COMMENTS AND RESPONSES

Management of Dyslipidemia for Cardiovascular Disease Risk Reduction

TO THE EDITOR: In their clinical guideline on the management of dyslipidemia, Downs and O'Malley state, "Muscle-related symptoms were the most frequent adverse effects of statins seen in trials in 10% to 20% of patients" (1). Three of the 4 references cited are observational studies, not trials. These studies can measure the frequency of adverse events reported during treatment but are at risk for confounding. Furthermore, compared with randomized, double-blind, placebo-controlled clinical trials, observational studies are generally less reliable for assessing causality. Without causality, an event is not an effect. The fourth reference that they cite is a meta-analysis that concludes, "When the placebo-controlled trials of statins were pooled as a class in a pairwise meta-analysis including 43 531 participants, statins were not significantly different than control treatment ([odds ratio], 1.07; 95% CI, 0.89–1.29; I^2, 22.1%) in terms of myalgia incidence" (2). This statement is consistent with other reports based on placebo-controlled clinical trials.

In a 5-year trial of more than 20 000 patients randomly assigned to simvastatin, 40 mg/d, or placebo and queried at every visit about muscle symptoms, approximately 6% in both groups reported such symptoms at each visit for a total incidence of 32.9% and 33.2%, respectively, over the course of the study (3). Except for rhabdomyolysis and muscle symptoms accompanied by an increase in creatine kinase levels greater than 10 times the upper limit of normal—which together occur in fewer than 0.1% of patients—the incidence of less serious muscle symptoms in clinical trials has been consistently similar in the placebo and statin groups (4). Consequently, a causal relationship of statins with these muscle symptoms has never been shown (2–5).

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IN RESPONSE: We thank Drs. Tobert and Newman for the opportunity to highlight some important strengths and limitations of available data to inform patient-centered decisions. Data from randomized, controlled trials are important. However, it is axiomatic that such trials cannot be done to inform every aspect of every clinical decision, especially adverse effects. Data within a larger universe need to be considered, synthesized, and clinically applied to individual patients. These data include observational trials.

The typical design of a published randomized trial has important limitations. These include generalizability due to inclusion criteria that exclude common comorbidities, the relatively short duration of trials and follow-up (when considering lifelong therapy), run-in periods, underappreciation of adverse effects due to dispersed reporting over many subcategories in the U.S. Food and Drug Administration Adverse Event Reporting System (1), and known suppression of data on adverse effects associated with industry-funded trials (2, 3). As Diamond and Ravnskov note (1), a largely undiscussed feature of the HPS (British Heart Protection Study) (4) is that 26% of all eligible participants withdrew during the run-in period, inherently biasing the study against representing the actual rate of adverse events by probably underestimating it.

Observational trials are subject to limitations due to potential confounding. However, they are currently the optimal way to identify adverse effects in free-living, "real-world" patients that go undetected because of the limitations of relatively small randomized, controlled trials (compared with the general population) of short duration (compared with lifelong therapy). Because of confounding, observational data cannot confer causality. However, the observational data on muscle-related effects of statins triangulate with clinician experience and with patients discontinuing statin therapy because of muscle-related symptoms. Estimating the incidence of those symptoms is clinically useful information.

Our guideline committee felt compelled to provide information relevant to the spectrum of what is available in the literature and what we know from active clinical practice. The challenge for providers will be to synthesize the evidence (with the inherent limitations) and apply it to individual patients in order to make patient-centered decisions.

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Cardiovascular Mortality Associated With 5 Leading Risk Factors

TO THE EDITOR: The paper by Patel and colleagues used data from 50 states plus the District of Columbia to develop a model to explain risk factors for cardiovascular disease (CVD) mortality in 2009–2010 (1). Their model included elevated cholesterol level, diabetes, hypertension, obesity, and current smoking. Because the data from NHANES (National Health and Nutrition Examination Survey) used in their model were provided, we decided to reexamine their model. We analyzed the data using SPSS 20.0 (IBM). In single linear regression analysis, only 3 of the factors were significantly correlated with CVD mortality rates: Hypertension was most important, followed by current smoking, and obesity. In multiple linear regression analysis, obesity was not significantly correlated with CVD. The adjusted R^2 for hypertension and current smoking was 0.81.

However, an important factor was omitted explicitly from their model: ethnic background. African Americans have much higher CVD mortality rates than Asian, Hispanic, or white persons, and they comprise large fractions of many state populations (2). When a fraction of the African American sample was run with hypertension, current smoking, and obesity in the multiple linear regression model, the best results were obtained (adjusted R^2 = 0.88). However, the risk factors are not independent. Hypertension is highly correlated with current smoking, African American race/ethnicity, and obesity, in that order, but is not correlated with cholesterol or diabetes.

The primary mechanism that increases blood pressure seems to be oxidative stress from reactive oxygen species (2). The Taiwan Society of Cardiology and the Taiwan Hypertension Society for the management of hypertension have issued guidelines, "starting with life style modification (LSM) including S-ABCDE (Sodium restriction, Alcohol limitation, Body weight reduction, Cigarette smoke cessation, Diet adaptation, and Exercise adoption)" (3).

