TO THE EDITOR: Sundström and colleagues (1) conclude that drug treatment “in the primary preventive setting is likely to reduce the risk for several important adverse health outcomes.” This finding is interesting given that the 2012 Cochrane review that they cite (2) found no evidence of mortality or morbidity benefit with drug treatment of mild hypertension. What changed?

The authors explain the different conclusions by stating, “Besides the inclusion of persons with diabetes or prior antihypertensive treatment, the disparity between the conclusions of this review and the one immediately preceding it is primarily attributable to statistical power.” The present review nearly doubled the number of patients, quadrupled the number of cardiovascular events, and provides data on end points not available in the prior meta-analysis.” Having recently examined this literature with colleagues (3), I have a different interpretation. To gain statistical power, Sundström and colleagues’ review combined high- and low-risk patients with mild hypertension, which is equivalent to mixing apples—that is, higher-risk persons with diabetes and prior treatment—with oranges—that is, persons without diabetes or prior treatment of hypertension.

To summarize Sundström and colleagues’ review a bit differently, I used Appendix Table 3 to compare trial participants as oranges (those from the Cochrane review) or apples (those from BPLTTC [Blood Pressure Lowering Treatment Trialists’ Collaboration] trials). A total of 96% of patients in BPLTTC trials had diabetes and 62% previously received antihypertensive treatment compared with 0% for both in the Cochrane review, making the relative difference (96%/0% and 62%/0%) infinite. Discrete outcomes, including total deaths, strokes, and coronary events, were higher by a factor of 3.8, 13.0, and 2.1, respectively, in participants in BPLTTC trials. (Cardiovascular deaths and heart failure could not be compared because of a lack of data.)

There is hope yet. Sundström and colleagues bury a worthy point when they conclude that “estimation of cardiovascular risk may aid prioritization in this patient group.” Rather than combining apples and oranges, we need to treat them as different fruits. Apples may benefit from drug treatment of mild hypertension, whereas oranges do not. Blending them serves neither fruit well. Although some share his taste, many like fruit salad. Our view, objectively supported (1), is that apples and oranges have far more commonalities than differences.

As Dr. Martin points out, our review differs from a previous one (2) in that it includes many persons with diabetes. Whereas Dr. Martin sees the presence or absence of diabetes as a good reason not to estimate summary effects for all, we disagree.

Our rationale for combining participants with and without diabetes is firmly evidence-based. Prior large overviews show quite clearly that lowering blood pressure produces similar relative risk reductions in persons with and without diabetes (3), in those with high and low cardiovascular risk (4) and blood pressure, and with and without overt cardiovascular diseases, as well as older and younger persons. As such, we can see no strong a priori rationale for expecting different relative effects of lowering blood pressure in persons with and without diabetes, and we found no corresponding statistical evidence of heterogeneity in treatment effects in our review or previous ones (3). We agree that the absolute benefit of treatment will vary with the baseline level of risk, but our meta-analysis combines relative, not absolute, effects. Indeed, we recently showed that blood pressure–lowering treatment will provide the greatest benefit if directed toward those at greatest risk, not those with hypertension (4).

Dr. Martin has previously written that he believes that hypertension is overdiagnosed and overtreated. We agree; blood pressure, not hypertension, causes disease, and lowering blood pressure in those at risk will produce the greatest benefits. Hypertension control is a concept that needs retiring to the history books. However, cardiovascular disease remains the leading cause of death globally, elevated blood pressure is the leading health risk, and the number of persons with high blood pressure is increasing. Hence, the unmet need for better approaches to lowering blood pressure is immense. Our data leave little doubt that blood pressure reduction will protect both apples and oranges, but the death of the hypertension paradigm will provide the greatest health gains.

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References

IN RESPONSE: In Dr. Martin’s opinion, mixing apples and oranges serves neither fruit well. Although some share his taste, many like fruit salad. Our view, objectively supported (1), is that apples and oranges have far more commonalities than differences.

Our rationale for combining participants with and without diabetes is firmly evidence-based. Prior large overviews show quite clearly that lowering blood pressure produces similar relative risk reductions in persons with and without diabetes (3), in those with high and low cardiovascular risk (4) and blood pressure, and with and without overt cardiovascular diseases, as well as older and younger persons. As such, we can see no strong a priori rationale for expecting different relative effects of lowering blood pressure in persons with and without diabetes, and we found no corresponding statistical evidence of heterogeneity in treatment effects in our review or previous ones (3). We agree that the absolute benefit of treatment will vary with the baseline level of risk, but our meta-analysis combines relative, not absolute, effects. Indeed, we recently showed that blood pressure–lowering treatment will provide the greatest benefit if directed toward those at greatest risk, not those with hypertension (4).

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References

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Letters


TO THE EDITOR: DeFilippis and colleagues (1) evaluated the predictive utility of the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) pooled cohort equations in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort and reported what they perceive to be overprediction. The guideline identified and thoroughly discussed this potential problem (2, 3). DeFilippis and colleagues attempted to explore it in more detail, but their analyses have substantial methodological problems.

