



Renal angioplasty stenting under embolic protection device: first human study with the FiberNet™ 3D filter

Background: Atheroemboli are the rule in any intervention and the leading cause of complications during percutaneous coronary intervention, carotid angioplasty (CAS), and probably after renal angioplasty stenting (RAS), which could explain the renal function deterioration after RAS in 20–30% of the cases. Several series of RAS under protection were reported using current embolic protection devices (EPDs), but these EPD have significant limitations that may be addressed by a new EPD, the FiberNet™ (Lumen Biomedical Inc, MN, USA). **Methods:** FiberNet is a 3D expandable filter made of fibers, which expands radially to fill the lumen, that is mounted onto a 190-cm long 0.014-inch wire. No delivery sheath is required. The crossing profile (1.7–2.9F) is low. With the retrieval catheter a focal suction can be performed during device removal allowing a meticulous cleaning of the vessel. The filter can fill vessels from 1.75 to 7 mm without requiring a long landing zone, allowing protection in the majority of renal arteries. FiberNet can capture particles as small as 40 μm without compromising the flow. **Results:** After a series of 139 protected renal angioplasties performed with current EPDs, we began the first human study with FiberNet. A total of 12 ostial lesions (R: 6, L: 6) were treated in 12 hypertensive patients (Male: ten). The mean age of patients was 64 years, with an average stenosis of 79%, two patients had moderate renal insufficiency. FiberNet crossed 11 lesions without predilatation (one predilatation was necessary for a subocclusive very calcified ostial lesion). Technical success was observed in 100% of patients with no reported complications. All samples visually contained significant amounts of emboli. The mean debris surface area was 106 mm^2 (aspirated debris: 82 mm^2 , debris in the filter: 24 mm^2). The mean number of particles 28–60 μm : 2136 \pm 776, greater than 60 μm : 5918 \pm 1362. At 6-month follow-up, we observed no deterioration of the renal function. **Conclusion:** The first human use of this new novel EPD in RAS is encouraging. FiberNet was easy to use and it captures particles of 30/40 μm without compromising the flow, which seems to be an improvement in comparison with current EPD. The amount of debris removed is comparable during RAS and CAS. Additional patients will demonstrate the overall performance of this new EPD and its role to preserve the renal function and improve long-term results of RAS.

KEYWORDS: angioplasty ■ embolic protection device ■ hypertension ■ renal artery stenosis ■ renal insufficiency ■ stent

Atherosclerotic renal artery stenosis (RAS) is frequent and increasingly diagnosed due to technical improvements in duplex ultrasound, magnetic resonance angiography, CT scanning, routine renal angiography during cardiac catheterization, particularly in hypertensive patients or those with multivessel disease, and in patients with renal insufficiency. Renovascular disease affects approximately 2–4 million people in the USA. The prevalence of RAS is high in patients with peripheral vascular disease, renal insufficiency and coronary heart disease [1–6].

The natural history of RAS is crucial [7–14]. Atherosclerotic renal artery stenoses have a high tendency to progress with time, resulting in renal artery occlusion (11–16%), loss of renal mass and a subsequent decrease in renal function (RF). Of these patients, where progression was noted over a 2-year period, the

progression of RAS and loss of RF are independent predictors of the ability to medically control blood pressure (BP) [9,14]. Atherosclerotic RAS can lead to different clinical conditions:

- Renovascular hypertension (secondary hypertension): accounts for 1–5% of all cases of hypertension [15,16];
- Renal insufficiency: a rise in serum creatinine following initiation of antihypertensive therapy with angiotensin-converting enzyme inhibitors may lead to the diagnosis of RAS. RAS can be severe enough to cause ischemia and tissue damage, as is often shown by asymmetry in kidney size [13]. In patients over 50 years of age, RAS is responsible for 5–15% of the renal failure population and dialysis dependence;
- Flash pulmonary edema: often the first clinical symptom of bilateral RAS [17];

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Atherosclerotic renovascular disease represents an important public health problem. It has been demonstrated to increase cardiovascular and all-cause mortality [18–21].

Indications for treatment of RAS are debated, but it is generally accepted to treat patients with a severe RAS (defined as a diameter stenosis of at least 70% and/or over 15 mmHg peak systolic pressure gradient) in the setting of uncontrolled hypertension, renal insufficiency, congestive heart failure (flash pulmonary edema), unstable angina and in patients with a solitary or a single functioning kidney. The treatment of RAS without hypertension or renal insufficiency is debatable but could be considered with a view to preserving RF and renal artery patency.

The treatment options for a RAS include medical therapy, balloon angioplasty (with and without stenting) and surgery. Surgery carries a significant risk with a 2–7% perioperative mortality rate and a 17–31% morbidity rate [22–24]. Indications for surgery should be limited to failed percutaneous approach, hostile aorta or in association with aortic surgery.

Percutaneous transluminal renal angioplasty (PTRA) has become the cornerstone of therapy for addressing RAS and is now the first-line treatment as balloon angioplasty alone was first proposed and is still the first-line therapy for fibrodysplastic RAS. Several authors have reported the successful use of endovascular stents for treating suboptimal angioplasty results. Stents are the primary intervention for atherosclerotic lesions (particularly ostial lesions) with better immediate and long-term results than with PTRA alone [25–30].

In the majority of cases, renal angioplasty is performed using the femoral approach, but a brachial approach can also be used. The procedure has benefited from the improvements in coronary technique: monorail systems for balloons and stents, low-profile devices and 0.014- or 0.018-inch guidewires. Direct stenting can be accomplished in 80–90% of the procedures. Procedural success for renal stenting is excellent (98–100%) with a low complication rate, a low restenosis rate and a good long-term patency rate of 85–98% [25–30]. There are clear benefits in restoring blood flow to the kidney and several reports have shown these positive effects of renal artery revascularization [25–32]:

- The benefit for hypertension includes complete cure (7–19%) or easier management in 52–74% of the cases and a reduction in the number of antihypertensive drugs;

- The kidney function may improve or stabilize in 70–80% of the patients following revascularization;
- Improvement in patient survival should be obtained after revascularization in patients with improved RF considering that the creatinine level is a predictor of increased mortality [33,34];
- A reduction of the left ventricular hypertrophy, probably due to the reduction in activation of the renin–angiotensin–aldosterone system, which can lead to lower heart failure and cardiovascular mortality/morbidity rates [35]. It is an argument to consider renal revascularization in patients with severe RAS.

