NEPHROLOGY

NEPHROLOGY 2010; **15**, S227–S233 doi:10.1111/j.1440-1797.2009.01245.x

Role of distal protection devices

Date written: November 2008
Final submission: August 2009
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[Correction added after online publication on 1 April 2010: Authors' names added.]

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based primarily on Level III and IV evidence)

- **Distal protection devices should be considered for patients requiring renal artery angioplasty to prevent renal atheroembolism. Discussion between the nephrologist and interventional radiologist (and other relevant specialists) regarding the benefits and harms of distal protection in this context is strongly encouraged.**
- **Clinicians should recognize that the use of distal protection devices does not completely remove the risk of renal atheroembolism.**

IMPLEMENTATION AND AUDIT

A registry of the use of distal protection devices would contribute to our knowledge of the benefits and harms of distal protection. This would work best within a larger registry of renovascular intervention procedures.

BACKGROUND

Atherosclerotic renal artery stenosis (ARAS) is often associated with vascular disease in other vessels and is becoming increasingly common as the population ages and more people are investigated for reduced kidney function.[1] The major clinical manifestations of ARAS are hypertension and reduced kidney function. Treatment options for ARAS include medical management and revascularization. Although restoration of perfusion of the kidney should in theory help preserve kidney function, it remains unclear whether patients should undergo revascularization of the kidney or not. Revascularization is predominantly performed by percutaneous transluminal angioplasty of the vessel with insertion of a stent to reduce the rate of restenosis.[2] In contrast to other vascular beds, such as the coronary or lower limb circulation, there are no symptoms to improve by restoring perfusion to the kidney.

One risk of this procedure that is difficult to precisely quantify is the release of cholesterol fragments from atheromatous plaque, which travel distally into smaller renal vessels.[3] The release of such fragments has been demonstrated in an *ex vivo* model of renal artery angioplasty and stent.[4] The best estimate of this risk comes from the ASTRAL study in which the risk of renal or stent embolisation at 24 hours post-procedure without distal protection devices was 1.5% and the risk of non-renal embolisation at 24 hours was 1%.[5] This complication can lead to permanent loss of kidney function and even end-stage kidney disease requiring dialysis, and can occur even weeks to months after the procedure. In order to prevent this complication, distal protection devices that are placed distal to the stenosis have been developed to trap embolic material that may be released during the angioplasty and stent insertion.[6] The available distal protection devices were made for coronary and carotid vessels and their major benefit has been demonstrated when used for angioplasty of coronary saphenous vein grafts.[6]

SEARCH STRATEGY

Databases searched: The terms used to define ARAS were 'Renal Artery Obstruction' (as a MeSH term and text word) and 'renal artery stenosis', 'renovascular disease$' and 'renal artery occlusion$' as text words. To define this further, the terms 'Atherosclerosis' and 'Arteriosclerosis', as both MeSH terms and text words along with text words 'angioplasty$' and 'stent$' were searched. In addition, various text words were searched to find references pertaining to distal protection devices. These were combined with the previous search, yielding 27 results. Ovid MEDLINE (1950–April 2009) was the database searched. The Cochrane Central Register of Controlled Trials and Database of Systematic Reviews were searched for trials and reviews not indexed in Medline. In addition, the reference lists of manuscripts retrieved by the above method were manually reviewed for additional studies.
Date of searches: 2 April 2009.

WHAT IS THE EVIDENCE?

Systematic reviews

There are no systematic reviews of randomized controlled trials comparing the use of distal protection devices with renal artery stenting to stenting alone.

Randomized controlled trials

There has been one randomized controlled trial that compared renal artery stenting with and without a distal protection device (Tables 1–4).[7] The 'RESIST' study had a 2 × 2 factorial design and randomized patients to an open-label distal protection device or not, and to double blind use of the platelet glycoprotein IIb/IIIa inhibitor abciximab or placebo. The sample size was based on providing 80% power to detect a difference in glomerular filtration rate (GFR) of 5 mL/min per 1.73 m^2 with a standard deviation of 8. The investigators required 85 participants and recruited 100 to allow for 15% loss to follow up. The primary outcome was change in GFR at 1 month measured by the 4-variable Modified Diet in Renal Disease (MDRD) equation and creatinine was measured by an isotope dilution mass spectrometry-traceable assay. In total, 390 patients were screened to achieve 100 randomized patients. Data were available for 91 patients; 5 refused follow up and 4 had insufficient sample to enable analysis.