Another recent paper found that lower income and educational level were strongly correlated with CVD mortality rates and that minority and low socioeconomic groups explained 44% of the variation in CVD mortality rates in the United States (4). This finding suggests that even if the important CVD risk factors were identified, many persons who might die of CVD would be unable to change lifestyle because of economic and educational level constraints.

Although other studies indicate that cholesterol is a risk factor for CVD, targeting cholesterol may not be wise. An observational study in Wales involving 1773 middle-aged men followed for an average of 15.4 years found a subhazard ratio related to cholesterol of 1.20 (95% CI, 1.05 to 1.37) for CVD mortality but 0.81 (CI, 0.72 to 0.90) for non-CVD mortality (5).

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IN RESPONSE: We recently reported that approximately half of national cardiovascular deaths among Americans aged 45 to 79 years could be attributed collectively to elevated cholesterol levels, diabetes, hypertension, obesity, and smoking—5 modifiable biomedical risk factors for CVD. Contrary to the conclusion by Dr. Grant and colleagues, we did in fact control for race/ethnicity, as well as educational attainment, in estimating the input hazard ratios for the attributable fraction calculations (please see the Methods and Appendix sections in our article).

We also estimated preventable fractions of cardiovascular mortality associated with each of the 5 risk factors individually. We found that hypertension and smoking were associated with the largest preventable fractions of cardiovascular

mortality nationally among both men and women. In contrast, elevated cholesterol individually was associated with preventable fractions that could not be statistically distinguished from zero among women.

The focus of our analysis was the independent contribution of modifiable biomedical risk factors for CVD to cardiovascular mortality. We wholeheartedly endorse investigation into the well-established, upstream social determinants of cardiovascular health, such as disadvantage related to race/ethnicity, education, and income, to better inform public health practice and health policy. Targeted, public health–oriented efforts to reduce onset of biomedical risk factors in the population are complementary to social welfare policies to improve socioeconomic conditions in which risk factors and disease more broadly arise.

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Prevention Strategies for Contrast-Induced Nephropathy

TO THE EDITOR: Subramaniam and colleagues report the results of a systematic review and meta-analysis funded by the Agency for Healthcare Research and Quality that evaluated specific interventions for prevention of contrast-induced nephropathy (CIN) (1). Of particular interest is their finding that "low-dose *N*-acetylcysteine compared with IV saline had clinically important and statistically significant benefits." Careful inspection of the primary studies included in this meta-analysis clearly demonstrates that this is incorrect. Specifically, the authors report that they used "a random-effects model to pool studies comparing *N*-acetylcysteine with IV [intravenous] saline versus IV saline with or without a placebo." Thus, among clinical trials in which all patients received IV saline, they assessed the benefit of *N*-acetylcysteine compared with either no *N*-acetylcysteine or to placebo. A review of the studies incorporated into this analysis confirms that this was in fact the comparison used in these trials. However, the authors inappropriately conclude that *N*-acetylcysteine is superior to IV saline for the prevention of CIN. Rather, what their analysis suggests is that among patients who receive IV saline, administration of *N*-acetylcysteine is associated with a lower incidence of CIN than the administration of placebo or no *N*-acetylcysteine.

The authors' erroneous and misleading conclusion is potentially dangerous. Providers may interpret this finding as justifying administration of *N*-acetylcysteine in lieu of IV crystalloid. It is, of course, much more feasible to administer oral *N*-acetylcysteine than IV fluids to the large number of at-risk patients who undergo contrast-enhanced procedures in the outpatient setting and/or under more urgent circumstances. However, current evidence supports administration of IV isotonic fluid before and following contrast-enhanced imaging procedures as the principal intervention to reduce the risk for CIN in patients at elevated risk. In fact, this intervention is recommended in several published guidelines on the prevention of CIN (2–4). Conversely, there has been remarkable inconsistency in the literature with regard to the benefit of *N*-acetylcysteine, leading some practice guidelines to recommend its use only in conjunction with IV isotonic fluid, whereas others recommend against its use at all (5). Until large-scale, randomized clinical trials that are adequately powered to determine the effectiveness of *N*-acetylcysteine for prevention of not only CIN but serious patient-centered outcomes are done, suggestions that this agent is effective and can be administered in lieu of IV isotonic fluid are inappropriate.

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IN RESPONSE: My coauthors and I thank Drs. Weisbord and Palevsky for calling our attention to questions regarding our recent article. We summarize our responses below.

We agree that the text should be clearer about how studies of *N*-acetylcysteine generally compared *N*-acetylcysteine plus IV saline to IV saline with or without placebo. This is also true for studies of statins and ascorbic acid, with use of IV saline in the intervention and comparator groups. To make this clearer, we have replaced Appendix Tables 2 with a data Supplement to present a more detailed version of the information about use of IV saline in the intervention and comparison groups.

