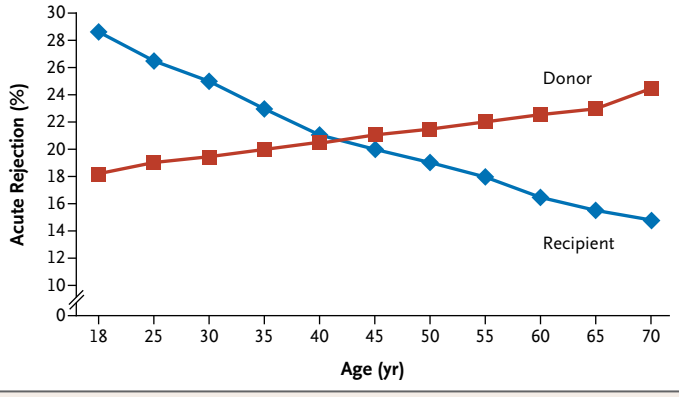

Figure 1. Association between the Age of Kidney Donors and Recipients and Acute Rejection Rates.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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1. Department of Health and Human Services. OPTN/SRTR annual report 2009. (http://optn.transplant.hrsa.gov/ar2009.)
2. Haynes L, Maue A. Effects of aging on T-cell function. Curr Opin Immunol 2009;21:414-7.
3. Tullius SG, Tran H, Guleria I, Malek SK, Tilney NL, Milford E. The combination of donor and recipient age is critical in determining host immunoresponsiveness and renal transplant outcome. Ann Surg 2010;252:662-74.
4. Denecke C, Bedi DS, Ge X, et al. Prolonged graft survival in older recipient mice is determined by impaired effector T-cell but intact regulatory T-cell responses. PLoS One 2010;5(2):e9232.

Eplerenone in Mild Heart Failure

TO THE EDITOR: In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), Zannad et al. (Jan. 6 issue)[1] address the important question of whether aldosterone blockade is clinically useful in patients with mild systolic heart failure. A remaining question is whether both drugs from this class (eplerenone and spironolactone) have the same benefits. Both agents block the aldosterone receptor, but spironolactone has progestogenic and antiandrogenic actions, effects that are minimized in eplerenone. Whether these differences would be associated with a differential effect in heart-failure prognosis is unknown. Deterioration of anabolic status is a hallmark of heart-failure progression and is associated with a worse prognosis.[2] Are the impressive benefits that were shown in EMPHASIS-HF due only to aldosterone antagonism or might they also be explained by other additional actions?

Our group recently showed that testosterone has a protective effect against cardiomyocyte apoptosis. This beneficial effect was lost after therapy with spironolactone but not with eplerenone.[3] Other investigators have shown that eplerenone and spironolactone have different effects on important metabolic measurements.[4] Thus, more data are needed as to whether both agents provide equivalent benefits.

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1. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.
2. Jankowska EA, Biel B, Majda J, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation 2006;114:1829-37.
3. Sánchez-Más J, Turpín MC, Lax A, Ruipérez JA, Valdés Chávarri M, Pascual-Figal DA. Differential actions of eplerenone and spironolactone on the protective effect of testosterone against cardiomyocyte apoptosis in vitro. Rev Esp Cardiol 2010;63:779-87.
4. Yamaji M, Tsutamoto T, Kawahara C, et al. Effect of eplerenone versus spironolactone on cortisol and hemoglobin A(1c) levels in patients with chronic heart failure. Am Heart J 2010;160:915-21.

TO THE EDITOR: In EMPHASIS-HF, Zannad et al. report the efficacy of eplerenone in reducing the risk of death from cardiovascular causes, as compared with placebo. Besides the reasons presented by the authors, the result may at least partially be explained by the blood-pressure–lowering ef-

fect of eplerenone when used in a high-risk group of normotensive patients. Mineralocorticoid-receptor antagonists are rescue agents recommended for patients with resistant hypertension.[1] The mean between-group difference in the reduction in systolic blood pressure during the study period was 2.2 mm Hg and may have been higher at the beginning of the follow-up. Meta-regression analyses have shown that differences of 1.6 mm Hg to 4.0 mm Hg that were observed in clinical trials were associated with an 8% reduction in the rate of cardiovascular events.[2] Moreover, cardiovascular benefits of blood-pressure reduction have been similar across the full range of blood pressures, starting at systolic blood pressures as low as 110 mm Hg.[3] The blood-pressure–lowering effect cannot be disregarded in the interpretation of trials that present a palpable difference in blood pressure between the study groups.

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1. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117(25):e510-e526.
2. Verdecchia P, Gentile G, Angeli F, Mazzotta G, Mancia G, Reboldi G. Influence of blood pressure reduction on composite cardiovascular endpoints in clinical trials. J Hypertens 2010;28:1356-65.
3. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.

