Samarendra mentions the greater frequency of withdrawals in patients who were randomly assigned to surgery than in those who were assigned to TAVR. This greater frequency, which was also seen in the PARTNER 1 cohort A trial, suggests a lack of equipoise with respect to patients and providers. We also agree that assessment of the durability of bioprosthetic valves will require at least 5 to 10 years of follow-up, although the 5-year echocardiographic results look encouraging.[2] Although the rate of total (of mild or greater severity) paravalvular aortic regurgitation in the PARTNER 2 cohort A trial was indeed 26.2%, moderate or severe paravalvular regurgitation was present in only 8.0% of patients, and mild paravalvular regurgitation was not associated with subsequent mortality. Finally, although neuroimaging studies suggest increased perfusion deficits with TAVR versus surgery, the size of the deficits was twice as large in the surgical patients.[3] We do not think that rates of clinical stroke were underreported, since careful neurologic assessments were performed in all patients.

In reply to Santarpino et al.: it is incorrect to label the surgical techniques in our trial as "outdated" and to imply that the surgical outcomes were therefore substandard. In the 57 surgical centers in the trial, the all-cause mortality at 30 days after surgery was 4.1% and the ratio of observed-to-expected mortality was 0.71, according to the Society of Thoracic Surgeons (STS) risk scores. The STS score equals the predicted mortality expressed as a percentage. Moreover, although specific surgical techniques were not mandated, 15% of the patients did receive minimally invasive aortic-valve replacement and there were no differences in outcomes; this is consistent with the surgical literature, which shows no differences in outcomes between patients who undergo surgery with a minimally invasive approach and those who do not. Short-term or long-term data on sutureless aortic valves are lacking, and none show clear benefits. An inpatient cost differential favors surgery because of the high cost of the transcatheter valve, but recently this differential has narrowed because of lower in-hospital costs associated with reduced lengths of stay in the intensive care unit and the hospital among patients undergoing TAVR.

Martin B. Leon, M.D.
Craig R. Smith, M.D.
Columbia University Medical Center
New York, NY
mleon@crf.org

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

1. Filardo G, Hamilton C, Hamman B, Hebeler RF Jr, Adams J, Grayburn P. New-onset postoperative atrial fibrillation and long-term survival after aortic valve replacement surgery. Ann Thorac Surg 2010;90:474-9.
2. Mack MJ, Leon MB, Smith CR, et al. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
3. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation 2010;121:870-8.

DOI: 10.1056/NEJMc1606814

Aliskiren, Enalapril, or Both in Heart Failure

TO THE EDITOR: McMurray et al. (April 21 issue)[1] report on the results of the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE). They found that in patients with heart failure, aliskiren combined with an angiotensin-converting–enzyme (ACE) inhibitor increased the risk of adverse events without any benefit. These results contrasted with those of previous studies showing that blockade with an ACE inhibitor and an angiotensin II receptor blocker (ARB) improved cardiovascular outcomes.[2,3]

McMurray et al. state that ATMOSPHERE is the only trial that used an evidence-based dose of an ACE inhibitor. However, it is conceivable that the combination of an ARB and an ACE inhibitor can provide an additional therapeutic effect, since these drugs increase levels of angiotensin-(1-7) (a heptapeptide component of the renin–angiotensin system), which antagonizes angiotensin II effects.[4] Although knowledge of the effects of angiotensin-(1-7) in patients with heart failure is still limited, experimental studies show cardioprotection.[4,5]

In addition, the distribution of use of beta-blockers and a mineralocorticoid-receptor antag-

onist differed in ATMOSPHERE, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Added (CHARM-Added) trial,[3] and the Valsartan Heart Failure Trial (Val-HeFT).[2] The percentage of patients who received beta-blockers was 92.0% in ATMOSPHERE, 55.0% in CHARM-Added, and 34.5% in Val-HeFT; the percentage of patients who received a mineralocorticoid-receptor antagonist was 36.6%, 5.0%, and 17.4%, respectively.

Finally, the large number of patients in whom therapy was discontinued in ATMOSPHERE did not alter the distribution of patients in the three groups at the end of the trial. Nevertheless, it would be useful to know whether the balance in baseline characteristics among the three groups was maintained among patients in whom treatment was discontinued and those in whom it was not discontinued.

Alessandra R. Silva, Pharm.B.S.
Alexandre Martini, M.D.
Francisco A.R. Neves, M.D.

University of Brasilia
Brasilia, Brazil
nevesfar@gmail.com

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

1. McMurray JJV, Krum H, Abraham WT, et al. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. N Engl J Med 2016;374:1521-32.
2. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
3. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767-71.
4. Santos RA. Angiotensin-(1-7). Hypertension 2014;63:1138-47.
5. Lee VC, Lloyd EN, Dearden HC, Wong K. A systematic review to investigate whether Angiotensin-(1-7) is a promising therapeutic target in human heart failure. Int J Pept 2013;2013:260346.

DOI: 10.1056/NEJMc1606625

THE AUTHORS REPLY: Silva and colleagues raise the interesting but complex subject of the effect of various renin–angiotensin system blockers and their combinations on nonclassic angiotensin peptides. As of this writing, the role, if any, of these peptides in humans is unknown.

We agree that not only the background dose of an ACE inhibitor but also the use of beta-blockers and mineralocorticoid-receptor antagonists may be relevant to the different outcomes in the trials mentioned. Also, inevitably, the characteristics of (and outcomes in) patients who discontinue a study drug differ from those who do not. However, as in any other trial, these different characteristics do not alter the interpretation of the results, which should be analyzed according to the intention-to-treat principle.

John J.V. McMurray, M.D.

University of Glasgow
Glasgow, United Kingdom
john.mcmurray@glasgow.ac.uk

Kenneth Dickstein, M.D., Ph.D.

Stavanger University Hospital
Stavanger, Norway

Lars V. Køber, M.D., D.M.Sc.

Rigshospitalet
Copenhagen, Denmark

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

DOI: 10.1056/NEJMc1606625

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

TO THE EDITOR: The article on the Insulin Resistance Intervention after Stroke (IRIS) trial by Kernan et al. (April 7 issue)[1] and the corresponding editorial by Semenkovich[2] overlook an interesting property of pioglitazone — that is, it has antihypertensive properties (probably associated with L-type channel blockade) that were associated with blood-pressure reduction in patients in the IRIS study.[3] These properties were recognized decades ago,[4,5] but they were generally overlooked.

More recently, pioglitazone was shown to reduce both daytime and nighttime ambulatory blood pressure.[6] The fingerprints of calcium-channel blockers are decreases in the risk of stroke and myocardial infarction and a tendency to increase the risk of heart failure.[7] Such properties probably partly explain the IRIS findings, independent of the effect of pioglitazone on insulin resistance.

Michael Bursztyn, M.D.

Hadassah–Hebrew University Medical Center
Jerusalem, Israel
bursz@mail.huji.ac.il