Primary stenting for atherosclerotic renal artery stenosis

Olivier Steichen, Laurence Amar, Pierre-François Plouin

Primary Stenting for Atherosclerotic Renal Artery Stenosis

Authors: Olivier Steichen,[a] MD, Laurence Amar,[b] MD, Pierre-François Plouin,[b] MD

[a] Assistance Publique - Hôpitaux de Paris, Centre d'Investigations Cliniques, Hôpital Européen Georges Pompidou, Paris, France ; Université Paris Descartes, Faculté de Médecine, Paris, France

[b] Assistance Publique - Hôpitaux de Paris, Service d'Hypertension Artérielle, Hôpital Européen Georges Pompidou, Paris, France ; Université Paris Descartes, Faculté de Médecine, Paris, France

Corresponding author:

Professeur Pierre-François Plouin

Service d'Hypertension Artérielle

Hôpital Européen Georges Pompidou

20 – 40 rue Leblanc

75015 Paris, France

pierre-francois.plouin@egp.aphp.fr

Abstract word count:

Manuscript word count:

Introduction

Atherosclerotic renal artery stenosis (ARAS) may lead to hypertension, impaired renal function and cardiac disorders (flash pulmonary edema, uncontrolled heart failure or unstable angina pectoris). Since the first report of ARAS angioplasty more than 30 years ago, endovascular approaches have supplanted surgical approaches for revascularization. However, few data are available to guide medical decisions in the treatment of ARAS. The objective of this review is to summarize the available evidence on primary stent placement for ARAS.

Methods

Many uncontrolled retrospective and prospective cohort studies of stent placement for atherosclerotic RAS have been published. However, due to the lack of control groups, their results fail to provide a sound basis for medical decision making. We therefore limited our review to studies comparing renal artery stenting with other treatment options for atherosclerotic RAS, or comparing different procedural strategies. We searched Medline, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov with combinations of the following keywords: “renal artery obstruction”, “renal artery stenosis”, “renovascular disease”, “renovascular hypertension”, “ischemic nephropathy”, “stent”, and “endovascular”. We also screened reference lists of original articles, guidelines and reviews. Levels of evidence were rated using a scale provided by the *Journal of Vascular Surgery* (Web Appendix 1).

Results

Benefit of renal artery stenting over angioplasty

ARAS predominantly involves the proximal third of the artery and is prone to restenosis after angioplasty alone. Primary stenting in ARAS was compared to the use of angioplasty alone in both a non-randomized study[1] and a randomized controlled trial[2] (RCT) (Table 1). The results were consistent with those of a meta-analysis indirectly comparing these two treatment strategies[3]: procedural success was higher and restenosis rate lower with stenting than with angioplasty alone, but clinical outcome did not differ significantly. Findings from the RCT suggest that, in order ensure long term patency, reintervention would be needed in 57% of patients after angioplasty alone, but only in 12% of patients after primary stenting.[2] Primary stent placement thus seems to show a more favorable cost-efficacy profile and lower risk-benefit ratio than angioplasty alone for ARAS that require intervention.[4]

Benefit of renal artery stenting over surgery

One RCT compared endovascular stenting with open surgical reconstruction in ARAS patients without concurrent aortic disease.[5] No significant difference in treatment outcome was found but surgery was associated with a longer initial hospitalization period (Table 1). This study thus suggests that stenting should generally be the preferred revascularization technique and that surgery should be limited to cases needing concomitant aortic reconstruction.[4]

Comparison of renal artery stenting with medication alone

Two small non-randomized studies[6, 7] and two RCTs of limited power[8, 9] compared stent placement with secondary prevention treatment alone (antihypertensive agents, statins and

aspirin) in ARAS patients with difficult-to-treat hypertension or unexplained renal function impairment. Overall, these studies did not show a clinically meaningful improvement in blood pressure control or renal function stabilization in patients receiving stents (Table 2).

The results of the much larger ASTRAL RCT further question the benefit of ARAS stenting over medical therapy.[10] Improvement in renal function and renal event-free survival did not differ significantly between the two strategies. Numbers of deaths and cardiovascular events were also similar in both study groups, but the confidence intervals (CI) of hazard ratios cannot exclude relevant differences in clinical outcome: 0.90 [95% CI: 0.69 to 1.18] for overall survival and 0.94 [95% CI: 0.75 to 1.19] for cardiovascular event-free survival.