Two randomized studies were recently published, the ASTRAL Study [36] and the STAR Study [37], comparing PTRA stenting and medical therapy. These studies concluded that stenting is not superior to medical management in patients with a RAS. However, these studies have numerous limitations and flaws. They do not agree with a meta-analysis published by Nordmann *et al.* who reported better results for BP with balloon angioplasty with stenting compared with medical therapy [38].

Renal artery stenting should be a treatment option proposed to a patient suffering from a significant RAS. However, some drawbacks have to be mentioned.

It is well-known that postprocedural deterioration of the RF occurs in 20–30% of the patients after renal stenting [30–32]. We hypothesize that atheroembolism during the procedure is a precipitating factor for this complication and a major factor limiting the benefits derived from renal stenting. This hypothesis is supported by recent studies [39], including the role of a renal atheroembolism demonstrated and reported by Scolari *et al.* [40]. Distal embolization of atherosclerotic debris during PTRA and stenting can be a major complication for renal artery intervention. In order to eliminate or reduce the risk of atheroembolic material being carried into the renal parenchyma, we applied an embolic protection device (EPD) using balloon or filters positioned distal to the lesion. This technique was developed and is currently approved for use in the coronary and cerebral circulations [41–43].

Different EPDs have been used and there are several series demonstrating promising results with the capture of thousands of atheroembolic particles [41–53]. However, the current EPDs used in renal vasculature have some limitations,

drawbacks and disadvantages. To overcome these problems, we have used the new FiberNet™ Embolic Protection System, a filter approved for carotid angioplasty (CAS) and stenting. We are presenting the results of the first human study of this filter during PTRAs during stenting procedures.

Material & methods

■ Device description

The FiberNet Embolic Protection System is a temporary, intravascular, 0.014-inch wire-based filter system that is placed distal to a lesion to be treated by interventional procedures (FIGURES 1 & 2). The system consists of an expandable, polymeric, fiber-based filter mounted on to a 190-cm coronary wire with a shapeable tip, a retrieval catheter that can perform aspiration and accessories. The FiberNet filter has radiopaque markers for visualization under fluoroscopic imaging.

The FiberNet filter is composed of numerous strands of polymer fibers of equal length bundled together to form a cartridge. When deployed, the distance between the proximal and distal ends of the filter cartridge is shortened, which causes the filter strands to flare out radially and seek the vessel wall. The deployed filter completely fills the vessel, providing excellent apposition to the wall, even in diseased or eccentric vessels. This FiberNet filter requires a shorter landing zone compared with other filter devices.

The FiberNet filter is designed to capture emboli while preserving physiological flow during the interventional procedure. Containment of emboli is accomplished by the 3D filter structure that provides a large number of pathways through which blood can pass. The filter is of sufficient density to allow adequate blood flow while simultaneously preventing particulate matter greater than 40 µm from following downstream. On the bench the particulate capture efficiency is 99% particulates greater than or equal to 100 µm and 93% particulates greater than or equal to 40 µm.

Upon completion of the procedure, the rapid exchange retrieval catheter is advanced over the wire and positioned just proximal to the expanded filter. Contained and captured emboli are recovered/removed by focal suction through the retrieval catheter and also by retention within the filter fibers. Aspiration is achieved using vacuum syringes and an extension/stopcock assembly. During aspiration the filter is retracted and drawn into the retrieval catheter. The filter and retrieval catheter are removed from the patient as a single unit.

The ability to perform aspiration with the retrieval catheter is an integral part of the procedure. This retrieval catheter has an excellent torque with a directional tip and a large single lumen, providing efficient and powerful aspiration (FIGURE 2). The manufacturer recommends two focal suctions – one at the base of the filter to remove any loose material bound to the filter and one during the collapse and retrieval of the filter. We opt for an additional early aspiration inside the stent to aspirate particles, which can be present against and protruding through the stent struts.

The FiberNet product family consists of three models to cover the target vessel size range of 3.5 to 7.0 mm. Since no delivery catheter is required, the crossing profile of the FiberNet device is smaller than comparable distal protection filters, ranging from 2.4 Fr in the smallest size to 2.9 Fr in the largest. The filter is atraumatic.

■ Patients

A total of 12 patients (ten men, two women) with a mean age of 64 years (between 53 and 81 years of age) underwent PTRAs and stent placement of 12 renal arteries with significant ostial stenosis (>70%). Written informed consent was obtained from all patients. Indication for intervention was poorly controlled hypertension in all patients despite three hypertensive drugs administered for at least 6 months. Renal insufficiency (serum creatinine level ≥ 1.5 mg/dl) was additionally present in two patients.

Mean percentage stenosis was 79% with a mean lesion length of 10.2 mm. Three patients had diabetes mellitus, eight were current smokers, seven had hyperlipidemia and three had severe coronary disease. Cerebrovascular disease was found in two patients and lower extremity peripheral artery disease in three.

■ Medications patient surveillance

As for all our stenting procedures, patients are given clopidogrel (75 mg/day) and aspirin (100 mg/day) before the procedure. During the procedure, an intravenous bolus of 5000–10,000 units of unfractionated heparin is routinely administered at the beginning of the procedure to have an activated clotting time of approximately 250–300 s.

