residual varicosities, if required, was more cost-effective and resulted in greater improvement in quality of life than the use of foam sclerotherapy alone.

The trial also showed that the majority of patients who underwent endothermal ablation did not require additional treatment for residual varicosities. This indicates that combinations of less invasive therapies are not always required to achieve the best result for the individual patient.

The trial did not set out to look at the effect of endothermal ablation alone, since this policy may lead to undertreatment of patients and prevent them from obtaining the best result. Thus, we do not consider that Jindeel's proposed post hoc analysis to determine the effect of laser therapy alone would help to direct clinical practice.

Julie Brittenden, M.D.

University of Glasgow
Glasgow, United Kingdom
julie.brittenden@glasgow.ac.uk

Since publication of her article, the author reports no further potential conflict of interest.

DOI: 10.1056/NEJMc1914045

Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease

TO THE EDITOR: A key assumption in the physiological assessment of coronary stenosis in the MR-INFORM (Myocardial Perfusion CMR versus Angiography and FFR to Guide the Management of Patients with Stable Coronary Artery Disease) trial by Nagel et al. (June 20 issue)[1] is that the two catheter systems used to measure the pressure gradient across a coronary stenosis are identical with respect to calibration and zero level. The article and Supplementary Appendix (available with the full text of the article at NEJM.org) do not provide this assurance.

The pressure gradient was measured between the catheter, which was positioned in the ascending aorta or coronary artery proximal to the stenosis, and the micromanometer at the tip of the guidewire, which had been advanced beyond the stenosis. The measuring sites could have been at different hydrostatic levels, and 10 mm Hg could have added to or subtracted from the gradient if positioned 13 cm above or below the reference level.[2] Such a problem, and discordant results, are discussed in an editorial by Alfonso and Rivero[3] — the same stenosis had a fractional flow reserve (FFR) of 0.72 (warranting percutaneous coronary intervention [PCI]) and an instantaneous wave-free ratio of 0.92 (not warranting PCI). Could more information on this issue be provided by switching manometers to the two sensors or by using the same manometric system at both sites?

Michael F. O'Rourke, M.D., D.Sc.
Audrey Adji, Ph.D.

St. Vincent's Hospital
Sydney, NSW, Australia
m.orourke@unsw.edu.au

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

1. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med 2019;380:2418-28.
2. The coronary circulation. In: Nichols WW, O'Rourke MF, Vlachopoulos C. McDonald's blood flow in arteries. 6th ed. London: Arnold, 2011:375-96.
3. Alfonso F, Rivero F. Value of different physiological indexes to defer coronary revascularization. JACC Cardiovasc Interv 2018;11:1450-3.

DOI: 10.1056/NEJMc1913968

TO THE EDITOR: In the United States, approximately 300,000 patients with stable coronary artery disease undergo PCI annually.[1] Cardiologists perform PCI in patients with stable angina despite a lack of evidence that PCI is superior to guideline-directed medical therapy. Data are lacking from trials comparing PCI plus guideline-directed medical therapy with guideline-directed medical therapy alone in patients with stable coronary artery disease to show a survival benefit associated with PCI.[1] Even the role of PCI in symptom relief has been questioned, as shown in the ORBITA (Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina) trial.[2]

Guidelines recommend PCI for patients with angina that causes unacceptable symptoms despite the use of medical therapy.[3,4] These guidelines are often not followed in clinical practice. One study showed that approximately half of all PCI procedures could not be classified as appropriate, often because the patients had not received an adequate course of medical therapy.[5] Imagine the outcry from regulators and insurers if the initial approach to stable back pain was surgery.

Trials of therapy for patients with cardiovascular disease should evaluate all guideline-recommended approaches, particularly those that do not involve the use of many resources and those with low risks. The MR-INFORM trial is no exception. PCI comes with risks. Although the trial showed that the use of cardiovascular magnetic resonance imaging (MRI) was associated with a lower incidence of invasive coronary angiography and coronary revascularization than was the use of FFR, PCI is often an end point of both approaches. The absence of a guideline-directed medical therapy–only cohort is a fundamental drawback of the MR-INFORM trial.

Max Deschner, M.D.

Western University
London, ON, Canada
mdeschne@uwo.ca

Anthony Glanz, M.D.

Windsor Regional Hospital
Windsor, ON, Canada

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

1. Mitchell JD, Brown DL. Harmonizing the paradigm with the data in stable coronary artery disease: a review and viewpoint. J Am Heart Assoc 2017;6(11):e007006.
2. Barakat MF, Simitsis P. Percutaneous coronary intervention for stable angina in ORBITA. Lancet 2018;392:26.
3. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60(24):e44-e164.
4. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
5. Chan PS, Patel MR, Klein LW, et al. Appropriateness of percutaneous coronary intervention. JAMA 2011;306:53-61.

