In contrast to Dr. Ibáñez and colleagues, we believe that the Council for International Organizations and Medical Sciences time relationship criteria are important to use (2). First, if the time window is too narrow, a delay between onset of agranulocytosis and diagnosis might obscure the causative drug. Second, some drugs associated with agranulocytosis have long half-lives and thus may be present in the body even more than 1 month after drug withdrawal. With respect to acetaminophen, an increased risk for granulocytosis has been reported (3), and this side effect is also listed in the German summary of product characteristics (4). We believe that treatment with granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor is also advantageous for primary symptomatic patients: If we analyzed the duration of neutropenia in these patients, it was borderline significantly different between treated and untreated patients if their neutrophil count nadir was less than 0.1×10^9 cells/L ($P = 0.063$) but not if it was 0.1×10^9 cells/L or greater ($P = 0.77$). If all primary symptomatic and asymptomatic patients were analyzed together, treated patients had a lower duration of neutropenia if the neutrophil count nadir was less than 0.1×10^9 cells/L ($P = 0.019$) but not if it was 0.1×10^9 cells/L or greater ($P = 0.199$).

Like Dr. Mossad, we also identified several case reports of ganciclovir-induced bone marrow damage, including agranulocytosis. However, "nonchemotherapy drug–induced agranulocytosis" generally refers to drugs causing agranulocytosis by noncytotoxic, idiosyncratic mechanisms. This categorization was difficult for some drugs. In the case of ganciclovir, the mechanism of action (inhibition of viral and human DNA polymerase), the high frequency of neutropenia listed in the summary of product characteristics (>10%), and the bone marrow suppression after overdosing also mentioned in the summary of product characteristics, suggest a nonidiosyncratic mechanism of neutropenia and agranulocytosis. Of note, other drugs, such as azathioprine, methotrexate, or colchicine, were also not included because of their known direct cytotoxic properties.

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Potential Financial Conflicts of Interest: None disclosed.

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Analyzing the Results of the Treating to New Targets Study

TO THE EDITOR: The title of the article by Wenger and colleagues (1) is misleading. The design of the TNT (Treating to New Targets) study notes a maximum age of 75 years. Therefore, a more accurate title would replace "in patients 65 years of age or older" with "in patients 65 to 75 years of age." All of the figures and tables should include similar language. Articles, textbooks, and advertisements often include such figures and tables without a description of the study population. When the study population age is clearly defined, authors should avoid imprecise terms that inappropriately generalize the results.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

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TO THE EDITOR: The analysis of the TNT trial by Wenger and colleagues (1) suggests benefit from top-dose atorvastatin in patients older than 65 years of age. However, the 22 additional deaths from noncardiovascular causes more than offset the 5 fewer deaths from cardiovascular causes (vs. patients receiving low-dose atorvastatin), a result consistent with the entire TNT study population.

This is ominous considering that this subgroup had the following characteristics at baseline: mean age of 70 years, 82% had angina, 18% had diabetes, 53% had a myocardial infarction, 49% had angioplasty, and 55% had bypass operations.

Because stable angina is a nonfatal pain, the significant reduction in angina in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) (2) may underlie much of the nonfatal "event" benefit of this and other trials that reported no mortality benefit from atorvastatin versus placebo.

When "event" benefit may result from the amount of hospital visits but without lowering all-cause mortality, we are clearly dealing with symptoms and not with causes. This should be made clear in articles, such as that by Wenger and colleagues, that are written by statin stakeholders, especially when not presenting discordant evidence.

Another placebo-controlled trial, SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) (3), ended with a statistically nonsignificant increase in deaths in patients taking top-dose atorvastatin. In March 2007, the sponsor of the TNT trial (Pfizer) refused [letter on file] to release the mortality data regarding 49 in-house atorvastatin studies (4).

No placebo-controlled trials or meta-analyses show a mortality benefit from statin treatment in women (5). It is therefore unfortunate that the authors did not publish the Kaplan–Meier all-cause mortality curves regarding both women and men in the TNT study and in their Figure 2.

Although the authors suggest, but do not prove, benefit from more aggressive treatment, the main goal of cardiologists is preventing deaths. Here, the role of atorvastatin should be clearly reported to sex- and age-based patient groups who may be motivated to take atorvastatin because they believe it may prolong their lives, which is not the case according to the trial data published so far. The release of the relevant age- and sex-based Kaplan–Meier mortality curves would help patients and physicians choose the most effective therapy.

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TO THE EDITOR: In their secondary analysis of the TNT study, Wenger and colleagues (1) concluded that the findings support the use of intensive low-density lipoprotein cholesterol–lowering therapy in elderly individuals with established cardiovascular disease (1). Close scrutiny of the data contradicts their conclusion.

The secondary analysis of the TNT study compared the outcomes of 10 mg with 80 mg of atorvastatin daily in the 3809 patients 65 years of age or older for the 4.9-year study duration. The overall mortality rate over the study duration was 9.1% in participants randomly assigned to 80 mg of atorvastatin daily and 8.5% in participants randomly assigned to 10 mg of atorvastatin daily.

The trend toward increased mortality in the high-dose atorvastatin group was largely due to an increase in cancer deaths, which was 2.8% in that group and 2.1% in the low-dose atorvastatin group. Death from coronary heart disease was 3.0% in the high-dose atorvastin group and 3.3% in the low-dose atorvastatin group.