The postprocedural drug regimen included aspirin (100 mg/day) indefinitely and clopidogrel (75 mg/day) for 1 month. Patients remained in the hospital for 24 h following the procedure to monitor serum creatinine levels

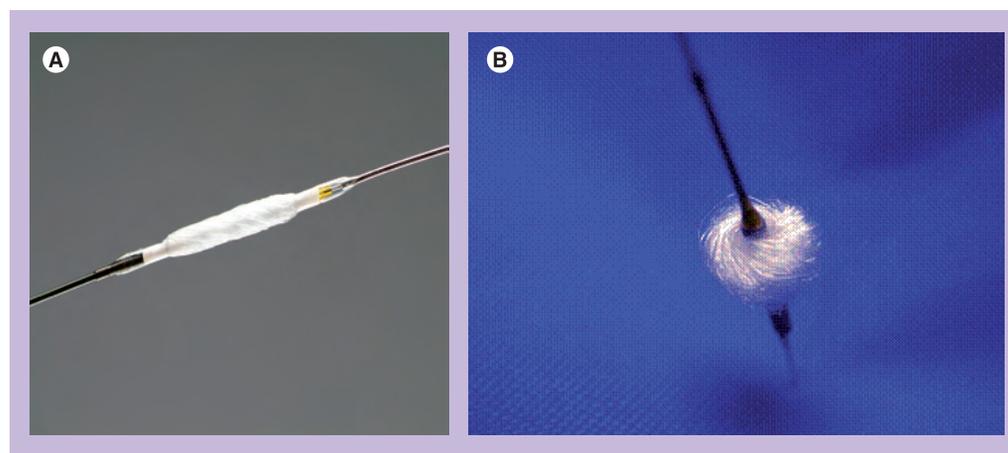


Figure 1. FiberNet™ embolic protection device. (A) Before deployment. (B) After deployment.

and adjust BP medication. Renal duplex scanning is scheduled the day after the procedure, at 6 and 12 months postprocedure and then annually. Angiography is performed when a restenosis is suspected on the basis of positive clinical and duplex scan findings. Serum creatinine values are measured before and after the procedure (day 1) and at 1 and 6 months, with biannual measurements thereafter.

■ PTR A stenting procedure

A 7 Fr guiding catheter was placed at the ostium of the renal artery via a percutaneous femoral approach in all patients. A small amount of contrast is injected to precisely locate and

analyze the stenosis. A total of 11 stenoses were easily crossed with the FiberNet filter. One patient required a predilatation with a 3 mm coronary balloon due to a subocclusive calcified stenosis. All filters were deployed distal to the stenosis and a small injection of contrast confirmed a good flow through the filter. Direct stenting was performed in all cases. All stents placed were dilated at a diameter of 6 mm (ten patients) or 5 mm (two patients).

After stent deployment, with the filter still in place an angiographic control was performed and if no problem was detected, the filter was removed with the retrieval catheter, which was introduced and advanced over the wire inside the guiding catheter. There was no difficulty collapsing and removing the filter. Three aspirations were done: inside the stent, between the stent and the filter and when we closed the filter. Aspirated blood was sent for debris analysis. A final angiogram was carried out and if the result was correct, we removed the guiding catheter.

■ Immediate results & follow up

A technical success was obtained for all arteries with good stent deployment, no significant residual stenosis and complete covering of the lesion. There were no major complications (e.g., dissection and visible embolism) or spasm at the location of the filter. The mean FiberNet deployment time was 9.4 min (6–21 min). At 1-month and 6-month follow-up we observed no complications with no deterioration of the RF. Two patients with RF deterioration were stabilized. Concerning BP, two patients were cured, two patients remained unchanged, eight patients were improved with normalization of the BP, the number of medications reduced from 3.2 to 2.1. We observed no worsening.

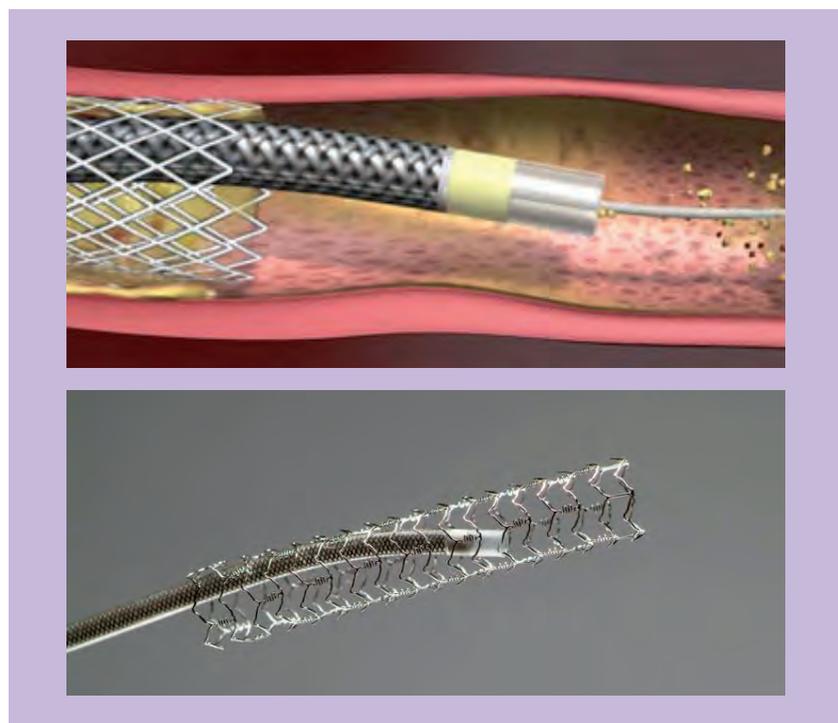


Figure 2. FiberNet™ aspiration catheter.

■ Debris analysis

Filter and emboli were fixed immediately following retrieval from the patient in 10% neutral buffered formalin. Once gross photographic documentation was performed, the samples were sent to the Biomedical Image Processing Lab at University of Minnesota, MN, USA for quantitative analysis. High-resolution images of the aspirate and the filter were taken to quantify the debris. Morphometric analysis was performed on these images using computerized edge detection to determine the length, shape factor and surface area of the particulate debris. Surface area was calculated using the two longest orthogonal diameters.

