duce mortality toward rates of death among those in the general population in the same age group. There are other pitfalls in presenting differences in absolute risks alone, such as low absolute rates of death among young adults, among whom relative risks may be very high. Such pitfalls are probably why relative measures have often been used as primary outcomes when investigators evaluate whether rates of death are converging toward those in the general population (see references 9 to 18 in our article and in the report by the Emerging Risk Factors Collaboration[1]).

When it comes to mortality, the time that a patient is exposed to the risk factor (in this case, diabetes) is important. A young person will be exposed to diabetes over many years, and any given risk factor will contribute over an extended period, with a major potential effect on life-years lost. In our study, among patients with diabetes, the number of life-years lost is estimated to decrease from 3 to 4 years at 65 years of age to 2 to 2.5 years at 75 years of age to 1 to 1.5 years at 85 years of age. Such estimations are complex, depending on the age at onset, changes in treatment over time, and whether a cure becomes available. Hence, very-long-term scenarios are inherently difficult to predict.

In response to Zhang et al.: the exclusion of patients with existing diabetes would constitute a sample that would not be representative of patients with diabetes. We also included prevalent cases because diabetes is a progressive disease. It is noteworthy that patients with diabetes of long duration in all age groups have higher rates of death than those with a short duration (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Hence, the exclusion of patients with prevalent diabetes in various cohorts would probably underestimate mortality in the group with diabetes. We also carried out a sensitivity analysis that included only incident cases of diabetes; that exploratory analysis showed similar but somewhat lower excess mortality on the basis of hazard ratios in all age groups, as compared with our original estimates.

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Since publication of their article, the authors report no further potential conflict of interest.

1. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829-41.

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Nicotinamide for Skin-Cancer Chemoprevention

TO THE EDITOR: Chen et al. (Oct. 22 issue)[1] report on the Oral Nicotinamide to Reduce Actinic Cancer (ONTRAC) trial, which showed a protective effect of oral nicotinamide in people who are prone to skin cancer. This treatment has an excellent safety profile; however, I have some concern about the infectious adverse events.

The patients who received nicotinamide, as compared with the patients who received placebo, had slightly, although not significantly, more total infections (90 vs. 73) and more grade 3, 4, and 5 infections (10 vs. 5). However, the patients in the nicotinamide group had significantly more skin infections than those in the placebo group (14 vs. 4, $P<0.05$ by Pearson's chi-square test). If you pool all the mucocutaneous infections (lip, mucosal, nail, skin, and wound infections, as well as paronychia and sinusitis), the patients who received nicotinamide would have significantly more of these adverse events (29 vs. 10, $P<0.01$ by Pearson's chi-square test). Taken together, the number of mucocutaneous infections in the nicotinamide group might not be deemed insignificant.

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1. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med 2015;373:1618-26.

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TO THE EDITOR: The article by Chen et al. prompted us to report our beneficial results with nicotinamide in patients who had undergone kidney transplantation and who had actinic keratosis.

After receiving written informed consent, we recruited 24 patients; 12 patients were randomly assigned to receive nicotinamide and 12 to receive placebo. At baseline, actinic keratoses and surrounding light-damaged areas were identified (visually, by touch, and by means of polarized-light dermoscopy), and they were measured and photographed. Three patients underwent biopsy to detect actinic keratoses before and after treatment. At baseline and 15 days after the initiation of nicotinamide (at a dose of 250 mg three times daily), blood levels of the immunosuppressive drugs regularly received by the patients were assessed to rule out the possibility that the use of nicotinamide was interfering with the action of these drugs.

At baseline, no significant differences were observed between the sizes of light-damaged areas in patients in the two groups. At 6 months, 88% of the patients who received nicotinamide had partial regression of some or all actinic keratoses and surrounding light-damaged areas; in 44% of the patients who received nicotinamide, there was complete resolution in some of these areas (no lesions were detected on biopsy). In 91% of the patients who received placebo, the size of light-damaged areas increased, new light-damaged areas developed, or both. Nicotinamide appeared to be effective in preventing and treating actinic keratoses in patients who had undergone kidney transplantation.[1-4]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Zhao notes numeric differences between the randomized groups with respect to the frequency of certain terms for adverse events (e.g., skin infections) and terms for groupings (e.g., mucocutaneous infections). Given the number of possible comparisons of individual terms for adverse events between the groups, as well as the number of ways in which the terms could be combined, chance remains a good explanation for the lower counts noted in the placebo group. In addition, in other instances that were not noted, counts of adverse events (e.g., upper respiratory infections, musculoskeletal disorders, and eye disorders) were higher in the placebo group than in the nicotinamide group. Although it is important to continue to monitor all categories of adverse effects, including mucocutaneous infections, we note that nicotinamide has been found to enhance the clearance of *Staphylococcus aureus* skin infections[1] and bacterial colitis[2] in mouse models and to inhibit the enzymatic activity of various fungi that are responsible for skin infections.[3]

In the study involving renal-transplant recipients by Drago and colleagues, the reduction in premalignant actinic keratoses with nicotinamide was similar to the changes observed in both our recent ONTRAC study and our previous phase 2 studies involving immunocompetent participants.[4] Data from phase 3 studies of the safety and efficacy of nicotinamide for chemoprevention in immunosuppressed persons are lacking.

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