TO THE EDITOR: In EMPHASIS-HF, eplerenone impressively reduced the risks of death and hospitalization in patients with New York Heart Association (NYHA) class II heart failure and an ejection fraction of 35% or less (depending on the QRS duration). In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study,[1] we showed that the level of plasma aldosterone was independently associated with cardiovascular risk in patients who had class III or IV NYHA heart failure and a preserved ejection fraction and in those with mild symptomatic heart failure (NYHA class I or II), with the acute coronary syndrome, with angiographically verified coronary artery disease, and with arterial hypertension. Of note, the mean left ventricular ejection fraction within these groups of patients was around 60%, indicating that mineralocorticoid-receptor blockade might exert protective effects beyond the neurohormonal activation occurring with systolic heart failure. In fact, excessive sodium intake and oxidative stress caused by preexisting tissue damage might amplify the deleterious cardiovascular effects of aldosterone.[2] In this context, further studies should evaluate potentially beneficial effects of mineralocorticoid-receptor blockade in concert with modifications in the intake of dietary salt in patients at cardiovascular risk who do not primarily have heart failure.

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1. Tomaschitz A, Pilz S, Ritz E, Meinitzer A, Boehn BO, März W. Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Eur Heart J 2010;31:1237-47.
2. Tomaschitz A, Pilz S, Ritz E, Obermayer-Pietsch B, Pieber TR. Aldosterone and arterial hypertension. Nat Rev Endocrinol 2010;6:83-93.

TO THE EDITOR: In EMPHASIS-HF, patients had to be in NYHA functional class II with an ejection fraction of 30% or less (or if >30 to 35%, a QRS duration of >130 msec). The patient's functional capacity was based on the investigator's opinion. In the Randomized Aldactone Evaluation Study (RALES),[1] spironolactone had similar benefits in patients with severe heart failure (i.e., NYHA class III or IV with an ejection fraction of <35%). The principal difference in the two study populations was the subjective NYHA class. The difference between NYHA class II and class III is quite subjective. Therefore, the distinction between the two trial cohorts needs further clarification. Moreover, the selection criteria excluded a substantial proportion of patients with NYHA class II heart failure with an ejection fraction of

30 to 54%. Thus, a benefit for mineralocorticoid-receptor antagonist therapy has not been shown for such patients.

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1. The RALES Investigators. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). Am J Cardiol 1996;78:902-7.

THE AUTHORS REPLY: In response to the comments by Pascual-Figal et al.: it is impossible to know whether eplerenone and spironolactone have the same benefits in the absence of a head-to-head comparison. There are differences between these agents with respect to side effects and the shorter elimination half-life for eplerenone. The effect of both drugs on potassium clearance is also uncertain.[1]

Although Gus and Fuchs suggest that the morbidity and mortality benefits of eplerenone may relate to blood-pressure reduction, some treatments that reduce blood pressure are not effective in patients with heart failure,[2] whereas others that have little or no effect on blood pressure, or even increase it, as compared with placebo, are beneficial. In addition, in heart-failure studies, the numbers of myocardial infarctions and strokes are relatively low. These rates were not affected by eplerenone in EMPHASIS-HF.

We agree with Tomaschitz et al. that the use of a mineralocorticoid-receptor antagonist might be of benefit in patients with heart failure and a preserved ejection fraction or even in patients without heart failure. Trials that are testing these hypotheses are under way.

Ghosh Dastidar is correct in stating that one of the main differences between EMPHASIS-HF and RALES[3] was the investigator-reported NYHA class. Although subjective, the NYHA class is a powerful predictor of prognosis, independent of ejection fraction and other measures. The fact that the annual rate of death was 25% in RALES but only 9% in EMPHASIS-HF suggests that the difference in NYHA class between these trials was real. We believe that from the totality of trial data, it is clear that mineralocorticoid-receptor blockade is of benefit in patients with systolic heart failure who have mild, moderate, or severe symptoms.

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

1. Sica DA. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. Heart Fail Rev 2005;10:23-9.
2. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure — results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547-52.
3. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.

Preexposure Chemoprophylaxis for HIV Prevention

TO THE EDITOR: Grant et al. (Dec. 30 issue)[1] report that once-daily emtricitabine–tenofovir (FTC–TDF) provided 44% relative risk reduction from human immunodeficiency virus (HIV) infection in a high-risk population. In their discussion and in the accompanying editorial,[2] potential limitations of this approach to curb the HIV epidemic, including side effects (e.g., renal insufficiency), the potential emergence of drug resistance (in patients with HIV and hepatitis B virus infection), and medication-use fatigue, are detailed. The economic implications of this prevention method, however, are not discussed. Given the absolute risk reduction of 2.26 percentage points reported in the study, about 44 people would have to receive preexposure therapy to prevent one infection. With an estimated monthly cost of $753 for FTC–TDF in the United States,[3] preventing one infection over a 1-year period would cost almost $500,000. This amount is about 20 times more expensive than treating a person with HIV infection for 1 year.[4] Among