Visible particulate debris was retrieved in all 12 patients. Debris analysis was performed in ten patients. The mean surface area of debris caught per patient was $103.75 \pm 70.10 \text{ mm}^2$ (aspirate 82.18 ± 53.77 , filter 23.96 ± 22.57). The mean number of particles per patient was 8609 (number of particles 28–60 μm was 2466, >60 μm 6143). There were 308 particles greater than 500 μm . FIGURE 3 shows the aspirate and filter debris area and TABLE 1 the size of the debris determined for each patient.

Discussion

Renal artery stenosis is increasingly diagnosed in patients suffering from hypertension, renal insufficiency and in multivascular diseased patients. PTRAs stenting is a treatment option that has a high technical success rate, low complication rate, low re-stenosis rate and good long-term anatomical results. However, renal stenting is controversial and two recent randomized studies have shown no benefit in comparison with medical therapy [36,37]. These studies are questionable and should be discussed.

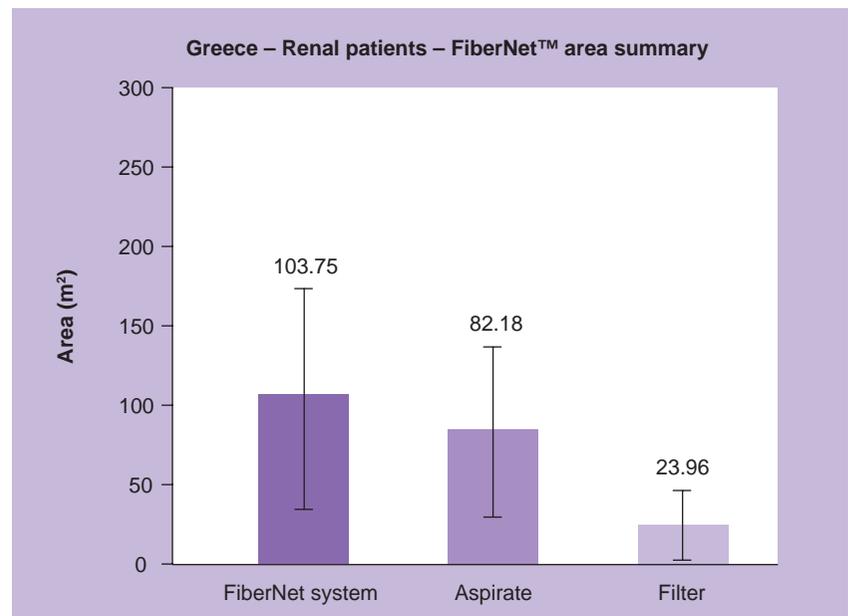


Figure 3. Debris analysis.

In the ASTRAL Study, 403 patients were treated by PTA with medical therapy or stent with medical therapy, and 403 patients by medical therapy alone [36]. One major issue is the number of people who had a stenosis <70%, 7% of patients were treated by PTA alone. The number of patients in the medical therapy group with a true stenosis of less than 70% is unknown. The complication rate after interventional procedure was high (7%) with 10% demonstrating RF deterioration. The technical success rate after PTRAs was only 82%, which is unacceptable and is an indicator of operator experience. In total, 58 centers were involved during the 7 years, which indicates only two patients/center/year enrolled in the study. This could indicate patient selection bias into the study. Furthermore, no EPD was used.

Table 1. Aspirate and filter debris area.

Patient ID	Aspirate	Filter	FiberNet™ system
01–18	13.52	12.53	26.05
01–29	138.85	69.19	208.04
01–69	51.89	11.67	63.56
01–70	183.44	43.37	226.80
01–71	123.48	NA	123.48
01–73	86.12	34.98	121.11
01–74	81.92	31.77	113.69
Renal 1 2009	79.05	4.23	83.29
Renal 2 2009	24.47	4.33	28.80
Renal 3 2009	39.08	3.57	42.66
Average FiberNet	82.18	23.96	103.75
Standard deviation	53.77	22.57	70.10
Percentile of total area	79.21	23.10	100.00

NA: Not applicable.

In the STAR Study, 140 patients with renal insufficiency were randomized [37]. A total of 76 patients were treated medically, 64 patients were included for PTRA with medical therapy. Only 46 of these patients received a stent. A total of 12 patients had a stenosis less than 50% while six patients were not stented for various reasons. A total of 22 patients had a low-grade stenosis (50–70%), which was not hemodynamically significant. Patients were enrolled upon noninvasive imaging. The hemodynamic significance of the stenosis was not assessed. A better study design would have been to randomize patients after angiography. In the STAR study, RAS was very unlikely to demonstrate a benefit to medical therapy because the lesions were milder. Furthermore, the interventionalists were not adequately skilled and experienced. There were numerous complications and technical failures were reported. Furthermore, no EPD was utilized in this study. These severe limitations create difficulties to draw true conclusions from these studies.

According to the literature data, some patients seem to benefit from the procedure with regard to hypertension and renal insufficiency with stabilization or improvement in RF. In selected patients, RAS could slow the progression of renovascular renal failure and may delay the need for renal replacement therapy [25–29,33,34,54–70]. But as we have noticed in many published series a deterioration in RF for patients undergoing renal artery stenting is observed in 20–30% of the patients. This is true in patients with renal insufficiency but also in patients with normal RF at baseline, even after successful initial technical results and good long-term patency [30–33,54–58,71–74]. This RF deterioration remains a major problem after renal stenting. We know that patient survival depends on the RF and improvement after stenting correlates with improved survival. Improvement in RF is one of the major goals of the procedure and any technique that can improve postrenal stenting RF should be considered.

Many factors may be responsible for this functional deterioration; contrast media-induced nephrotoxicity, progression of concomitant nephrosclerosis, lesion recurrence, hyperperfusion syndrome and glomerular injury. However, atheroma embolism seems to play an important role and is an increasingly recognized cause of RF deterioration. It is demonstrated that atherosclerotic debris commonly embolize from lesions in many vascular territories during percutaneous intervention [75]. Evidence of distal embolization is a cause of complications and was first noted in saphenous vein graft interventions [76].

