CORRESPONDENCE

Stenting for Renal-Artery Stenosis

TO THE EDITOR: The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study by Cooper et al. (Jan. 2 issue)[1] seems to put the final nail in the coffin of renal-artery stenting for the treatment of atherosclerotic renal-artery stenosis. A subgroup analysis did not reveal a clinically significant benefit for any group of patients. However, we would like to draw attention to a specific subgroup: patients with truly resistant hypertension (hypertension that was uncontrolled despite the use of three antihypertensive agents, including a diuretic) that was either moderate (systolic blood pressure >160 mm Hg) or severe (systolic blood pressure >180 mm Hg).

This condition is increasingly recognized nowadays because of the revival of interventional therapy with renal sympathetic denervation.[2-4] Renal arteriography is performed in all candidates for renal denervation as an essential part of the procedure, and it is not unusual to find considerable renal-artery stenosis.[5] This poses a therapeutic dilemma to the interventional cardiologist as to whether opening the artery will confer any clinically significant benefit for the patient. Therefore, relevant information is of major interest, and we would be grateful to the authors if they could provide it.

Barbara Nikolaidou, M.D.
Andromachi Reklou, M.D.
Aristotle University
Thessaloniki, Greece

Michael Doumas, M.D., Ph.D.
George Washington University
Washington, DC
michalisdoumas@yahoo.co.uk

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TO THE EDITOR: Cooper et al. report that renal-artery stenting, when added to comprehensive medical therapy in patients with atherosclerotic renal-artery stenosis, was not effective in preventing clinical events. Nevertheless, the results of a large trial may not reflect an important clinical benefit in smaller subgroups of patients. There is a consensus, although not evidence-based, that certain groups of patients with severe renal-artery stenosis need to be treated with revascularization,[1] but they were probably not included in this study. In particular, renal-artery stenting is rec-

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ommended for patients with renal-artery stenosis and recurrent, unexplained episodes of heart failure and flash pulmonary edema, especially when they have severe bilateral renal-artery stenosis or stenosis in a renal artery to a solitary functioning kidney.[1,2] Similarly, rapidly progressive renal failure, despite aggressive medical therapy, in patients with global renal ischemia due to renal-artery stenosis tends to respond favorably to renal-artery angioplasty and stenting.[1-3] These patients are analogous to those with acute coronary syndromes, who benefit from coronary stenting, whereas the patients in clinically stable condition in this study may correspond to patients with stable coronary disease who are treated with medical therapy or coronary-artery stenting.[4]

Haruo Tomoda, M.D., Ph.D.

Tokyo Heart Institute
Tokyo, Japan
tokyoheart@abelia.ocn.ne.jp

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

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TO THE EDITOR: Cooper et al. report that renal stenting did not confer a significant benefit when added to medical therapy in patients with renal-artery stenosis. Although the study was well designed, the inclusion of patients with 60% stenosis without hemodynamic significance could have induced a type II error.

Mitchell et al.[1] reported that stenting in 17 patients with renal-artery stenosis resulted in improvement in hypertension in patients with a renal fractional flow reserve of less than 0.80. Mangiacapra et al.[2] found that a mean pressure gradient of at least 20 mm Hg induced by intrarenal dopamine was highly predictive of improvement in hypertension after renal stenting, and we[3] found that a hyperemic gradient of at least 21 mm Hg induced by intrarenal papaverine had the highest predictive accuracy in improvement of hypertension (see Table 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).[3] We hypothesized that patient selection based on a pressure gradient measured by means of a pressure wire would have led to drastically different conclusions. Data are lacking from randomized studies to assess the value of measurements of the renal-artery pressure gradient with respect to outcomes and the improvement of hypertension in patients with renal-artery stenosis.

Massoud Leesar, M.D.

University of Alabama at Birmingham
Birmingham, AL
mleesar@uab.edu

Christopher White, M.D.

Ochsner Medical Center
New Orleans, LA

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

Cardiovascular Center Aalst
Aalst, Belgium

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

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TO THE EDITOR: In their randomized, controlled trial, Cooper et al. found that renal-artery stenting did not reduce major adverse renal and cardiovascular events. Unfortunately, in their study, as well as in the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL)[1] and Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR²) trials, the investigators did not take into account the renal resistance index, a functional marker of renal vascularize-

tion.[3] The renal resistance index, calculated with the use of the following equation:

$$\left(1-\frac{\text{end-diastolic velocity}}{\text{maximal systolic velocity}}\right)\times 100,$$

can be noninvasively and easily measured by means of color Doppler ultrasonography.[3,4] After a follow-up of 60 months, Radermacher et al. showed the importance of the renal resistance index in a population with a nearly similar average stenosis of 70%.[4] In this study, Radermacher et al. concluded that "a renal resistance-index value of at least 80 reliably identifies patients with renal-artery stenosis in whom angioplasty or surgery will not improve renal function, blood pressure or kidney survival." Therefore, in our opinion, future randomized, controlled trials should analyze the renal resistance index to determine whether it is beneficial to perform renal stenting as compared with the use of medical therapy alone.

