

difference. The observed loss of FEV₁ was neither a time-dependent nor a dose-dependent effect in the withdrawal group, as compared with the maintenance group. A difference of 38 ml between groups became apparent only after the final step of inhaled glucocorticoid withdrawal and did not change to a meaningful extent thereafter.

Singanayagam et al. point out that we included only patients receiving maintenance therapy with inhaled glucocorticoids who had a history of exacerbation in the previous year. This reflects current treatment recommendations. In the recent Indacaterol: Switching Nonexacerbating Patients with Moderate COPD from Salmeterol/Fluticasone to Indacaterol (INSTEAD) trial involving patients with moderate COPD who had no exacerbations during the previous year, switching patients from a combination of a long-acting β -agonist (LABA) and an inhaled glucocorticoid to an ultra-long-acting LABA did not increase the exacerbation rate during 26 weeks of treatment.¹ We agree that clinicians prescribe inhaled glucocorticoids because they see value in their use, but there may be reasons other than the prevention of exacerbations for this practice, such as the convenience of combination inhalers.²

Brightling et al. suggest that we stratify our results according to the baseline blood eosinophil count. A major objective of the WISDOM

trial was to identify a subgroup of patients who have a response to inhaled glucocorticoids,³ but so far we have not been able to identify a responsive phenotype on the basis of data from our prespecified subgroups.

Helgo Magnussen, M.D.

Pulmonary Research Institute
Grosshansdorf, Germany
magnussen@pulmoresearch.de

Kay Tetzlaff, M.D.

Boehringer Ingelheim Pharma
Ingelheim, Germany

Peter M.A. Calverley, M.D.

University of Liverpool
Liverpool, United Kingdom

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

1. Rossi A, van der Molen T, Olmo RD, et al. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. *Eur Respir J* 2014;44:1548-56.
2. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med* 2013;1:51-60. [Erratum, *Lancet Respir Med* 2013;1:101.]
3. Magnussen H, Watz H, Kirsten A, et al. Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. *Respir Med* 2014;108:593-9.

DOI: 10.1056/NEJMc1413308

Fractional Flow Reserve–Guided PCI

TO THE EDITOR: De Bruyne et al. (Sept. 25 issue)¹ conclude that the high rate of death within 7 days after randomization in the percutaneous coronary intervention (PCI) group in their study was due to benign periprocedural infarctions, but there were more myocardial infarctions in the medical-therapy group after the initial 7 days following randomization. However, after 7 days, there were more revascularizations in the medical-therapy group; this suggests that there were more periprocedural infarctions.² Thus, the high rate of myocardial infarctions after the initial 7 days following randomization in the medical-therapy group could also be caused by the same benign periprocedural infarctions, since there was no difference in overall mortality.² Unfortunately, the percentage of late myocardial infarctions caused by periprocedural infarctions was not reported.

Furthermore, the primary outcome in this study was driven mainly by urgent revascularization, which could have been confounded by the open-label nature of the study. Since patients in the medical-therapy group knew that they had untreated stenosis, they were more likely to report symptoms.³ Coupled with bias from treating physicians, this would lead to a higher incidence of hospitalization, cardiac catheterization, and ultimately revascularization.⁴ Therefore, a double-blind, controlled trial is required to determine the true effect of fractional flow reserve–guided PCI on urgent revascularization.⁵

Rahman Shah, M.D.

University of Tennessee
Memphis, TN

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

1. De Bruyne B, Fearon WF, Pijls NHJ, et al. Fractional flow reserve–guided PCI for stable coronary artery disease. *N Engl J Med* 2014;371:1208-17.
2. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med* 2011;364:453-64.
3. Rothberg MB, Sivalingam SK, Ashraf J, et al. Patients' and cardiologists' perceptions of the benefits of percutaneous coronary intervention for stable coronary disease. *Ann Intern Med* 2010;153:307-13.
4. Lin GA, Dudley RA, Redberg RF. Cardiologists' use of percutaneous coronary interventions for stable coronary artery disease. *Arch Intern Med* 2007;167:1604-9.
5. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet*. 2002;359:696-700.

DOI: 10.1056/NEJMc1412894

THE AUTHORS REPLY: Shah's point with regard to periprocedural infarctions could be plausible. However, an analysis of the entire duration of the follow-up period shows that there were 8 periprocedural infarctions (1.8%) in the PCI group versus 5 (1.1%) in the medical-therapy group (hazard ratio, 1.59; 95% confidence interval [CI], 0.52 to 4.86). Conversely, there were 18 spontaneous myocardial infarctions (4.0%) in the PCI group versus 25 (5.7%) in the medical-therapy group (hazard ratio, 0.70; 95% CI, 0.38 to 1.29); this provides support for our initial conclusions.

As we acknowledged in our article, the awareness of the presence of stenoses may indeed influence patients' or physicians' decisions. Yet, registry patients had a low number of events

despite their awareness of functionally significant coronary disease. Ensuring that patients and clinicians were unaware of the assigned treatment theoretically could have added methodologic rigor, but this hardly seems feasible. In addition, the largest meta-epidemiologic study to date showed no evidence of relevant bias associated with awareness of study-drug assignments by patients and therapists when objective outcomes were used.¹ Rather, outcome assessors should be unaware of study-drug assignments when they adjudicate these types of outcomes, as was the case in our trial.

Bernard De Bruyne, M.D., Ph.D.

Cardiovascular Center Aalst
Aalst, Belgium
bernard.de.bruyne@olvz-aalst.be

William F. Fearon, M.D.

Stanford University Medical Center
Stanford, CA

Peter Jüni, M.D.

University of Bern
Bern, Switzerland

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

1. Savović J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med* 2012;157:429-38.

DOI: 10.1056/NEJMc1412894

Health and Health Care in South Africa

TO THE EDITOR: Mayosi et al. (Oct. 2 issue)¹ note that South Africa's local challenges to improving health are a microcosm of worldwide impediments to better population health. The causal factors of inequality are complex interactions of sociopolitical–economic factors and cultural attitudes.

Similarly, it would be simplistic to attribute the origins and perpetuation of legislative discrimination to a moral failing and myopia unique to South Africans. To do so would be to accept the attribution error of apartheid — namely, that groups of people are inherently different. Political oppression and social suffering arising from the failure to recognize common humanity and shared interest are not specific to one people or period.

The current global inequalities in health² re-

flect the darkest history of South African society. International legislative barriers to common access to, and benefit from, education, natural resources, and economic progress are associated with profound differences in health outcomes. As global citizens today, we should recognize and act on the fundamental lesson of apartheid's local history: We are not that different.

Paul G. Firth, M.B., Ch.B.

Massachusetts General Hospital
Boston, MA
pfirth@partners.org

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

1. Mayosi BM, Benatar SR. Health and health care in South Africa — 20 years after Mandela. *N Engl J Med* 2014;371:1344-53.
2. Murray CJL, Lopez AD. Measuring the global burden of disease. *N Engl J Med* 2013;369:448-57.

DOI: 10.1056/NEJMc1413160