There was a significant decline in GFR in all groups except the group given the combination of distal protection device and abciximab. There was a significant interaction for these therapies at $P < 0.05$, indicating that the addition of abciximab to stenting with distal protection was more effective in preventing a decline in GFR than either therapy alone. Analysis of all patients randomized to the distal protection device demonstrated a percent change in GFR of –1 ± 28% compared with –10 ± 20% in those not receiving the device ($P = 0.08$). For abciximab, this was 0 ± 27% compared with –10 ± 20% in those receiving placebo ($P < 0.05$).

This trial does not provide evidence that the use of distal protection devices prevents decline in GFR but suggests the possibility when used with abciximab. However, this is a small trial with an outcome based on serum creatinine measurement rather than the gold standard nuclear GFR and was reported at only 1 month.

Controlled non-randomized studies

A dual centre non-randomized study retrospectively analysed 78 renal artery stenting procedures performed between 2002 and 2005 and demonstrated no significant difference in kidney function between patients undergoing renal artery angioplasty and stent procedures receiving distal protection devices and those not receiving distal protection (Table 5).[8] They compared 31 patients treated with distal protection devices with 17 patients who received stenting alone and demonstrated that estimated GFR (eGFR) improved in both groups at 6 months, but that the difference in this increase was not significantly different between those receiving a distal protection device and those not (2.9 mL/min per 1.73 m^2 compared with 7.6 mL/min per 1.73 m^2, respectively, $P = 0.15$). There was also no difference at 12 months, although there were 10 fewer patients overall by this stage. Two patients who received distal protection devices and one patient who received stenting alone required dialysis by the end of 12 months. Of the initial 78 procedures analysed, 13 were excluded because of eGFR > 60 mL/min per 1.73 m^2 and 9 were lost to follow up before 6 months. The 25 who received stenting alone underwent adjudication for eligibility to receive a distal protection device and 8 were considered ineligible for anatomical reasons. Thus, this study is prone to bias due to this selection of the control group and the loss to follow up.

Uncontrolled studies

There have been a number of uncontrolled case series published (Table 6) and these demonstrate that the use of distal protection devices is generally technically feasible, results in retrieval of debris in the majority of cases (that would presumably have otherwise lodged in the kidneys), and no excess of complications is reported. The conclusions about renal function are difficult to interpret and based on measurement of serum creatinine with or without calculation of the GFR, by the MDRD equation. Outcomes are described in terms of 'improved', 'stabilised', 'unchanged' or 'deteriorated', and in some studies, before and after creatinine values are given. A published guideline for renal artery revascularization studies recommends such an approach for renal function outcomes, and use of at least two measurements of serum creatinine before and after the procedure to reduce the influence of variation that might arise from a single measurement.[9] In the absence of an appropriate control group in these studies, it is difficult to conclude or deny that there has been benefit from the procedure in terms of kidney function.

Technical aspects

There are two major types of distal protection devices currently available and although used in the renal circulation, the current devices were designed for either coronary or carotid arteries. The balloon occlusion device deploys a balloon distal to the lesion to occlude the vessel, and trapped material is aspirated before the balloon is deflated and removed. Thus, blood flow to the kidney is stopped for a brief period (5–15 min) but could cause ischaemic injury if a longer time is required. The filter devices have a basket that is deployed distal to the lesion. Different filters have pores of varying sizes (70–150 μm), and themselves have different diameters.[10] In renal atheroembolism, cholesterol crystals are predominantly seen in the arcuate and interlobular arteries that have a diameter of 150–200 μm, where they induce inflammation leading to occlusion of the vessel over time.[11]

Distal protection devices may fail to completely protect the kidney from distal atheroembolism because: (1) atheroemboli may dislodge before the device is deployed, as a guide wire must be passed across the lesion first; (2) current embolic protection devices were not designed for the renal circulation and a study comparing the length and diameter of devices to measurements of length and diameter of renal arteries demonstrated that few devices were compatible.[12,13] Hence, not all procedures are able to achieve complete

occlusion (and therefore protection) of the target vessel by these devices (Table 6); and (3) cholesterol crystals of smaller size than the filter pores may still deposit in distal smaller vessels and affect kidney function. An *ex vivo* study of aortorenal atheroma specimens examined the distal effluent collected after each step in the angioplasty procedure.[4] Cholesterol fragments of varying sizes were detected at each stage, including with initial passage of the guidewire. Fragments less than 60 μm, smaller than the filter pores, were numerous.

