

Controversies

The ASTRAL trial

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Introduction

Balloon angioplasty and/or endovascular stenting are being used increasingly often among patients with atherosclerotic renovascular disease (ARVD). Although these procedures do result in obvious improvements in arterial patency, there is currently no good evidence that they delay progressive decline of renal function. However, since revascularisation is associated with a definite procedural risk, such a procedure might not be justified if the benefits to renal function were small and outweighed by the procedural hazards. The ASTRAL (angioplasty and stent for renal arterial lesions) trial is designed to address the issue of whether renal arterial revascularisation with balloon angioplasty and/or endovascular stenting can safely prevent progressive renal failure among a wide range of patients with ARVD.

For further details see <http://www.astral.bham.ac.uk/trial/protocol/>

treatment, and some objective and worthwhile outcomes measured. ASTRAL is a group of trials in patients with varying clinical problems and significant other illnesses. There is no point in analysing these together, and I don't think the trial will be able to analyse meaningfully the separate scenarios.

By analogy with heart disease, a good trial might be the effects of coronary angioplasty on heart attack and death rates in patients with severe coronary artery disease. The ASTRAL trial would be like agreeing to include patients with mild coronary artery disease (i.e. mild renal artery disease), including all grades of LV function (i.e. all grades of renal function), and including patients with other causes of angina and breathlessness such as anaemia or valvular disease but some coronary artery disease (i.e. poor function in both kidneys but unilateral renal artery stenosis).

Clearly, the overall results of such a trial would depend on the proportion of different scenarios included. Whatever the results, they would be impossible to extrapolate to individuals.

There are some specific scenarios which would lend themselves to a trial of intervention, which I will list. Undoubtedly, many such cases will be included in ASTRAL, but I fear that these subgroups have not been adequately identified in advance, and that numbers in some will be inadequate. Furthermore, ASTRAL allows investigators to not enter patients if they already think they know best.

With regard to preventing end-stage renal failure (ESRF), there are at least three distinct scenarios.

One functioning kidney with a stenosis. Even this apparently discrete group can of course be subdivided by degree of stenosis and degree of function. Function in a single kidney with a tight stenosis is however not only susceptible to degree of ACE inhibition but also simple BP level—but as we're probably chiefly trying to prevent ESRF by preventing occlusion, we have a good endpoint if follow-up is long enough. We've also got the problem that many more of those with successful intervention will go onto an ACEi than in the control group—yet another

The problem with ASTRAL

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I don't think the ASTRAL trial will help us to know in the future what best to do for our patients with atheromatous renal artery stenosis. I'm grateful for the chance to expand on my views. Ultimately, however, I suspect there is a fundamental belief that determines attitudes here—do you believe that a flawed trial is worse or better than no trial? Also, I'd like to make clear that I'm not against ASTRAL because I don't believe in intervention or I already think I know what to do in every case. I just don't see how the results of ASTRAL will be applicable to individual cases.

The chief problem is that ASTRAL is not a single trial, in which a clearly defined clinical entity is randomised to different specific reproducible standard treatments or no

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subgroup. And did we exclude all those with recurrent pulmonary oedema at the start or not?

Two good-sized kidneys, normal creatinine, unilateral RAS (again of varying severity). Well, if we're focusing on hard endpoints like ESRF, we'd better follow these ones for at least 10 years (and of course hope that drug treatments, BP control etc remain equal in the groups over that time).

Gradually rising serum creatinine, now 200–400 (excluding ACEi, A2Ra effects of course). Symmetrical modest-sized kidneys, with unilateral or bilateral RAS (of varying severity). The theory here is that RAS produces ischaemic nephropathy i.e. gradual nephron loss due to reduced renal blood supply. The problems are that such a physio-pathological entity may not exist (kidneys beyond tight FMD stenoses don't shrink), and certainly in those with a creatinine >200 and unilateral stenosis, there must be another disease process damaging the kidneys.

Quite how anyone thinks a single trial will shed useful light on these complex issues is a mystery to me. Even if ASTRAL clearly specified its subgroups in advance and recruited sufficient patients into each, it faces two further insuperable problems. Firstly, negative results are likely to be at least partially attributable to imperfect revascularisation—that is, the problem isn't that revascularisation wasn't the solution, but rather that revascularisation was incomplete, short lived, or produced unacceptable side effects. By the time the trial is complete, angioplasty and stent technology will undoubtedly have moved on (e.g. sirolimus eluting stents). If the results are negative, you'll have to do it all again with the new technology.

