem appears even worse if the quality of care that led to death is taken into account. The authors reported that 10.2% of deaths rated “borderline in care”; 22.7%, “possibly preventable by optimal care”; 6.0%, “definitely preventable”; and 6.0%, “substandard”—together leading to an unacceptable 44.9% of care deemed suboptimal or worse.

We agree with the study’s conclusion that “[m]edical errors are a major concern regardless of patients’ life expectancies,” but we believe a focus on reporting errors creates a diversion from safety.² A general call to embrace safety by reporting errors more frequently may influence a few people but will not change systems.³ Care will be safer when caregivers learn to work in patient-centered teams and design the teams as a microsystem—a small, clinically focused, organized unit of patients, technologies, and physicians, with the latter striving to produce high-quality care. Framed in this context, the role of the hospital, for example, is to create the environment for improving patient safety by providing the resources and support that the microsystems within the organization need for continual improvement and system redesign.⁴

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In Reply: Previous studies¹ estimating preventable deaths have assumed that the error assessment had unbiased interrater reliability and that if care had been optimal, the patient would

have had a 100% chance of living. Our study found that both assumptions were incorrect and led to dramatic overestimation. We see no merit in Drs Barach and Mohr’s concern that our study is too small. Our study’s statistical power is comparable to that of the Harvard Medical Practice Study (HMPS),² and the 95% confidence interval for our key finding is 1.0-1.5. Therefore, our 383 reviews of 179 deaths (including 111 active-care deaths) is more than adequate.

We included cautions about generalizability; however, the first 2 sources of overestimation are intrinsic to the analytic approach used in previous studies, not to the generalizability of our study population, and are therefore almost certainly applicable to the HMPS statistics. We have requested the HMPS interrater reliability data so that we can demonstrate this directly in the HMPS. Our study suggests that substantial overestimation will occur in *any* study that uses the same flawed analytic approach for estimating the preventability of adverse events.

We used sampling weights to correct for oversampling. Barach and Mohr erred when they computed that 45% of cases were deemed to be suboptimal or worse because they inadvertently double-counted some numbers and then combined categories that are not mutually exclusive. The actual frequency was 26%. More important, they quote the same statistics that past studies have quoted and ignore our main finding—that these statistics are invalid. Unless one adjusts for the skew in interrater reliability, these statistics would greatly overestimate the frequency of errors.

We agree with Barach and Mohr that there are major quality and safety problems in medicine. Indeed, we believe that a strong case can be made that a comprehensive quality improvement and patient safety program could save an additional 100000 lives a year if it considers inpatients *and* outpatients, quality enhancement *and* error reduction.¹ Misleading statistics are not helpful in this effort. We need to intelligently and rigorously pursue problems in proportion to their seriousness and preventability.³

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