Guillaume Mahé, M.D., Ph.D.

Clinical Investigation Center 1414
Rennes, France

Vincent Jaquinandi, M.D., Ph.D.

Clinique Saint-Léonard
Trélazé, France

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

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TO THE EDITOR: The results of the CORAL trial are largely negative and in accordance with the ASTRAL and Stenting of Renal Artery Stenosis in Coronary Artery Disease (RAS-CAD)[1] trials. In all these trials, the most important selection and classification criterion was the percentage of renal-artery stenosis in the patients. In a study that involved the cohort of the RAS-CAD study,[1] and in accordance with the Prospective Randomized Study Comparing Renal Artery Stenting With/Without Distal Protection (RESIST) trial,[2] we recently reported that the absolute reduction of less than 5.2 mm in the reference diameter and of less than 2.9 mm in the minimal diameter were more likely associated with a low glomerular filtration rate and resistant hypertension than a level of renal-artery stenosis that was greater than 47%.[3] Moreover, a minimal diameter of less than 2.9 mm was an independent predictor of cardiovascular events.[4] Since there was great variability in the reference diameters in the patients who were enrolled in the CORAL trial (from 3.5 to 8.0 mm), specific, separate analyses of the prognostic role of reduced reference diameters and reduced minimal diameters could be performed.

Luca Zanoli, M.D., Ph.D.

University of Catania
Catania, Italy

Carmelita Marcantoni, M.D.

Cannizzaro Hospital
Catania, Italy

Pietro Castellino, M.D.

University of Catania
Catania, Italy

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

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THE AUTHORS REPLY: Nikolaidou et al. suggest that patients with moderate-to-severe hypertension who receive 3 or more antihypertensive medications may benefit from renal-artery stenting. Patients in the CORAL study received 3.3 to 3.5 antihypertensive medications, yet the clinical outcomes were not improved by stenting. As we reported, there was also not a significant interaction effect for systolic blood pressure of 160 mm Hg or higher on the rate of clinical events according to treatment group.

Tomoda suggests that specific subgroups of patients, including those with severe stenosis or heart failure, may benefit from stenting. In our study, we found no benefit in patients with severe stenoses (≥80% according to investigator evaluation) or with global ischemia, and we found no benefit in preventing hospital admissions for heart failure. Approximately 12 to 15% of the patients had heart failure at study entry. Some people, such as those with severe kidney disease or rapidly progressive renal failure, may not have been well represented in the study. Renal-artery stenting may benefit some of the patients described by Tomoda; however, data are lacking from randomized, controlled clinical trials to support that hypothesis. The results of our study suggest that most patients in stable condition should receive medical therapy regardless of the initial level of kidney function.

In reply to Leesar and colleagues: a type II error is possible, but the CORAL study was designed to achieve and did achieve adequate power to exclude a meaningful benefit with respect to the prevention of clinical events. Leesar et al. ask whether patients with a pressure gradient across the renal-artery stenosis might benefit from renal-artery stenting, as is suggested in several studies that used a surrogate end point, systolic blood pressure, as the outcome. In our study, we found a small but significant reduction in systolic blood pressure of 2 mm Hg favoring stent treatment; this reduction did not translate into a benefit with respect to event-free survival. In our study, we did obtain data on translesional renal-artery pressure gradients, and analyses of these data should be informative about the value of determinations of pressure gradients.

With regard to the letter by Mahé and Jaquinandi: we considered the renal resistance index as a variable that might be predictive of treatment outcomes, and we prospectively included that measure in an analysis involving the ultrasonographic findings in a subgroup population. However, the renal resistance index has not been proved conclusively to be useful in selecting patients for renal-artery revascularization.[1-3]

Zanoli and colleagues report that smaller renal arteries (<5.2 mm) and smaller renal-artery lumen diameters (<2.9 mm) are associated with lower glomerular filtration, resistant hypertension, and a higher risk of cardiovascular events among people undergoing coronary angiography. Data are lacking from observational studies to replicate this relationship. If we assume that this relationship will be replicated in future observational studies, the conclusion of our study remains that medical therapy appears to work as well as stenting with medical therapy in patients with renal-artery stenosis.

Timothy P. Murphy, M.D.
Lance D. Dworkin, M.D.
Rhode Island Hospital
Providence, RI

Christopher J. Cooper, M.D.
University of Toledo
Toledo, OH
christopher.cooper@utoledo.edu

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

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Variant *GADL1* and Response to Lithium in Bipolar I Disorder

TO THE EDITOR: Chen et al. (Jan. 9 issue)[1] report a dramatic association between the response to lithium therapy and the presence of intronic single-nucleotide polymorphisms (SNPs) mapped to *GADL1*, suggesting a link to GADL1 function in the brain. However, a review of multiple databases of adult brain expression (both microarray and RNA sequencing) reveals that GADL1 shows at most very low expression across diverse brain regions.[2,3] Furthermore, we have observed minimal if any GADL1 expression in 600 brains obtained on autopsy, including those from patients with bipolar disorder (in samples from the Lieber Institute for Brain Development) that were ana-