Coronary artery calcium (CAC) was scored in MESA participants at least twice during the study. Knowledge of the results was associated with greater initiation of preventive therapies, especially among those at higher risk or with higher CAC scores (4). Thus, persons more likely to have atherosclerotic cardiovascular disease (ASCVD) events were also more likely to be treated, which undoubtedly contributed to “under-performance” of MESA event rates compared with the predicted natural history.

Use of preventive therapies in the MESA cohort is extraordinarily higher than that in the U.S. population (as Table 2 shows). From baseline to follow-up, use of aspirin increased from approximately 25% to 55% (ever), blood pressure medications from 35% to 60%, lipid-lowering drugs from 15% to 44%, and any drug from 53% to more than 80%. Therefore, using these data to evaluate the accuracy of estimated risk according to natural history is impossible.

DeFilippis and colleagues attempted to account for use of preventive treatments with several methods, all of which are flawed. Simple statistical adjustments for use or censoring at initiation of therapy clearly do not account for treatment effects. Excluding all participants who were ever treated yielded a highly biased analysis subject to major confounding by indication. Furthermore, only 14 (6%) of 218 observed events occurred in untreated patients, leading to highly unstable estimates.

The authors seem to have included Chinese and Hispanic Americans, who make up one third of the MESA cohort. The ACC and AHA pooled cohort equations were derived and strongly recommended for non-Hispanic white and African American men and women, with a weak recommendation for others. The guideline noted that the equations would overestimate risk in Hispanic and East Asian American persons. A more appropriate analysis would have evaluated each race or ethnic group separately.

These concerns raise important questions about the interpretation of DeFilippis and colleagues’ findings. The new ACC and AHA guideline represents a major advance that will reduce the population burden of cardiovascular disease (5). Although future and better evidence will likely lead to even better guidelines, implementation of the current one should be a national priority now.

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References

IN RESPONSE: The study cited by Dr. Goff and colleagues (1) shows an association between CAC score and medication use, not an association with decreased events. As the authors acknowledge in the guideline (with the tepid grade IIb recommendation for CAC testing), evidence for a direct effect of CAC scoring on hard outcomes is limited (2). For CAC scoring
to explain the overestimation of the risk for ASCVD, the reporting of CAC scores in MESA would have had to prevent almost one half of all ASCVD events predicted by the AHA-ACC-ASCVD risk score.

The purpose of our sensitivity analysis was to evaluate whether eliminating preventive therapies qualitatively changed the study’s main findings. It did not. Furthermore, available data do not support Dr. Goff and colleagues’ claim that “use of preventive therapies in the MESA cohort is extraordinarily higher than that in the U.S. population.” For example, NHANES (National Health and Nutrition Examination Survey) 2001–2002 estimated that approximately 30% of the U.S. population older than 40 years was treated for hypertension (3). When similar age-adjusted data were used, 31% of MESA participants were receiving blood pressure medications in 2000 to 2002. Cholesterol-lowering medication use was reported in 20% of the U.S. population older than 40 years in NHANES 2003-2004 and in 19% of age-adjusted MESA participants in 2002 to 2004. These percentages increased to an estimated 28% of U.S. adults in 2011 to 2012 and 34% of participants in our study over the same time period (4).

In simple stratified analysis, the AHA-ACC-ASCVD score overestimated risk among all ethnic groups studied in MESA: 103% for African American persons, 311% for Chinese persons, 61% for Hispanic persons, and 49% for white persons. A full multivariable, adjusted analysis of the factors most associated with risk overestimation in MESA is currently being peer-reviewed.

Any new therapy or diagnostic or prognostic test should be compared with existing standards of care. When evaluated by us and others (5), the AHA-ACC-ASCVD risk calculator did not show improved calibration or discrimination compared with 4 other scores used in clinical practice. Dr. Goff and colleagues also do not explain the good calibration of the Reynolds Risk Score was well-calibrated.

We speculate that risk scores derived from cohorts assembled decades ago exclude pertinent factors or are poorly calibrated for modern populations. Diet, exercise, air pollution, ethnic diversity, intensity of tobacco use, content of tobacco products, and effectiveness of antihypertensive therapy are among the cardiovascular risk factors that have changed over the past 25 years. Risk prediction is an evolving science and will require continual updating through the study of well-characterized, contemporary, primary prevention cohorts.

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References

Use of Life-Sustaining Therapies for Patients With Ebola Virus Disease

TO THE EDITOR: Halpern and Emanuel (1) state that “cardiopulmonary resuscitation (CPR) for most patients with Ebola . . . carries a highly unfavorable risk–benefit ratio” and that a default policy of not routinely providing CPR is preferable. This reasoning should also apply to patients who do not have Ebola virus disease who have a similarly remote prospect of surviving CPR, yet few advocate for such a policy. Because attempting CPR regardless of medical utility is the default in contemporary practice, arguments to withhold expectedly ineffective CPR in patients with Ebola, to be consistent, must ignore inefficacy and rest solely on risks to clinicians. Personal protective equipment can reduce the risks for harm to clinicians, and the time required to access it should not additionally harm patients whose expected benefit from CPR is already remote. If inefficacy is not a compelling imperative and clinician harms can be managed, then the argument that should follow—albeit a counterlogical one—is that CPR should not be presumptively withheld in patients dying of Ebola.