Secondly, in some respects, the results will be uninterpretable. Take scenarios and above. If it were possible to magically dissolve the stenosis without risk to the patient, there wouldn't be a trial. We need a trial because the intervention can do what we're trying to prevent—kill the kidney or even the patient. All you will know will be that in this trial, intervention killed the kidney in a% and the patient in b% of cases. However, if the patient survived, successful intervention reduced risks by x and y% over z years. (You won't know the natural history of true non-intervention, because not everyone was randomised.) In fact, you should already know the figures for a and b% in your own unit, and the literature suggests that even in bilateral RAS the rate of progression to ESRF annually isn't very high. But how do you meaningfully compare a risk of disaster now with the risk of potential disaster in the vague future? (This isn't like consenting for CABG where patients are usually very symptomatic or have a very high risk of early MI and death—our scenario 1 might be a bit like the latter, but we think we already know this which is why lots of you haven't randomised in that setting!)

It is of course deeply unfashionable to suggest that randomised controlled trials might be not only futile but also a waste of precious financial and manpower resources. Nevertheless, I am convinced that the all-inclusive criteria for ASTRAL have sacrificed any hope of answering spe-

cific questions. 'Atheromatous renal artery stenosis' isn't a disease—it's an acquired anatomical pathology which co-exists with many other pathologies and specific clinically defined diseases, and can cause a variety of specific diseases or none at all. The concept of the worth of intervention in this non-disease is ultimately meaningless.

Why we need a trial in atherosclerotic renovascular disease

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ARVD is a very common condition which occurs in patients with generalised vascular disease and with ageing. It is frequently the cause of secondary hypertension, and it is commonly associated with chronic renal failure (CRF)^[1] and ESRF^[2]. However, it should be noted that a directly causal relationship between ARVD and the latter conditions is not always clear. Revascularisation procedures (usually angioplasty with or without stenting, direct stenting or much less often, reconstructive surgery) are frequently performed in ARVD patients with high-grade renal artery stenoses (RAS) but currently there is uncertainty regarding the beneficial effects of such procedures, which are themselves associated with a significant risk of serious complications^[3].

Definite indications for renal revascularisation

Despite the lack of an adequate evidence base, most clinicians would agree that revascularisation is indicated for significant RAS in patients with recurrent flash pulmonary oedema. Other patients often considered worthy of this treatment include those with severe hypertension resistant to all medical therapy and those with ACE-inhibitor-related uraemia who require ACE inhibitors or angiotensin II blockers (e.g. for cardiac failure). With respect to patients with RAS and chronic renal failure, clinical practice varies widely, reflecting the absence of clinical trial evidence. However, one subgroup of patients for whom revascularisation would be justified by most clinicians is those with dialysis-dependent renal failure and severe RAS; in such patients there is probably little to be lost and much, potentially, to be gained by intervention.

Outcomes of randomised clinical trials of renal revascularisation in ARVD

At the present time there are only four published clinical trials which have tried to clarify the place of interven-

tional procedures in patients with ARVD, and all have contained only relatively small patient numbers. Hence, van Jaarsveld *et al.*^[4] randomised 106 patients with RAS >50% and significant hypertension [but only mild-moderate renal impairment (creatinine <200 $\mu\text{mol/l}$)], to angioplasty or medical therapy. No differences were noted in the primary endpoint of blood pressure control, or in renal function. Plouin *et al.*^[5] and Webster *et al.*^[6] incorporated a similar trial design in only 49 and 55 patients, respectively. Blood pressure control was not improved by angioplasty in the former study, but a significant effect was noted in the latter, Scottish and Newcastle study, albeit only in patients with bilateral disease. No differences in renal function were ascertained in either study. Finally, van de Ven *et al.*^[3] compared the effects of angioplasty with or without stenting in 87 patients with ostial RAS. The primary outcome measure was arterial patency, which was significantly improved after stenting; no differences were noted in the secondary endpoint of renal function between the two groups.

Uncertainty regarding the effects of renal revascularisation

The vast majority of the published literature that considers the clinical outcomes after renal revascularisation contains reviews of patient series, usually based in individual centres^[7]. Several of these studies have involved meticulous examination of the effects of baseline clinical parameters, such as severity of renal dysfunction, hypertension and cardiovascular comorbidity, upon renal functional and mortality outcomes after the interventional procedure. However, the clinical application of these findings is limited by the usual deficiencies of non-trial evidence, which are worthy of mention as they are central to the main argument of this article. Hence, all of the retrospective studies have necessarily failed to include a control group, which limits the assessment of the effect of revascularisation as no non-intervention groups were available for comparison. Further, in such patient series it is difficult to determine whether any form of patient selection occurred; also, the lack of similarity and clinical consistency in patient populations creates an inherent problem when trying to compare the findings of different investigating centres.

There are, therefore, several areas of uncertainty regarding the indications for and the effects of renal revascularisation in patients with ARVD, and most of these can only be properly addressed by randomised control trial (RCT) evidence. Each of the major issues worthy of further clarification are considered below.