A cohort study evaluated the change in left ventricular mass (LVM) after stent placement in patients with ARAS and hypertension or impaired renal function.[11] Patients with essential hypertension were used as controls. After adjustment for various potential confounding variables, the results suggested a beneficial effect of stent placement on LVM, which could not be fully accounted for by the observed reduction in blood pressure. A comparative study in patients with ARAS was unable to confirm this benefit, but it was grossly under-powered, with only eight patients in the stent group.[12] The undergoing ASTRAL-heart sub-study[13] and RADAR study[14] were designed to properly assess cardiac outcomes after stent placement.

Stent placement is a minimally invasive procedure but patients with ARAS are frail and prone to complications. In ASTRAL, the proportion of patients experiencing at least one adverse event was 9% during the first 24 hours following stent placement and 20% between the 2nd and 30th days; overall, 6% experienced serious complications related to revascularization.[10]

The Web Appendix 2 lists the adverse events reported in 22 large prospective cohorts (3453 patients) after stent placement for ARAS[15] and in the ASTRAL trial.

Procedure improvements

In some patients, acute deterioration of renal function may be due to contrast-induced nephropathy and atheroembolism. Prophylactic treatment for contrast-nephropathy should therefore be considered. Effective antithrombotic treatment and use of distal embolic protection devices during the procedure could prevent the consequences of atheroembolism. However, a comparative study[16] and a RCT[17, 18] did not find any convincing beneficial effect of protection devices on clinical outcome (Table 3). In the RCT, no change was seen in glomerular filtration rate following intervention in a small patient subgroup receiving both abciximab and a distal protection device, whereas glomerular filtration rate declined in the three other groups.

Restenosis occurred in 10% to 21% of cases studied over a follow-up period of 3 to 40 months after stent placement for ARAS.[15] Optimal long-term antithrombotic treatment and coated stents may improve these rates. Patients usually receive long-term treatment with antiplatelet agents following stent placement. The US multicenter trial found no beneficial effect of three-month warfarin treatment following the procedure.[19] Four comparative studies showed no improvement in restenosis rate and clinical outcome with gold-, carbon- or sirolimus-coated stents[20-23] (Table 3).

Discussion

The past decade has seen the development of highly effective treatment regimens in patients with atherosclerosis, also exerting a protective effect on renal function in patients with ARAS.

Renal function decline was very gradual in patients in ASTRAL, even in those with severe anatomical disease.[10] Optimal medical treatment without stent placement should be the preferred option for asymptomatic patients or for patients who do not have a compelling clinical indication for revascularization, like accelerated hypertension, unexplained rapidly declining renal function, declining renal function after the administration of angiotensin-converting-enzyme (ACE) inhibitors, or flash pulmonary edema.

Outcome following renal artery stenting in specific subgroups

However, the basis for this recommendation comes from comparative studies that included heterogeneous populations, including some patients with stenosis of debatable hemodynamic significance. Overall negative results do not exclude the possibility that several subgroups of patients may benefit from stenting.

There are clues suggesting that hypertension or impaired renal function in a patient are consequences of ARAS rather than merely associated essential hypertension or nephrosclerosis. As such, rapidly deteriorating renal function or worsening hypertension control, low renal resistance index, low proteinuria, and severe stenosis, particularly affecting either both renal artery or a solitary kidney, are considered to be predictors of good outcome after stent placement.

However, these predictive factors were established from cohort studies, often with defective methods and showing conflicting results. Moreover, even if they truly predict a better response to stent placement, they may also predict a better response to optimized medical treatment. Only comparative studies can definitely assess the relative efficacy of both treatment strategies in specific subgroups.

For example, severe stenosis is thought to justify a more aggressive approach than moderate stenosis. However, ASTRAL showed no difference in outcome between ARAS subgroups of varying severity.[10] Furthermore, a post hoc analysis showed very gradual renal function decline in 163 patients with ≥ 70% ARAS on both sides or affecting a solitary kidney, with a similar outcome observed for patients treated medically and those treated with stent placement.

Similarly, a high renal resistance index (RI) is considered as a marker of severe nephrosclerosis. An often cited study found that a RI ≥ 0.8 was associated with poor blood pressure and renal outcome in ARAS treated by revascularization, predominantly involving angioplasty alone.[24] However, more recent prospective studies of ARAS treated with stent placement were unable to replicate this finding.[25, 26] Some studies even showed improved renal function[27] or blood pressure[28] after stent placement in patients with a high RI. The ongoing CORAL study should provide a definitive answer to this issue.[29]