Antiplatelet therapy

The Cooper *et al.* trial randomized participants to abciximab or placebo and demonstrated some benefit in the antiplatelet therapy.[7] This is important because analysis of particles demonstrates not just cholesterol crystals, but fibrin, thrombi and platelets as well.[14,15] In one study, patients receiving aspirin had lower captured particle counts.[16] Antiplatelet therapy was not routinely reported in the uncontrolled studies, although more recent studies included clopidogrel, aspirin or a combination in their protocols.[14,17,18] In the Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) study, all participants undergoing angioplasty will receive aspirin indefinitely and clopidogrel for 4 weeks.[19] In the Angioplasty and Stent for Renal Artery Lesions (ASTRAL) study, antiplatelet therapy was at the discretion of the local investigator,[20] and in the Renal Atherosclerotic Revascularization Evaluation (RAVE) study, antiplatelet therapy is recommended in the medical therapy arm but not specified in the revascularization arm.[21]

SUMMARY OF THE EVIDENCE

The evidence for the use of distal protection devices currently rests solely on the one randomized controlled trial that had 1 month of follow up and is insufficient to make a guideline.[7]

While it seems logical that a device that prevents atheromatous debris lodging in the renal circulation would be beneficial, there remains insufficient evidence of benefit to recommend widespread use. Furthermore, the limitations of such devices should be appreciated.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1. Anticipated randomized controlled trials vary in their use of distal protection devices, with CORAL incorporating their use but ASTRAL and RAVE not specifying their use. Data on the use of such devices may thus be available at the conclusion of the CORAL study, although this is not the primary aim of this study.
2. Future research should consider careful measurement of kidney function at clinically relevant time points, preferably by radioisotope GFR.
3. The role of antiplatelet therapy in the prevention of atheroemboli should be further explored.
4. The development of stents and distal protection devices designed to be used in renal arteries, rather than coronary or carotid arteries, is required. In this context, the development of covered stents may provide extra benefit that could be the subject of future studies.

CONFLICT OF INTEREST

Matthew Roberts has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Characteristics of included study

Study	*N*	Study design	Setting	Participants	Intervention	Control	Follow up
Cooper *et al.* (2008)[7]	100	Randomized controlled trial with 2 × 2 factorial design (other treatment: abciximab)	7 US centres	≥1 renal artery stenosis ≥ 50%; lesion treatable with embolic protection device; history of vascular comorbidities; poorly controlled blood pressure (>140/90 mmHg)	Positioning of genesis stent to lesion after positioning angioguard embolic protection device	Positioning of genesis stent without angioguard embolic protection device	1 month

Table 2 Quality of randomized controlled trial

Study	Allocation concealment	Blinding	Intention to treat	Loss to follow up
Cooper *et al.* (2008)[7]	Adequate	Participants, investigators and outcome assessors not blinded	Yes	Stated as zero. However nine participants were randomized but not evaluated: five participants withdrew and four had insufficient sample.

Table 3 Results of continuous outcomes

Study	Outcome	Intervention (mean ± standard deviation)	Control (mean ± standard deviation)	Difference in means (95% CI)
Cooper *et al.* (2008)[7]	% change in Modified Diet in Renal Disease glomerular filtration rate	–1 ± 28%	–10 ± 20%	Not stated, but $P = 0.08$ for comparison
	Blood pressure	Data not presented	Data not presented	No effect stated in text

CI, confidence interval.

Table 4 Results for dichotomous outcomes

Study ID	Outcome	Intervention	Control	Relative risk (95% CI)	Risk difference (95% CI)
Cooper *et al.* (2008)[7]	Dialysis	0/44	1/47	–	–
	Dissection	0/44	1/47	–	–
	Distal embolization	1/44	0/47	–	–
	Renal artery spasm	2/44	0/47	–	–

CI, confidence interval.

Table 5 Controlled non-randomized study reporting the use of distal protection devices

Study	Patients (arteries)	Study design	Setting	Participants	Device	Renal function (method)	Debris retrieved	Technique success
Singer *et al.* (2008)[8]	48 (78)	Retrospective	Two centres, 2002–2005	GFR ≤ 60 mL/min, hypertensive	GuardWire RX Accunet	At 6 months: DPD: eGFR 37 ± 15 mL/min pre and increased by 7.9 post	Not stated	Not stated
					FilterWire EZ	No DPD: eGFR 34 ± 13 mL/min pre and increased by 2.9 post No difference comparing DPD to no DPD		

DPD, distal protection device; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