Hypertension

As discussed above, there is uncertainty regarding the benefits of revascularisation upon hypertension control

in patients with ARVD. The three RCTs which have investigated this issue have included small patient numbers^[4–6]; two studies showed no significant difference in blood pressure control after angioplasty, whereas the other indicated a benefit to hypertensive patients with bilateral ARVD^[6].

Renal function

An overall improvement in renal function may be seen following revascularisation, and the results of the various endoluminal procedures and direct surgery are broadly similar^[8]. The existing literature would suggest that renal functional stability after revascularisation is more likely to be seen in patients with mild—moderate chronic renal failure [e.g. serum creatinine 132–265 $\mu\text{mol/l}$ (1.5–3.0 mg/ml)], whereas those with severe renal failure [creatinine > 265 $\mu\text{mol/l}$ (>3.0 mg/ml)] are more at risk of progression to ESRF^[8,9]. However, the latter compose the group with greatest mortality risk^[2,10] and it would appear counter-intuitive to deny individual patients the chance of revascularisation on the basis of limited evidence. The renal functional outcome dilemma is enhanced by recent studies which show that function is often unrelated to RAS severity in ARVD^[10,11], inferring that intra-renal parenchymal injury (usually manifest by proteinuria^[12]) may be more important than the haemodynamic effects of a stenosis in many patients with ARVD. The rate of renal functional progression prior to the revascularisation procedure is also thought to have a major bearing upon outcome^[13], but this has not been systematically investigated.

Mortality

There are numerous studies which indicate that ARVD is a strong independent predictor of long-term mortality, and the almost invariable co-morbid association of ARVD with extra-renal vascular disease is undoubtedly a major contributor^[14]. There is also a strong link between decreasing renal function and mortality, with patients at ESRF having a relative risk of death almost 30 times greater than those ARVD patients with well-preserved renal function^[10]. Indeed, once ARVD patients reach the dialysis programmes they have a very poor outlook, with an even higher likelihood of mortality than diabetics; mean survival on dialysis may only be 27 months and 5-year survival 18%^[2]. To date, no investigations have shown any survival benefit from revascularisation procedures in this high-risk population.

What constitutes a ‘significant’ RAS lesion

There is currently no consensus regarding what degree of luminal narrowing at renal angiography is representative of significant RAS; many studies select 75% narrowing,

while others suggest a cut-off of >50% narrowing^[15]. The measurement of pressure gradients across RAS lesions has attempted to provide a scientific basis for intervention. A recent investigation involving three-dimensional MRA coupled with direct intra-arterial pressure measurements suggested that a functionally significant stenosis was associated with a pressure gradient of >15 mmHg; most RAS lesions >50% were shown to manifest this gradient^[16]. Other investigators believe that a gradient of 20 mmHg should be accepted as the cut-off for functional significance, and hence the rationale for non-intervention in lesser grade (e.g. <60–75%) lesions^[17]. However, it should be noted that such gradients have been assimilated according to the outcome of hypertension control rather than of any renal functional change after revascularisation. Evidence is again lacking in the latter situation.

Renal size

Uncertainty also surrounds the issue of what minimum size of kidney, supplied by an RAS lesion, is worthy of revascularisation. Detailed consideration is beyond the scope of this brief review.

The ASTRAL (angioplasty and stent for renal artery lesions) trial

Within the ASTRAL trial design about 1000 patients with ARVD will be recruited from multiple centres during a 5-year period. Half of these will be randomised to each of revascularisation (angioplasty with or without stenting, but with best medical therapy) or best medical therapy. The progress of patients will be followed for at least a year. The primary comparison is the rate of progression of renal failure, as assessed by reciprocal creatinine plots over the course of the trial. Secondary endpoints include blood pressure control and the occurrence of serious vascular events (e.g. myocardial infarction and stroke). The following pre-specified subgroup analyses will enable the effects of important baseline characteristics on renal functional outcome to be compared:

- Serum creatinine: three groups of <150, 150–300 and >300 $\mu\text{mol/l}$.
- Creatinine clearance (as an estimate of GFR): measured by the Cockcroft and Gault method. Three groups of <25, 25–50 and >50 ml/min.
- Severity of RAS: three groups of RAS <50%, 50–70% and >70%.
- Ultrasound renal length: groups of <8, 8–10 and >10 cm.
- Rate of progression of renal dysfunction: the renal functional changes of the patient prior to randomi-

sation will be taken into account (rapid increase in creatinine—yes, no or not known).

Rationale for and potential benefits of the ASTRAL trial

There are thus several areas of uncertainty regarding the indications for renal revascularisation in patients with ARVD, as well as the outcomes after such procedures. Despite this, many revascularisation procedures are still performed in the Western world, often without clear indications; it is well recognised that these procedures carry a significant risk of morbidity, and a distinct, albeit small, risk of mortality^[3]. The arguments in favour of a randomised controlled trial, such as ASTRAL, which will help guide future practice, are listed below.