The benefit of stenting still has to be properly evaluated in patients with the aforementioned compelling indications, who have been explicitly or implicitly excluded from randomized trials. Cohort studies strongly suggest that ARAS patients with deteriorating renal function after the administration of ACE inhibitors or angiotensin-receptor blockers may tolerate them better after stent placement if they are necessary.[30-33] There are no published reports comparing current optimized medical treatment to stent placement in patients with flash pulmonary edema, uncontrolled heart failure or unstable angina pectoris; however, a pathophysiological rationale and the dramatic results of small series[30, 34, 35] have provided the basis for recommendation for stent placement.[4]

Perspectives

CORAL[29] and RADAR[14] are the two largest ongoing RCTs registered under ClinicalTrials.gov evaluating the benefit of stent placement over current best medical treatments. CORAL plans to enroll 1080 patients with ARAS ≥ 60% and with hypertension or renal dysfunction. The primary endpoint is cardiovascular and renal event-free survival; secondary endpoints include evaluation of the renal resistance index as an outcome predictor after stent placement and the benefit of stent placement in important patient subgroups (women, African-Americans, diabetics, bilateral stenosis). RADAR plans to recruit 300 patients with impaired renal function and ARAS estimated at ≥ 70%, using Doppler indices. The primary endpoint will be the change in renal function; clinical and echographic cardiac outcomes are secondary endpoints of the study.

Conclusion

Impaired renal function associated with ARAS is probably more stable over time than previously thought. On the opposite, potential complications of stent placement for ARAS are often underestimated. According to the results of recent RCTs, optimal medical treatment should be the preferred option for most patients with ARAS: antihypertensive agents including ACE inhibitors or angiotensin-receptor blockers, statins, and antiplatelet agents. Results of ongoing trials are awaited to properly address the role of stenting in patients with severe anatomical disease and to look for an effect of stent placement on left ventricular hypertrophy, beyond blood pressure lowering. Only pathophysiological rationale and anecdotal evidence support compelling indications for revascularization in ARAS, including rapidly progressive hypertension or renal failure, and flash pulmonary edema.

References

1. Baumgartner I, von Aesch K, Do DD, Triller J, Birrer M, Mahler F. Stent placement in ostial and nonostial atherosclerotic renal arterial stenoses: a prospective follow-up study. *Radiology* 2000;216:498-505.

2. van de Ven PJG, Kaatee R, Beutler JJ, Beek FJ, Woittiez AJ, Buskens E, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet* 1999;353:282-6.

3. Leertouwer TC, Gussenhoven EJ, Bosch JL, van Jaarsveld BC, van Dijk LC, Deinum J, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology* 2000;216:78-85.

4. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;113:e463-654.

5. Balzer KM, Pfeiffer T, Rossbach S, Voiculescu A, Modder U, Godehardt E, et al. Prospective randomized trial of operative vs interventional treatment for renal artery ostial occlusive disease (RAOOD). *J Vasc Surg* 2009;49:667,74; discussion 674-5.

6. Arthurs Z, Starnes B, Cuadrado D, Sohn V, Cushner H, Andersen C. Renal artery stenting slows the rate of renal function decline. *J Vasc Surg* 2007;45:726,31; discussion 731-2.

7. Zalunardo N, Rose C, Starovoytov A, Djurdjev O, Fox R, Taylor P, et al. Incidental atherosclerotic renal artery stenosis diagnosed at cardiac catheterization: no difference in kidney function with or without stenting. *Am J Nephrol* 2008;28:921-8.

8. Bax L, Woittiez AJ, Kouwenberg HJ, Mali WP, Buskens E, Beek FJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med* 2009;150:840-8.

9. Ziakka S, Ursu M, Poulikakos D, Papadopoulos C, Karakasis F, Kaperonis N, et al. Predictive factors and therapeutic approach of renovascular disease: four years' follow-up. *Ren Fail* 2008;30:965-70.

10. Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;361:1953-62.

11. Zeller T, Rastan A, Schwarzwalder U, Muller C, Frank U, Burgelin K, et al. Regression of left ventricular hypertrophy following stenting of renal artery stenosis. *J Endovasc Ther* 2007;14:189-97.

12. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Progression of cardiac dysfunction in patients with atherosclerotic renovascular disease. *QJM* 2009;102:695-704.

13. Hegarty J, Wright JR, Kalra PR, Kalra PA. The heart in renovascular disease--an association demanding further investigation. *Int J Cardiol* 2006;111:339-42.

14. Schwarzwalder U, Hauk M, Zeller T. RADAR - A randomised, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with haemodynamically relevant atherosclerotic renal artery stenosis. *Trials* 2009;10:60.