Although weighing patient benefit against clinician harm is a vexing bioethical concern (2), weighing no clinical benefit against defined clinician harm should be a simple ethical calculus. It is made challenging because, in routine practice, inefficacy of CPR is an insufficient reason to withhold its use by default.

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References

IN RESPONSE: We appreciate Dr. Berger’s interest in our commentary, but his argument is based on inaccurate information. It is true that attempting CPR is the “default” policy in contemporary practice. However, among all patients who do not opt out of this default and who experience in-hospital sudden cardiac arrest, survival to hospital discharge is now 15% (1). Furthermore, time is of the essence. For example, among patients with shockable rhythms (ventricular fibrillation or tachycardia), resuscitation within 2 minutes leads to nearly twice the survival rate as resuscitation after 2 minutes (2). Thus, the need to first don personal protective equipment in the case of Ebola—which requires at least 10 minutes among even experienced practitioners—means that CPR in this setting confers a fundamentally different prognosis from CPR in patients who do not have Ebola. As such, using the same weighing of benefits to the patient versus risks to the clinician that both Berger and we advocate yields a fundamentally different conclusion in the case of Ebola.

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References

Observation
Anakinra Improves Pyoderma Gangrenosum in Psoriatic Arthritis: A Case Report

Background: Anakinra is an antagonist of the receptor for interleukin-1. Pyoderma gangrenosum is a poorly understood condition that causes necrosis of skin and other tissue.

Objective: To report the first case to our knowledge of anakinra improving pyoderma gangrenosum in a patient with psoriatic arthritis.

Case Report: We assumed the care of a 46-year-old white woman with a painful, deep ulcer in the left leg. She was diagnosed with plaque psoriasis at age 7 years and had experienced symmetrical, destructive axial and peripheral polyarthritis since age 18 years. She was negative for rheumatoid factor and anti–cyclic citrullinated peptide antibodies but positive for HLA-B27 antigen. Computed tomography documented sacroiliitis typical of psoriatic arthritis. The patient had no extra-articular damage associated with her rheumatism, which had been treated with methotrexate since diagnosis. She also had previously received prednisone, sulfasalazine, and infliximab, but treatment with these agents was discontinued in 2004 because of infection after knee arthroplasty.

The ulcer was deep with an irregular border and surrounding skin that was erythematous and indurated (Figure, top). She had no fever, adenopathy, or other symptoms of infection. The patient’s C-reactive protein level was 390.48 nmol/L (normal, <47.62 nmol/L). Doppler ultrasonography found no signs of venous or arterial thrombosis or arteriopathy. Bacterial and mycobacterial cultures were negative. Biopsy of the ulcer border found an infiltrate of chronic inflammatory cells in the dermis and a predominance of polymorphonuclear neutrophils with no indication of infection or cutaneous vasculitis.

Figure. Deep ulcer of the left leg associated with pyoderma gangrenosum.

We diagnosed pyoderma gangrenosum. The ulcer did not respond to oral prednisone (1 mg/kg of body weight per day) and an increased methotrexate dosage (to 15 mg/wk) or to oral dapsone (100 mg/d) with pulse therapy using intravenous methylprednisolone at 500 mg/wk for 5 weeks. During 4 months of therapy with weekly doses of 50 mg of subcutaneous etanercept, which is an inhibitor of tumor necrosis factor, the ulcer continued to worsen and eventually exposed tendons. The wound continued to worsen until it circled the leg despite an additional 6 months of therapy with ustekinumab, which blocks interleukin-12 and interleukin-23.

We started therapy with anakinra, 100 mg once daily, and noticed improvement after 15 days with the appearance of granulation tissue. The ulcer continued to heal relatively quickly during the next 3 months (Figure, middle). However, we had to discontinue the therapy for 5 months because of surgery for a complicated dorsal pressure ulcer, and during this time the leg ulcer worsened. Finally, 7 months after anakinra therapy was resumed, it continued to heal (Figure, bottom).

Discussion: Pyoderma gangrenosum is an idiopathic inflammatory disease frequently associated with inflammatory bowel disease; rheumatologic disease; cancer; and rare disorders, such as the syndrome of pyogenic sterile arthritis, pyoderma gangrenosum, and acne. Treatment of pyoderma gangrenosum is largely empirical and frequently consists of corticosteroids. Recently, anti-tumor necrosis factor-α therapy has been found to be useful in some patients (1).

We started anakinra therapy in this patient after other treatments failed. This agent is used in autoinflammatory disease and rheumatoid arthritis but also for many other disorders (2), such as the pyoderma gangrenosum that occurs with the pyogenic sterile arthritis, pyoderma gangrenosum, and the acne syndrome (3). We are also aware of 1 report of failure of anakinra to improve pyoderma gangrenosum associated with inflammatory bowel disease (4).

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References