Atheroembolism has also been shown during catheter treatment of certain native coronary lesions [77] and during carotid and renal stenting procedures [41–44,46,78]. Distal protection devices have been able to recover embolic debris in all these territories and significantly reduce its incidence of these complications. Animal studies suggest that platelets could also play a role in ischemic nephropathy.

During a renal angioplasty, cholesterol atheromatous embolism is caused by the release of microscopic plaque fragments and cholesterol crystals from the renal artery lesion or the atherosclerotic aorta into the parenchymal renal vasculature during the procedure. Instruments manipulated in the aorta and renal arteries can result in detachment and embolism of atheromatous debris from ulcerated plaques. The large size of the devices used or difficulties during the procedure may also be contributory. Walker *et al.* recently demonstrated the great potential for embolic debris during the placement of the guiding catheter, sheath or diagnostic catheter [78]. He proposed that careful aspiration of catheters before injections or interventions should be performed routinely. Patients with severe atheromatous disease of the aorta and its branches, ulcerated plaques, and associated lesions, such as an aneurysm, or dissection are each candidates for complications from distal embolization.

Hiramoto *et al.* demonstrated that angioplasty and stenting of *ex vivo* aorto-renal atheroma specimens using a 0.018-inch guide wire system was associated with thousands of atheroemboli [39]. Among the embolic debris, there was a predominance of small particles less than 60 μm . Recently, Edwards M *et al.* using the PercuSurge® balloon occlusion device during 28 renal stenting procedures reported the removal of a large number of debris with predominance of small particles [45]. The total number of embolic particles counted per procedure was:

- 20–60 μm : 2033 \pm 1553
- >60 μm : 265 \pm 132

The authors concluded that the results of these procedures could be improved by placing EPDs to prevent atheroembolization. All these fragments are of sufficient size to create vascular occlusion and initiate significant renal parenchyma damage. Atheroemboli typically occlude the medium-sized arterioles (150–200 μm in diameter) and glomerular capillaries. The pathogenesis of renal failure may be due entirely to occlusion of these vessels. However, a reactive

inflammation surrounding the cholesterol crystals may play a significant role in causing the luminal occlusion and subsequent renal failure.

We could expect that modern techniques of PTRAs with stenting using low-profile systems, coronary techniques and the no touch technique could prevent atheroembolism and RF deterioration. Despite these new techniques, RF deterioration is still reported [79,80].

The true incidence of atheroembolism is uncertain. Many patients can have a silent course owing to the large functional kidney reserve, which allows normal serum creatinine values despite a significant decline in total glomerular filtration capacity. Therefore, only the most severe cases may be detected, especially in patients with pre-procedural renal dysfunction and limited functional reserve. Abnormal serum creatinine may only be observed if 50% of the nephron population is destroyed. Most patients reach a peak serum creatinine level at 3–8 weeks but onset can also be sooner.

Few studies have addressed the problem of atheroembolism following renal stenting [25,32,79,81,82].

Atheroembolism can lead to different degrees of renal impairment:

- Moderate decline of RF
- Severe renal failure requiring dialysis
- Abrupt and sudden onset of renal failure
- More frequent and progressive loss of RF over 3–8 weeks
- Chronic stable and asymptomatic renal insufficiency

Scolari *et al.* recently reported a series of 354 patients suffering from documented atheroembolic renal disease [40]. The majority of cases (76.5%) were due to the procedure with catheter manipulation in the aorta. There was acute or subacute onset due to massive shower of emboli in 78.7% of the patients. For the authors, atheroembolization should be considered a major adverse effect of renal artery stenting procedures.

Other observations of distal embolization can be seen with skin manifestations, blood eosinophilia and gastrointestinal symptoms. Scolari *et al.* reported skin manifestations in 75.1% of cases, blood eosinophilia in 67.2% and gastrointestinal involvement in 12.1% [40].

Thadani *et al.* reported a series of patients with both renal failure and histologically proven atheroembolism after angiography in cardiovascular surgery [83]. For Haqqie *et al.*, most

patients reached a peak serum creatinine level over 3–8 weeks and he reported four patients with proteinuria and nephritic syndrome [84].

The diagnosis of atheroembolism is difficult after PTRAs stenting procedures. Renal biopsy is the only definitive tool, but its routine application is problematic. Scolari *et al.* performed a renal biopsy in 30.3% of cases and a skin biopsy in 37.5% [40]. The diagnosis was made clinically in only 37.3% of the cases. Atheroembolism after renal intervention is often misdiagnosed as dye-induced nephrotoxicity or the progression of nephrosclerosis. Nephrotoxicity due to contrast media generally appears 1 or 2 days after the procedure.

The prognosis of renal embolism is poor. Boero *et al.* recently highlighted the bad prognosis of renal atheroembolism in a series of 22 patients [85]. A total of 11 patients (50%) were put on dialysis with a partial functional recovery in four, 11 patients (50%) died.

Scolari *et al.* reported in his series of 354 patients followed for a mean of 2 years [40]:

- 116 patients (32.7%) required dialysis therapy;
- 102 patients died, 80% from cardiovascular disease;
- The 1- and 2-year patient survival probabilities are 83 and 75%, respectively;
- Independent predictors of dialysis/death are: baseline chronic kidney disease; baseline diabetes mellitus; baseline chronic heart failure; acute/subacute presentation and gastrointestinal involvement.

An important point to note is that the authors observed a 50% reduction in dialysis/death among patients started on statins.

Renal atheroembolism not only poses a risk of RF deterioration but also seems to decrease survival in patients undergoing endovascular procedures for RAS. Krishnamurthi *et al.* evaluated and confirmed its impact on survival in 44 patients who had surgery for atherosclerotic RAS and concomitant intraoperative renal biopsy for detection of atheroemboli [86]. Atheroembolic disease was identified in the biopsy specimens in 16 (36%) patients and correlated significantly with decreased survival (54% achieved 5-year survival in this group versus 85% in patients without atheroembolism; $p = 0.011$).