DOI: 10.1056/NEJMc1913968

TO THE EDITOR: Nagel et al. report that a noninvasive approach with myocardial-perfusion cardiovascular MRI was noninferior to an invasive approach including coronary angiography and FFR assessment for the evaluation of patients with stable angina. In our opinion, the trial is interesting and well conducted and adds another tool to the physician's armamentarium to detect ischemia. At the same time, the calculation of the sample size may have led to nondefinitive results. The authors based their sample-size calculation on event rates from the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial[1]; those rates are higher than event rates in the current population of patients with stable coronary artery disease (10% vs. approximately 5%).[2] Most importantly, Nagel and colleagues chose a noninferiority margin of 6 percentage points, meaning that they would have accepted an upper confidence bound that was 60% higher in the experimental group than the expected 10% event rate in the control group in order to declare noninferiority. We acknowledge that this statistical approach is widely used in noninferiority trials, but it probably reduces the power of the results to a hypothesis requiring confirmation in bigger studies.

Matteo Tebaldi, M.D.
Simone Biscaglia, M.D.
Gianluca Campo, M.D.

Azienda Ospedaliero–Universitaria di Ferrara
Cona, Italy
tblmtt@unife.it

Dr. Tebaldi reports receiving speaking fees from Abbott. No other potential conflict of interest relevant to this letter was reported.

1. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213-24.
2. Ahn JM, Park DW, Shin ES, et al. Fractional flow reserve and cardiac events in coronary artery disease: data from a prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). Circulation 2017;135:2241-51.

DOI: 10.1056/NEJMc1913968

THE AUTHORS REPLY: In reply to O'Rourke and Adji: we can confirm that FFR was measured according to established methods.[1,2] The standard setup in the cardiac catheter laboratory is to ensure that the measuring sites (guiding catheter for the mean aorta pressure and distal guidewire

for the mean distal coronary pressure) are approximately in the same position in relation to the right atrium. The position of the sensor of the diagnostic guidewire should usually be 6 to 9 cm from the end of the guiding catheter and 3 cm distal to the lesion. There may be variations according to the specific circumstances (e.g., lesion location). All these factors reflect the strengths and limitations of measuring "lesion-level," pressure-derived estimates of flow limitation, which underpin the clinical evidence supporting the guideline recommendations for FFR-guided management in contemporary practice.[3] Each of the diagnostic strategies involving noninvasive MRI or invasive angiography with FFR has merits and limitations.[4] Our trial was designed and powered to assess health outcomes between the randomized groups, and noninferiority criteria were met.

Deschner and Glanz comment about a guideline-directed medical therapy–only group in our trial. All treatment options were possible, including guideline-directed medical therapy, PCI, and coronary-artery bypass grafting. The composite primary outcome was death, nonfatal myocardial infarction, or target-vessel revascularization within 1 year. As expected, the noninvasive strategy reduced the need for coronary angiography and associated coronary revascularization. At the outset of this trial, we did not know whether not using invasive management and revascularization in some patients would be safe, associated with a need for an unplanned procedure at a later stage, or both. Although ISCHEMIA (the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) is under way to answer the question regarding a strategy of guideline-directed medical therapy only, the majority of deaths in the MR-INFORM trial occurred in patients with severe ischemia.

Finally, with regard to the comments by Tebaldi et al.: in the FAME trial, one third of the participants had a history of medically stabilized acute coronary syndrome, which may explain why the incidence of major adverse cardiovascular events was higher in the FAME trial than in the MR-INFORM trial. We accept that the upper bound of the noninferiority margin in our trial may be viewed as being comparatively high. Nonetheless, given that the percentages of patients in whom the primary outcome occurred in the MRI- and FFR-guided groups were 3.6% and 3.7%, respectively, (risk difference, −0.2 percentage points; 95% confidence interval, −2.7 to 2.4), noninferiority criteria were clearly met.

Eike Nagel, M.D.
Goethe University Frankfurt am Main
Frankfurt, Germany
eike.nagel@cardiac-imaging.org

Colin Berry, M.D.
University of Glasgow
Glasgow, United Kingdom

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

1. Berry C, Corcoran D, Hennigan B, Watkins S, Layland J, Oldroyd KG. Fractional flow reserve-guided management in stable coronary disease and acute myocardial infarction: recent developments. Eur Heart J 2015;36:3155-64.
2. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213-24.
3. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019 August 31 (Epub ahead of print).
4. Puntmann VO, Valbuena S, Hinojar R, et al. Society for Cardiovascular Magnetic Resonance (SCMR) expert consensus for CMR imaging endpoints in clinical research: part I — analytical validation and clinical qualification. J Cardiovasc Magn Reson 2018;20:67.

DOI: 10.1056/NEJMc1913968

Treatment of Hypertension in Patients with Asthma

TO THE EDITOR: In their review article, Christiansen and Zuraw (Sept. 12 issue)[1] summarize the current management of hypertension in patients with asthma. However, the article does not mention the potential merits of the use of anticholinergic agents, which have less cardiovascular stimulation and interaction with drugs for hypertension than β_2-agonists, as alternative or add-on medications to β_2-agonists in such patients.

Anticholinergic bronchodilators have been recommended for patients with asthma who could not receive β_2-agonists or for patients with asthma attacks induced by beta-blockers.[2,3] In addition, a long-acting anticholinergic broncho-