15. Balk E, Raman G, Chung M, Ip S, Tatsioni A, Alonso A, et al. Effectiveness of management strategies for renal artery stenosis: a systematic review. *Ann Intern Med* 2006;145:901-12.

16. Singer GM, Setaro JF, Curtis JP, Remetz MS. Distal embolic protection during renal artery stenting: impact on hypertensive patients with renal dysfunction. *J Clin Hypertens (Greenwich)* 2008;10:830-6.

17. Cooper CJ, Haller ST, Colyer W, Steffes M, Burket MW, Thomas WJ, et al. Embolic protection and platelet inhibition during renal artery stenting. *Circulation* 2008;117:2752-60.

18. Kanjwal K, Haller S, Steffes M, Virmani R, Shapiro JI, Burket MW, et al. Complete versus partial distal embolic protection during renal artery stenting. *Catheter Cardiovasc Interv* 2009;73:725-30.

19. Rees CR. Stents for atherosclerotic renovascular disease. *J Vasc Interv Radiol* 1999;10:689-705.

20. Zeller T, Muller C, Frank U, Burgelin K, Sinn L, Horn B, et al. Gold coating and restenosis after primary stenting of ostial renal artery stenosis. *Catheter Cardiovasc Interv* 2003;60:1,6; discussion 7-8.

21. Zeller T, Rastan A, Kliem M, Schwarzwalder U, Frank U, Burgelin K, et al. Impact of carbon coating on the restenosis rate after stenting of atherosclerotic renal artery stenosis. *J Endovasc Ther* 2005;12:605-11.

22. Zahringer M, Sapoval M, Pattynama PM, Rabbia C, Vignali C, Maleux G, et al. Sirolimus-eluting versus bare-metal low-profile stent for renal artery treatment (GREAT Trial): angiographic follow-up after 6 months and clinical outcome up to 2 years. *J Endovasc Ther* 2007;14:460-8.

23. Nolan BW, Schermerhorn ML, Powell RJ, Rowell E, Fillinger MF, Rzucidlo EM, et al. Restenosis in gold-coated renal artery stents. *J Vasc Surg* 2005;42:40-6.

24. Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 2001;344:410-7.

25. Rivolta R, Bazzi C, Stradiotti P, Paparella M. Stenting of renal artery stenosis: is it beneficial in chronic renal failure?. *J Nephrol* 2005;18:749-54.

26. Rocha-Singh K, Jaff MR, Lynne Kelley E. Renal artery stenting with noninvasive duplex ultrasound follow-up: 3-year results from the RENAISSANCE renal stent trial. *Catheter Cardiovasc Interv* 2008;72:853-62.

27. Zeller T, Frank U, Muller C, Burgelin K, Sinn L, Horn B, et al. Stent-supported angioplasty of severe atherosclerotic renal artery stenosis preserves renal function and improves blood pressure control: long-term results from a prospective registry of 456 lesions. *J Endovasc Ther* 2004;11:95-106.

28. Garcia-Criado A, Gilabert R, Nicolau C, Real MI, Muntana X, Blasco J, et al. Value of Doppler sonography for predicting clinical outcome after renal artery revascularization in atherosclerotic renal artery stenosis. *J Ultrasound Med* 2005;24:1641-7.

29. Cooper CJ, Murphy TP, Matsumoto A, Steffes M, Cohen DJ, Jaff M, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. *Am Heart J* 2006;152:59-66.

30. Gray BH, Olin JW, Childs MB, Sullivan TM, Bacharach JM. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. *Vasc Med* 2002;7:275-9.

31. Gross CM, Kramer J, Waigand J, Uhlich F, Olthoff H, Luft FC, et al. Ostial renal artery stent placement for atherosclerotic renal artery stenosis in patients with coronary artery disease. *Cathet Cardiovasc Diagn* 1998;45:1-8.

32. Khosla S, Ahmed A, Siddiqui M, Trivedi A, Benatar D, Salem Y, et al. Safety of angiotensin-converting enzyme inhibitors in patients with bilateral renal artery stenosis following successful renal artery stent revascularization. *Am J Ther* 2006;13:306-8.

33. van de Ven PJG, Beutler JJ, Kaatee R, Beek FJ, Mali WP, Geyskes GG, et al. Transluminal vascular stent for ostial atherosclerotic renal artery stenosis. *Lancet* 1995;346:672-4.

34. Bloch MJ, Trost DW, Pickering TG, Sos TA, August P. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. *Am J Hypertens* 1999;12:1-7.

35. Khosla S, White CJ, Collins TJ, Jenkins JS, Shaw D, Ramee SR. Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. *Am J Cardiol* 1997;80:363-6.