Thus, it can be concluded that cholesterol embolism is a frequent cause of renal failure leading to dialysis and is associated with a high mortality rate. The increasing number

of such patients, the cost due to RF deterioration and subsequent end stage renal disease requiring dialysis, represents a significant long-term problem.

No specific treatment can be suggested for renal atheroembolism. Therefore, the main aim should be prevention during renal interventions. The selection of the patients may limit the risk, but more and more high-risk elderly patients with advanced atheromatous diseases need treatment and it is difficult to refuse these patients the benefits of the procedure.

Certain technical points are very important and need to be mentioned. The procedures should be as atraumatic as possible with the use of small devices and adaptation of coronary angioplasty techniques. Direct stenting is not sufficient to avoid embolism. As mentioned earlier, Walker *et al.* proposed the careful aspiration of the catheters. The 'no touch' technique was also proposed to minimize atheroembolization [87]. Beyond these technical considerations to circumvent atheroembolism, we applied the concept of protection using EPDs during renal angioplasty and stenting [41–43].

The rationale for distal embolic protection is similar to that of brain protection during angioplasty and stenting of the carotid arteries. Several studies have shown that protection devices with occlusion balloon or filter are effective in reducing the risk of embolization to the brain [88,89], and that these techniques are now mandatory in this field and represent the standard of care [90]. We postulated that the same technique could be suitably applied during renal angioplasty and stenting to reduce the risk of atheroembolism and deterioration of the RF.

Before using the FiberNet EPD, we performed renal stenting with other EPD and have published a series of 139 RAS treated in 119 patients with occlusion balloon (46 procedures) and other filters (EPI: $n = 66$, Angioguard™ $n = 19$, Emboshield® $n = 6$ and Accunet™ $n = 2$) [53]. Technical success was 100% for all arteries treated. Visible debris were removed in all patients with the PercuSurge device and in 80% of the patients treated with filters. At the 6-month follow-up, we observed only one deterioration of RF, 99% of the patients were stabilized or improved and at 2 years only 5% of the patients had RF deterioration.

Holden *et al.* reported a first series of 46 procedures in 37 patients with preprocedural renal impairment performed with the Angioguard filter [44]. They also found that RF stabilized or improved in 95% of cases and only 5% of

the patients demonstrated a decline. No patients experienced acute postprocedural deterioration. A total of 65% of the filters contained embolic material, including fresh thrombus, chronic thrombus, atheromatous fragments and cholesterol clefts. More recently, Holden *et al.* published a larger series of 106 RAS treated under protection with filters and 90 patients presented with ischemic nephropathy [47]. They reported only one acute deterioration of RF. At a mean follow up of 18.2 months, RF was improved in 36% of cases and stabilized in 55%. Only 8% with progressive decline of RF was reported.

Chen *et al.* reported a randomized study comparing 13 patients treated by PTRAs under protection with Angioguard and 13 patients treated medically [51]. PTRAs with protection leads to better improvement of single kidney GFR in patients with a renal stenosis when compared with medical therapy.

Edwards *et al.* used the PercuSurge device (Medtronic, Inc., CA, USA) to treat 32 RAS [52]. Renal insufficiency was the indication for treatment in 92% of the patients. RF response at 4–6 weeks follow up was improved in 50% of the patients and unchanged in 50%. RF did not appear to worsen after any procedure in all patients. For the patients with RF deterioration at baseline, 54% of the patients showed an improvement. For the authors, the results with this technique of RAS under protection represent a marked improvement in short-term RF response rates compared with previously published experiences and approximate the short-term results reported after open surgical revascularization. They concluded that these data suggest this technique may prevent RF during renal artery stenting as a result of atheroembolism and warrant further investigation.

In a different study, Edwards reported a series of 28 PTRAs performed under protection with PercuSurge [45]. The column of blood proximal to the balloon was aspirated and submitted for embolic particle analysis. As mentioned previously, he removed a large number of particles with predominance of small particles of 20–60 μm (2033 ± 1553) and 265 ± 132 particles more than 60 μm . Significant positive associations with the quantity of captured particles of 20–60 μm were observed for African-American race ($p = 0.002$), predilatation ($p = 0.005$) and stent diameter ($p = 0.001$). A significant negative association was observed for preoperative aspirin use ($p = 0.016$). The quantity of captured particles greater than 60 μm was positively associated with the ratio of stent to renal artery diameter

($p = 0.009$). Change in eGFR was positively associated with preoperative aspirin use ($p = 0.006$) and preoperative eGFR ($p < 0.001$), while a negative association was observed for captured particle counts greater than $60 \mu\text{m}$ ($p = 0.015$). These results demonstrate that we can capture thousands of atheroembolic particles during renal stenting procedures under protection, and that increasing captured particle counts greater than $60 \mu\text{m}$ were associated with inferior RF results.

Cooper *et al.* recently reported the RESIST study, a prospective randomized multicenter study comparing the safety and efficacy of renal stenting with and without the use of a distal protection device (Angioguard) and with and without the use of abciximab [46]. A total of 100 patients were treated with the Palmaz Genesis Stent. A total of 50 patients were randomized to stent with Angioguard and 50 patients to stent alone. In addition, 50 patients were randomized to receive abciximab versus and 50 patients no abciximab.

With the Angioguard embolic protection system alone, the benefit was not statistically significant ($p = 0.08$) but there was a trend to show less deterioration of the RF. The decline in the eGFR was -2% in the protection group versus -10% in the no protection group. But the association Angioguard with abciximab was beneficial with a significant reduction in platelet rich thrombi.

