Editorial

# Misleading Results of Randomized Trials: The Example of Renal Artery Stenting

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Randomized controlled trials are considered the most reliable form of evidence. However, when their results disagree with clinical experience, the validity of their findings merits critical examination. In the recent randomized multicenter Stenting in Renal Dysfunction Caused by Atherosclerotic Renal Artery Stenosis (STAR) trial that assessed the efficacy of renal artery stenting, Bax and colleagues[1] reported little or no benefit compared with medical treatment. The authors therefore recommended, particularly in view of the risks of the procedure, that stenting be avoided in treating patients with renal artery stenosis.[1]

This conclusion, along with the previously reported results of the Dutch Renal Artery Stenosis Intervention (DRASTIC) trial,[2] will likely reduce the use of renal artery stenting and might also affect insurer authorization for such procedures. The purpose of this editorial is to: (1) challenge the conclusion of the STAR trial, and (2) more broadly raise concern about uncritical acceptance of misleading conclusions from randomized trials, particularly when they disagree with clinical experience.

Having personally observed many patients who, following renal artery angioplasty with or without stenting, experienced dramatic and nearly immediate amelioration of problems such as refractory hypertension, congestive heart failure, and renal insufficiency, it is inconceivable to us, and to many others, that these procedures are of no benefit. When a renal artery procedure is followed by diuresis of 6 L within 24 hours and a dramatic amelioration of heart failure, or by a rapid and sustained fall in blood pressure and/or serum creatinine level, the benefit of the procedure is indisputable, at least in some patients. This clinical experience is supported by many uncontrolled case series that have documented benefit.

Unfortunately, there is also no doubt that renal artery stenting is overused and employed in cases where there is little or no expectation of benefit, while exposing patients to harm. The question that needs to be asked is not whether the procedure can help patients, but how to select patients most likely to benefit from stenting while avoiding the procedure and its associated risks in those least likely to benefit. This trial did not address that important question.

An obvious question is: if renal artery stenting does benefit patients, why did this randomized controlled trial not show it? In this case, several factors can explain the misleading negative result.

In this and other studies, a crucial issue is the criteria used for selection of patients. In the STAR trial, 62.5% (40 of 64) of the patients randomized to the stenting group and included in the intention-to-treat analysis were predictably unlikely to benefit for the following reasons: (1) 12 patients who met entry criteria of >50% renal artery stenosis, determined largely by noninvasive imaging, turned out to have stenoses of <50% and were not even stented; (2) an additional 22 patients had 50% to 70% stenosis, which usually is not hemodynamically significant; and (3) in 6 other patients, stenting was

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not performed for various reasons.[1] In addition, some stenoses of 70% to 90% are also physiologically insignificant, sometimes because of inaccuracy and overestimation of the degree of stenosis.[3] In addition, the report does not indicate performance of any physiologic test, such as renal scintigraphy or recording of renal artery blood pressure gradient, as indicators of hemodynamic significance of the stenoses. Finally, all patients were required to have a treated blood pressure <140/90 mm Hg on entry. This excluded patients with resistant hypertension, who are more likely to have true renovascular hypertension and ischemic nephropathy.[4]

For all of these reasons, few of the patients randomized to stenting in the STAR trial would have been expected, a priori, to benefit. If nothing else, a subgroup analysis of the outcomes of the 22 patients who underwent stenting for >90% stenosis would have been helpful in overcoming this problem.

Finally, in this and other randomized trials, other unmentioned, unintended, and sometimes unavoidable biases in patient selection greatly lessen the chance of observing benefit and increase the likelihood of a misleading negative study result. The patients who are most likely to have true renovascular hypertension and ischemic nephropathy, and who are therefore the most likely to respond to stenting, are those with ≥90% stenosis and resistant hypertension, rising creatinine, an abnormal scintigram, or bilateral stenosis with recurrent pulmonary edema. Yet, such patients would be very likely to have been sent for stenting, rather than being entered into a randomized trial that could deny them the procedure. In this manner, the patients who are most likely to respond are least likely to be entered. In this regard, determination of the number of patients who underwent stenting outside the randomized trial during the enrollment period, and comparison of the characteristics of the stenoses of such patients with those of the enrolled patients, could have elucidated this issue. There is no easy answer for this problem, and in such situations, where the population enrolled differs from the population that needs to be enrolled, a randomized trial is the wrong type of study. The investigators' conclusions should have acknowledged this likely difference in patient population, rather than advocate abandonment of a procedure that is invaluable in appropriate patients.

For the population that was studied in this trial, the conclusions are actually in harmony with clinical experience. In fact, most specialists would not have recommended stenting in most of the study patients. It is in patients who more clearly have renovascular hypertension or ischemic nephropathy that the procedure appears to have great value, and extrapolation of the study's results to this group is unwarranted and wrong.

Clearly, there is a gray zone where risk/benefit considerations cloud the clinical decision. For example, in elderly patients or in patients with severe aortic atherosclerosis who are at high risk for postprocedure atheroemboli, does the benefit exceed the risk? These are truly difficult clinical dilemmas. Unfortunately, trials such as the present one are not helpful in clinical decision-making in such cases. We are left, for better or worse, with the art of clinical judgment.

The overuse of renal artery angioplasty and stenting, given their associated risks and costs, clearly merits condemnation. However, the benefit of renal artery stenting in appropriate patients should not be withheld based on the results of randomized trials that are subtly but fatally flawed. Instead, clarification of the indications for stenting is needed.

Randomized trials can help us confirm what clinical experience and case series suggest to us, but when their conclusions contradict a critical mass of previous studies and clinical experience, it is wrong to accept their results uncritically. In this case, the results of the STAR, DRASTIC, and probably the Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trials should not be allowed to prevent the use of renal artery stenting in patients who need it and would benefit from it.

## References


1 Bax L, Woittiez AJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function. A randomized trial. *Ann Intern Med.* 2009;150:840–848.

2 Van aarsveld JBC, Krijnen P, Pieterman H, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N Engl J Med.* 2000;342:1007–1014.

3 van Jaarsveld BC, Pieterman H, van Dijk LC, et al. Interobserver variability in the angiographic assessment of renal artery stenosis. DRASTIC study group. Dutch Renal Artery Stenosis Intervention Cooperative. *J Hypertens.* 1999;17:1731–1736.

4 van Jaarsveld BC, Krijnen P, Derkx FH, et al. Resistance to antihypertensive medication as predictor of renal artery stenosis: comparison of two drug regimens. *J Hum Hypertens.* 2001;15:669–676.