For maximum clarity, we made the following changes in the text: 1) In several places we changed the text from "*N*-acetylcysteine" to "*N*-acetylcysteine plus IV saline" and 2) in the first paragraph of the Discussion, we changed "ascorbic

acid" to "ascorbic acid plus IV saline." The fourth paragraph of the Results section explains that analyses were based on studies comparing "*N*-acetylcysteine with IV saline versus IV saline with or without a placebo." The second paragraph of the statins discussion in the Results section indicates that studies "compared a statin plus IV saline with IV saline alone," and the third paragraph states that studies "compared statins added to *N*-acetylcysteine and IV saline with *N*-acetylcysteine plus IV saline." Also, in the third paragraph of the Discussion, we refer to the guideline, which "suggests using oral *N*-acetylcysteine with IV fluids."

We checked the meta-analysis and confirmed that the 95% CI for high-dose *N*-acetylcysteine is correct and changed the corresponding text to the following: "High-dose *N*-acetylcysteine plus IV saline had a small effect on reducing CIN risk that was clinically unimportant and not statistically significant."

To address concerns about the accuracy of information in Appendix Tables 2, we had reviewers recheck all information presented and prepared a more detailed version (now as a data Supplement) that includes the following changes, none of which alter the main findings or conclusions.

1. We added a footnote to clarify why the appendix only referred to use of IOCM and LOCM in the study by the ACT Investigators: "The study included patients who received HOCM, but reported results separately by type of contrast media received, so we were able to focus on the results from patients receiving IOCM or LOCM."

2. We added information about the type of saline (or other fluid) that was used in the intervention and comparison groups of all studies, with footnotes to note when a study did not report the concentration of saline, and a footnote addressing one of the reader's comments: "The study protocol recommended hydration with 0.9% saline with 93% or more of patients in both groups receiving 0.9% saline."

3. We added wording and footnotes to clarify and provide more detail about characteristics of the studies, including more information about patient characteristics in ACT 2011 (patients had at least one risk factor for contrast-induced acute kidney injury, and "about half of patients had a creatinine clearance less than 60 mg/min"); clarification of the type of cardiac condition included in Aslanger 2012; clarification of how the contrast media was left to the discretion of the cardiologists in Azmus 2005; clarification of how the study by Erturk 2014 had 3 groups; addition of a footnote to clarify that the study by Hsu 2012 included patients with renal dysfunction; addition of a footnote to clarify that the study by Kefer 2003 included patients with renal dysfunction; clarification that the study by Ochoa 2004 left the choice of contrast media to the discretion of the clinicians and did not report results separately by type of contrast media; clarification that the study by Seyon 2007 included patients with cardiac conditions; clarification that the studies by Beyazal 2014, Boucek 2013, Brar 2008, Kooiman 2014, and Lee 2011 included patients with chronic kidney disease; clarification that Masuda 2007 and Ueda 2011 did not report the concentration of saline used in the comparison group; clarification that the study by Yeganehkhah 2014 included patients at high risk for contrast-induced nephropathy (CIN); clarification that in Patti 2011 hydration was not reported, and only those with pre-existing renal failure were given normal saline; and clarification that in Yun 2014 IV saline was given at physician's discretion for both arms.

4. We corrected typographical errors, including: correction of the route of administration used for *N*-acetylcysteine in ACT with confirmation that it was correctly included in the analysis; correction of the type of contrast media listed for Jaffery 2012 with confirmation that it was correctly included in the analysis; correction of the type and route of administration for the contrast media listed for Boucek 2013 with confirmation that it was correctly included in the analysis; and clarification that the intervention infusion was for 7 hours in Boucek 2013.

5. We added two studies (Gomes 2012 and Jo 2009) with confirmation that the studies were correctly included in the analyses and text.

After preparing the revised Appendix Tables 2 (now Supplement), we identified places in the body of the article where wording changes could help to clarify the information presented.

1. Results on IV sodium bicarbonate versus IV saline, paragraph 2: changed from "Contrast medium was administered via IV in 3 studies and IA in 14 studies, and 1 study did not report the route of administration," to "Contrast medium was administered via IV in 2 studies, IA in 14 studies, and IV or IA in 1 study, and 1 study did not report the route of administration."

2. Results on IV sodium bicarbonate versus IV saline, paragraph 2: changed from "Seven studies used IOCM, 11 used LOCM, 1 used either IOCM or LOCM, and 1 did not report the type of contrast type," to "Six studies used IOCM, 12 used LOCM, and 1 study did not report the type of contrast media."

3. Results on *N*-acetylcysteine plus IV saline versus sodium bicarbonate, paragraph 1: changed from "1 used IV administration" to "1 did not report route of administration."

4. Results on statins, paragraph 2: changed from "and 1 included only patients with diabetes mellitus" to "and 2 studies included patients with diabetes mellitus and chronic kidney disease."

5. Results on statins, paragraph 3: changed from "high CIN risk" to "diabetes mellitus and chronic kidney disease."

6. Results on ascorbic acid, paragraph 2: changed from "All of these studies included patients receiving cardiovascular interventions via IA LOCM" to "These studies included patients receiving cardiovascular interventions with IA administration of LOCM (3 studies), IOCM (1 study), or either LOCM or IOCM (2 studies)."

We greatly appreciate the readers' careful attention to the details presented in the article, and we hope the changes clarify the issues and concerns that were raised.

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