These published data demonstrate that PTRAs with stenting under EPD is feasible, safe, and does not increase the complication rate of the procedure. However, the technique of PTRAs with protection has some limitations. First, distal protection devices do not prevent emboli from reaching the kidney during initial catheter manipulation, angiography and during crossing the lesion. Second, the use of distal EPDs may be limited by the renal anatomy, the stenosis location and the lack of devices currently available on the market dedicated for this application; in the case of large vessels, we have to carefully select the device and choose one device with a diameter at least equal to the diameter of the renal artery. In case of an early renal artery bifurcation, it is not possible to protect all arteries. The protection device could be placed in the main branch, or alternatively, two protection devices can be placed, but this technique could be limited by technical, anatomical problems and by the cost. In fact, in daily practice, 90% of the renal arteries can be protected with current protection devices. In addition, to place the protection device we need a landing zone of at least 1.5–2.0 cm, which

may be a problem with long stenosis or non-ostial stenosis. Current protection devices are not dedicated to renal arteries and have to be modified and improved.

Occlusion balloons have their own advantages:

- Smaller crossing profile, higher flexibility;
- Short landing zone;
- The occlusion of the renal artery avoids embolization of small particles;
- All sizes of debris may be aspirated.

However, there are also disadvantages and limitations:

- It may deflate or may be non-occlusive during the procedure;
- Some particles may be too large for suction (very rare);
- Below the balloon there is a shadow zone where some particles may remain blocked and are difficult or impossible to aspirate with the aspiration catheter. These particles may migrate to the kidney when the balloon is deflated;
- Occlusion balloon could lead to transient nephron ischemia. In our series the mean occlusion time was short, 6.5 min. We do not think that this transient ischemia could cause any damage to the kidney. This occlusion time is less than that of the clamping required during a surgical procedure. Edwards *et al.* also used this technique without any complication [45,52].

Filters have some advantages:

- A filter allows a continuous arterial blood flow;
- The visualization of the renal artery is possible during device deployment.

However, they also have several disadvantages and limitations:

- Poor wall apposition with the possibility of migration of some particles around the filters, particularly in eccentric or diseased landing zone;
- Restrictive landing zone requirements;
- A filter may plug up with suspended particles that will embolize when the filter is retrieved. In this case before retrieving the filter we have to very carefully aspirate the blood column below the filter;
- A filter may thrombose and need an effective anticoagulation with an ACT greater than 250;

- Closure and retrieval of filters can dislodge their content collected during the procedure;
- Some difficulties in retrieving a filter may be encountered. The filter could get caught on the struts of the stent during retrieval;
- The major limitation of the filters is the pore size, which in general is greater than 100 μm . This is larger than the size of microcholesterol crystals and allows small particles to pass to the kidney.

To overcome some of the problems encountered with current filters and occlusion balloons we have used the new EPD, the FiberNet Embolic Protection System that we first utilized in CAS and stenting with excellent results [91]. The FiberNet had been also used in the US carotid EPIC Trial with very promising results compared with other EPDs [92].

This FiberNet is a new EPD that has the capability to capture much smaller particles. In addition, the device allows blood flow during the procedure to preserve native tissues and can be delivered as a standard coronary guidewire. The FiberNet device provides:

- Good deliverability: the device is delivered on a 0.014-inch guidewire, has a low crossing profile and does not require a delivery sheath. These specifications allow easy access to most lesions without predilatation. The device has good flexibility, pushability, and maneuverability allowing placement in angulated renal arteries. Its landing zone requirements are minimal and shorter than with other distal filters and the deployed filter is atraumatic to the endothelium;
- Improved capture efficiency: apposition of the device with the vessel wall is excellent, which prevents debris migration to the kidney. Debris captured by the mesh is efficient, trapping particles as small as 40 μm . The numbers of particles removed appear to be higher than with other filters. We carried out a study in carotid arteries comparing the FiberNet to other filters, available on the market and we removed five-times more debris in square area than with other filters [91];
- Focal suction included: the retrieval catheter delivers suction during filter removal using vacuum syringes. This may be one of the major improvements with this system. Contained and captured emboli are recovered both by focal aspiration through the retrieval catheter (inside the stent and between stent and filter) and also by retention within the filter fibers.

This aspiration modality is different from aspiration with the PercuSurge device.

In our series of renal procedures, we have removed a large number of particles of all sizes, more than 8000, a third less than 60 μm , which is impressive. Hiramoto *et al.* demonstrated a predominance of small particles (<60 μm) among embolic debris liberated during PTRAs stenting [39]. This distinction may have relevance to RF, as demonstrated by Edwards *et al.* who reported an association between RF response and protected PTRAs stenting with both size and quantity of embolic particles released [45,52]. This possibility of removing a large quantity of embolic particles in comparison with other devices seems an important advantage. The FiberNet filter traps debris in 3D compared with the other devices on the market that trap material in a single plane. A macroembolus may be propelled during a procedure into the filter and subsequently disintegrated into smaller particles that can easily pass through the micropores of competitor filters. These particles could be more easily trapped in the 3D FiberNet filter. This could lead to more efficient retrieval with the FiberNet. Other distal filters also may not adequately cover the entire renal artery, allowing some emboli to pass by. In addition, the FiberNet is stable in the vessel once deployed. Considerable movement of other distal filters in the artery may cause microtrauma or spasm of the vascular wall, which, in turn, may result in an increased embolic load. Finally, the aspiration of the dilated area and of the inner part of the stent may reduce the risk of delayed embolic events. This technique allows aspiration of the debris that can protrude through the struts of the stent after placement and dilatation. We had noticed that in carotid series 30% of debris was aspirated through the stent, which shows the importance of a meticulous cleaning of the dilated area and of the inner part of the stent. Focal suction on retrieval of the filter is another likely advantage of FiberNet as explained earlier.

Although no device-related complications occurred in this small series of patients, adding another instrument to the procedure while trying to prevent complications could create new problems. The potential for renal artery thrombosis during protection is extremely small, because the patients are on heparin and anti-platelet therapy. The risk of dissection with a protection device is negligible, but one has to consider the possibility of spasm, which is usually treatable with medication.