Table 6 Uncontrolled case series reporting the use of distal protection devices

Study	Patients (arteries)	Study design	Setting	Participants	Device	Renal function (method)	Debris retrieved	Technique success
Holden *et al.* (2006)[22]	63 (83)	Prospective	Single centre, 2002–2005	RAS by MRI, objective deterioration in function over 6 months	Angioguard XP (73), Filterwire EZ (10)	At 6 months: 40% improved, 57% stabilized (MDRD GFR)	38/63	7 (8) had small branch unprotected; 4 were excluded as not able to be protected
Holden & Hill (2003)[23]	37 (46)	Retrospective	Single centre, 2000–2002	Referred with decline in kidney function over 6–12 months	Angioguard	At 6 months: 14 improved, 21 stabilized (compared with 0 and 15 of 20 patients without distal protection 1998–2002) (Serum creatinine)	30/46	All successful
Henry (2008)[3,15,24,25]	121 (141)	Prospective	four centres, 1999–2008	Hypertension and RAS	Percusurge GuardWire (balloon) (46); EPI Filters (95), EPI Filter in 65, plus four other types	No change in creatinine from baseline up to 3 years ($n = 74$); at most time points, 75% unchanged, 25% improved. By 3 years, 4 of 74 had a decline in renal function (Serum creatinine)	All Percusurge procedures had visible debris; 80% of the filters showed visible debris	All successful (but did not do if diameter >6 mm, bifurcated/trifurcated vessels and lesion < 2 cm from division); 3 required pre-dilatation
Edwards *et al.* (2006)[26]	26 (32)	Retrospective	Single centre, 2003–2005	ARAS, ≥60% stenosis, and hypertension	GuardWire	At 6 weeks: improved in 13, unchanged in 13 (MDRD GFR)	14/32	All successful
Edwards *et al.* (2007)[16]	27 (28)	Prospective	Single centre, 2005–2006	ARAS, ≥60% stenosis, and hypertension	GuardWire	At 4–8 weeks: improved in 8, unchanged in 14 (of 22) (MDRD GFR)	Mean particle (20–60 μm) count 2033 ± 1553 per procedure	Balloon occlusion complete in 26/28 procedures
Hagspiel *et al.* (2005)[27]	4 (5)	Retrospective	Single centre	ARAS, >70% stenosis	FilterWire EX	Stabilized in 3 (serum creatinine)	Debris in 3/4	Protection successful in 3/5

Corriere *et al.* (2008)[18]	99 (110)	Retrospective	Single centre, October 2003–September 2007	ARAS, ≥60% stenosis on Doppler, hypertension	GuardWire	At median 9.4 weeks: eGFR (mL/min per 1.73 m^2) 46.8 ± 17.3 pre and 50.2 ± 19.7 post procedure, $P = 0.0114$	Not stated	Attempted in 100 Complete occlusion in 74, partial in 22, failed in 4
Misra *et al.* (2008)[17]	23 (32)	Retrospective	Single centre, June 2005–October 2006	ARAS, >50% stenosis, GFR ≤ 60 mL/min	FilterWire EZ SpideRX	At 12 months: eGFR (mL/min per 1.73 m^2) 32.9 ± 12.9 pre and 41.3 ± 13.7 post procedure, $P < 0.05$	None in FilterWire EZ, 6 of 17 (35%) in SpideRX	9/12 for FilterWire EZ (1 complete occlusion, 4 partial, 4 incomplete apposition) 17/17 for SpideRX (complete occlusion 10, partial occlusion 7) Complications: 1 difficulty removing device requiring repeat intervention the following day; 1 renal artery dissection after deployment of DPD
Klonaris *et al.* (2008)[14]	14	Retrospective	Single centre June 2002–September 2007	Single functioning kidney, >80 mm length, ≥60% stenosis	FilterWire EX/EZ RX Accunet	At 6 months: Creatinine (μmol/L) 266 ± 102 pre and 191 ± 60 post, $P = 0.02$	9/14	12/14 had complete occlusion; 2/14 had partial occlusion
Singer *et al.* (2008)[8]	48	Retrospective	Two centres 2002–2005	GFR ≤ 60 mL/min, hypertensive	GuardWire RX Accunet FilterWire EZ	At 6 months: DPD: eGFR 36 ± 15 mL/min pre and increased by 7.6 post No DPD: eGFR 34 ± 13 mL/min pre and increased by 2.9 post No difference comparing DPD to no DPD	Not stated	Not stated

ARAS, atherosclerotic renal artery stenosis; DPD, distal protection device; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modified Diet in Renal Disease; RAS, renal artery stenosis.