Renal functional change

The chief aim of ASTRAL is to identify whether or not revascularisation in ARVD is associated with any overall improvement in renal function.

Guiding selection of appropriate patients for revascularisation—better use of resources and minimising unnecessary patient morbidity

It is hoped that the pre-specified subgroup analyses within the ASTRAL trial will identify those patients most likely to manifest clinical improvement (e.g. in terms of renal function, hypertension or survival) after revascularisation. This will help to avoid many patients being unnecessarily subjected to such procedures, with concomitant benefit in terms of use of resources, cost and patient morbidity.

Financial benefits to the Health Service

The techniques involved in renal revascularisation are not cheap, especially if endovascular stenting is employed. The future appropriate selection of patients to undergo this procedure can only improve its overall cost-effectiveness. Further, once patients progress to ESRF, the majority are offered dialysis therapy, and the cost of this can be over £25,000 per annum. Preventing or delaying the need for dialysis in even a minority of UK ARVD patients in the future is likely to result in substantial savings to the Health Service.

Evidence-based practice

Why should we overlook the opportunity to accumulate the evidence for best management of ARVD patients

when simple coordination, within a multi-centre trial, will allow this?

References

- [1] Dean, RH, Tribble, RW, Hansen, KJ, O'Neil, E, Craven, TE, Redding, JF II. Evolution of renal insufficiency in ischemic nephropathy. *Ann Surg* 1991; 213: 446–56.
- [2] Mailloux, LU, Napolitano, B, Bellucci, AG, Vernace, M, Wilkes, BM, Mossey, RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates and outcomes: A 20 year clinical experience. *Am J Kidney Dis* 1994; 24: 622–9.
- [3] van de Ven, PJ, Kaatee, R, Beutler, JJ *et al.* Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet* 1999; 353: 282–6.
- [4] van Jaarsveld, BC, Krijnen, P, Pieterman, H *et al.* The effect of balloon angioplasty on hypertension in atherosclerotic renal artery stenosis. *N Engl J Med* 2000; 342: 1007–14.
- [5] Plouin, PF, Chatellier, G, Darne, B, Raynaud, A. (for the EMMA study group). Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis. A randomized trial. *Hypertension* 1998; 31: 823–9.
- [6] Webster, J, Marshall, F, Abdalla, M *et al.* Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. *J Hum Hypertens* 1998; 12: 329–35.
- [7] Conlon, PJ, O'Riordan, E, Kalra, PA. New insights into the epidemiologic and clinical manifestations of atherosclerotic renovascular disease. *Am J Kidney Dis* 2000; 35: 573–87.
- [8] Textor, SC. Revascularisation in atherosclerotic renal artery disease. *Kidney Int* 1998; 53: 799–811.
- [9] Middleton, JP. Ischemic disease of the kidney: how and why to consider revascularisation. *J Nephrol* 1998; 11: 123–36.
- [10] Cheung, CM, Wright, JR, Shurrah, AE *et al.* Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol* 2002; 13: 149–57.
- [11] Suresh, M, Laboi, P, Mamtora, H, Kalra, PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. *Nephrol Dial Transplant* 2000; 15: 631–6.
- [12] Makanjuola, AD, Suresh, M, Laboi, P, Kalra, PA, Scoble, JE. Proteinuria in atherosclerotic renovascular disease. *Quart J Med* 1999; 92: 515–8.
- [13] Harden, PN, MacLeod, MJ, Rodger, RS *et al.* Effect of renal artery stenting on progression of renovascular renal failure. *Lancet* 1997; 349: 1133–6.
- [14] Connolly, JO, Higgins, RM, Walters, HL *et al.* Presentation, clinical features and outcome in different patterns of atherosclerotic renovascular disease. *Quart J Med* 1994; 87: 413–21.
- [15] Blum, U, Krumme, B, Flugel, P *et al.* Treatment of ostial renal artery stenosis with vascular endoprosthesis after unsuccessful balloon angioplasty. *N Engl J Med* 1997; 336: 459–65.
- [16] Wasser, MN, Weatenberg, J, van der Hulst, VP *et al.* Haemodynamic significance of renal artery stenosis: digital subtraction angiography versus systolically gated three dimensional phase contrast MR angiography. *Radiology* 1997; 202: 333–8.
- [17] Nahman, NS Jr, Manian, P, Hernandez, RA Jr *et al.* Renal artery pressure gradients in patients with angiographic evidence of atherosclerotic renal artery stenosis. *Am J Kidney Dis* 1994; 24: 695–9.