The indications for renal protection are debatable. Is this technique indicated for all patients? There is no level one evidence supporting the

routine use of EPD in PTRAs stenting procedures. However, several studies demonstrated very encouraging results with a low incidence of early postprocedural deterioration of the RF, a high technical success rate and no detectable increase in procedure associated complications. An important drawback with this procedure is the extra cost of the EPD. However, at the present time, selective indications should be at least considered in these patients:

- Patients with renal insufficiency and a creatinine level of more than 1.4 mg/dl or possibly better still an eGFR of less than 50 ml/mn
- Elderly patients
- Patients with ischemic nephropathy
- Bilateral RAS
- Solitary or single functioning kidney
- Patients with diseased aorta and renal ostium
- Possibly diabetes

The indications for protection in patients with normal RF need to be considered. The incidence of procedure-related decline in RF is considered to be low in this patient group. However, we have to point out the series published by Zeller *et al.*, where the highest proportion (36%) of patients with worsening RF was found in the subgroup with normal baseline creatinine [33].

In our published series, 79 hypertensive patients were treated with protection despite a normal serum creatinine [53]. Only one patient experienced a RF deterioration detected at 2-year follow-up. This technique of including renal protection may, therefore, become the standard of care in the future and in particular if we have EPD easy to use, efficient without increasing the risk of the procedures.

Severe iatrogenic renal parenchymal damage due to interventional or diagnostic procedures can be masked in patients with normal pre-intervention global serum creatinine values. Thus 50% of total renal mass can be destroyed without any change in RF. There can be extensive damage to the kidneys that, in many patients with normal preintervention RF, may not be apparent during or after renal intervention. It is difficult to know exactly which patient needs protection. For example, a patient with 60% RF reserve (normal serum creatinine) before the procedure could be in renal insufficiency after the procedure if cholesterol embolism destroyed 20% of the nephrons.

A good evaluation of the eGFR is necessary before the procedure and particularly in patients with limited RF, elderly patients and patients with extensive atheromatous disease.

The choice of protection device to use merits discussion. This new FiberNet device seems promising, allowing the capture of smaller particles, with a good wall opposition and a short landing zone requirement which should enlarge the possibilities of renal protection.

The role of antiplatelet therapy seems important. The RESIST study demonstrated that the abciximab EPD improved the RF and reduced platelet-rich thrombi [46]. Edwards *et al.* demonstrated that preoperative aspirin use is positively associated with a change in eGFR and negatively associated with the quantity of captured particles 20–60 μm [45,52]. In the future the measure of systemic platelet activation prior to the procedure will maybe define the patients at risk for platelet embolization and also those who require more aggressive antiplatelet therapy.

Conclusion

Percutaneous transluminal renal angioplasty stenting has a place in the treatment of patients with a significant RAS despite the two recent randomized studies (ASTRAL and STAR studies) but a good selection of the patients and of the lesions is mandatory. However, the deterioration of the RF in a third of the patients after the procedure is a concern. Atheroembolism seems to play an important role but can be prevented with EPDs. Several studies have been reported with different EPDs showing that the technique is feasible, safe and seems to reduce the RF deterioration rate after PTRAs stenting. There are limitations with this technique and no specific EPD has been designed for this indication. The new FiberNet EPD seems promising, easy to use and efficient. It captures particles of 30–40 μm without compromising the flow and seems an improvement in comparison with current EPD. The amount of debris removed is comparable during CAS and RAS. However, our study is limited by the small number of patients treated and larger randomized studies are awaited to prove the role of EPD and particularly the role of FiberNet in PTRAs stenting.

Future perspective

Within the next 5–10 years, the role of atheroembolism in the deterioration of RF after renal angioplasty and stenting will probably be proven by randomized studies. Renal protection will, therefore, be justified and recommended similarly to CAS and stenting. The current EPDs are not designed for renal arteries and have several limitations.

The new FiberNet filter appears much better adapted for renal angioplasty and stenting (good deliverability, improved capture insufficiency, possibility of focal suction with the retrieval catheter, short landing zone required). It seems an improvement in comparison with other filters and should be the EPD of choice for the coming years in renal artery territory.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- A renal artery stenosis (RAS) is frequent and increasingly diagnosed.
- RAS has a high tendency to progress with time resulting in renal artery occlusion, loss of renal mass and a subsequent decrease in renal function (RF).
- RAS can lead to different clinical conditions:
 - Renovascular hypertension
 - Renal insufficiency
 - Cardiac disturbance syndrome
 - Increases in cardiovascular and all-cause mortality
- Indications for treatment of RAS are debated, but it is generally accepted to treat patients with a severe RAS greater than or equal to 70% in the setting of uncontrolled hypertension, renal insufficiency, congestive heart failure and unstable angina.
- PTRAs and stenting is the first treatment to be proposed and keeps indications despite two recent studies (ASTRAL and STAR studies) which concluded that stenting is not superior to medical therapy.
- However, there are some limitations to PTRAs stenting:
 - It is now well known that the post procedural deterioration of the RF occurs in 20–30% of the patients after PTRAs stenting. Atheroembolism seems the main cause and seems to play an important role;
 - Renal atheroembolism is difficult to diagnose, presents a poor prognosis and there is no specific treatment available. Only a prevention can be proposed;
 - New coronary techniques with low profile devices, the ‘no touch’ technique are not sufficient to prevent embolism. The use of an embolic protection device (EPD) seems the best method to prevent renal atheroembolism.
- Several series have been reported in the literature with promising results. Different filters and protection balloons have been used, but all these devices have limitations and some disadvantages.
- We have used for the first time, the new FiberNet™ filter, which seems much better adapted for renal angioplasty and stenting. The EPD has a good deliverability, an improved capture insufficiency (with the possibility of removing debris of 30/40 µm), provides the possibility of focal suction with the retrieval catheter, and requires a short landing zone. It seems to be an improvement in comparison with other filters and should be the EPD of choice for the renal artery territory.

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