Therefore, the increase in cancer deaths was greater than the decrease in coronary heart disease deaths in the high-dose atorvastatin group. Perhaps the investigators can provide additional data on the incidence of new nonfatal cancer diagnoses in each group, just as they provided data on nonfatal coronary heart disease events.

Other trials have demonstrated an increase in cancer incidence and deaths in elderly participants randomly assigned to statins compared with those randomly assigned to placebo, results that cancelled any mortality benefit of decreasing coronary heart disease (2). The TNT study suggests that there might be a dose–response relation of statin therapy in increasing cancer mortality in elderly patients.

With these uncertainties, the suggestion that this study supports the use of intensive low-density lipoprotein cholesterol–lowering therapy in elderly patients with established cardiovascular disease is questionable.

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Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: We thank Dr. Alter, Dr. Mascitelli and Mr. Vos, and Dr. Goldstein for their careful reviews of our paper. Treatment effect was qualitatively similar in participants age 35 to 64 years and age 65 to 75 years, providing some reassurance that age does not importantly modify treatment effect. Because treatment duration was 4.9 years, some follow-up is derived from participants older than 75 years. Nonetheless, we agree that the TNT study results do not provide definitive efficacy or safety information for the 5% of the U.S. population older than 75 years. A manuscript comparing outcomes by sex is being published (1).

The primary study outcome for TNT overall, and this subanalysis in particular, was time to first occurrence of a major cardiovascular event, such as coronary heart disease death; nonfatal, non–procedure-related myocardial infarction; resuscitated cardiac arrest; and fatal or nonfatal stroke (2). Angina was not included in the primary TNT end point, and neither the overall trial nor the subanalysis was powered to determine whether small differences in total mortality were real or were simply due to chance. Apparent differences in total and noncardiovascular mortality between subgroups should be interpreted with great caution, especially in an older population in which competing causes of death (such as cancer) closer to the end of the normal life span are likely to play a larger role. Analyses by type of cancer in this and other statin trials do not show any organ specificity (3, 4). Ancillary analysis of noncardiovascular mortality in TNT (4) showed no relationship between cancer mortality and achieved low-density lipoprotein cholesterol level; participants in the lowest quintile of achieved low-density lipoprotein cholesterol (the majority taking 80 mg of atorvastatin) had the lowest cancer mortality rate (4). Data on incidence of nonfatal cancer by age subgroup are not available. Given study design and power, such analyses are unlikely to yield definitive results. We agree that our study does not support

intensive lipid-lowering therapy among older or younger patients to reduce total mortality; but mortality should not be the sole measure of treatment benefit. Nonfatal cardiovascular events, such as myocardial infarction and stroke, significantly affect functional status and quality of life, worsen prognosis, and result in substantial health care expenditures. Nonetheless, a 2008 hierarchical meta-analysis of statin therapy versus placebo in patients age 65 years or older showed a reduction in all-cause mortality (relative risk reduction of 22% over 5 years) (5). We affirm our conclusion that intensive lipid-lowering therapy (atorvastatin, 80 mg daily vs. 10 mg daily) in patients age 65 years or older with established coronary heart disease prevents potentially disabling cardiovascular events, with an absolute risk reduction similar to that in younger individuals.

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Cystatin C, Renal Function, and Cardiovascular Risk

TO THE EDITOR: We read with interest the article by Menon and colleagues (1) concerning cystatin C as a cardiovascular risk factor. We believe their paper considerably increases the quality of articles published on this topic, especially because glomerular filtration rate (GFR) was measured with a reference method.

We have some comments. First, it is important to keep in mind that this study analyzes cystatin C as a cardiovascular risk factor. Because all the patients had chronic kidney disease (CKD) (GFR <55 mL/min per 1.73 m^2), this study cannot be used to assert that cystatin C is definitively better than creatinine for detecting stage 3 kidney disease (GFR <60 mL/min per 1.73 m^2). Regarding the study methods, the authors do not mention when cystatin C was measured in the frozen samples. Were the samples measured retrospectively? If so, are the authors sure of the stability of the cystatin C in samples frozen, for example, for more than 10 years? The authors found that cystatin C is associated with body mass index. This interesting result should be discussed in light of the recent literature (2). The authors compared cystatin C with estimated GFR to predict cardiovascular risk. Why have they not studied an equation based on cystatin C, such as the one published by Rule and colleagues (3)?

In their interesting discussion, Menon and colleagues speculate as to why cystatin C may be a better predictor of cardiovascular risk than actual GFR by iothalamate clearance. We suggest another hypothesis. Of course, cystatin C is strongly related to GFR. Nevertheless, cystatin C concentration seems also to be influenced by other factors, such as muscle mass (2), dysthyroidism (hyperthyroidism increases cystatin C concentration, although it also increases GFR), and corticotherapy (which increases cystatin C concentration) (3). From comparative physiology, we know that GFR is strongly related to basal metabolic rate (4). Moreover, corticotherapy and hyperthyroidism also increase basal metabolic rate. Basal metabolic rate is also influenced by muscular mass, which is the greatest reserve of nucleated cells in the body and produces cystatin C (2). All the factors influencing cystatin C concentration could thus be related to a common "superior" factor: basal metabolic rate. This working hypothesis is further reinforced by data from the comparative physiology that suggest basal metabolic rate (like cystatin C) could be an important predictor of life span (5).

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Acknowledgment: The author thanks Dr. Jamie Macdonald for his help in the redaction of the manuscript.

Potential Financial Conflicts of Interest: None disclosed.

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