

# Atheroembolic renal disease

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Atheroembolic renal disease develops when atheromatous aortic plaques rupture, releasing cholesterol crystals into the small renal arteries. Embolisation often affects other organs, such as the skin, gastrointestinal system, and brain. Although the disease can develop spontaneously, it usually develops after vascular surgery, catheterisation, or anticoagulation. The systemic nature of atheroembolism makes diagnosis difficult. The classic triad of a precipitating event, acute or subacute renal failure, and skin lesions, are strongly suggestive of the disorder. Eosinophilia further supports the diagnosis, usually confirmed by biopsy of an affected organ or by the fundoscopic finding of cholesterol crystals in the retinal circulation. Renal and patient prognosis are poor. Treatment is mostly preventive, based on avoidance of further precipitating factors, and symptomatic, aimed to the optimum treatment of hypertension and cardiac and renal failure. Statins, which stabilise atherosclerotic plaques, should be offered to all patients. Steroids might have a role in acute or subacute progressive forms with systemic inflammation.

## Introduction

Atheroembolic renal disease, sometimes referred to as renal cholesterol crystal embolisation, is a form of renal failure that is secondary to occlusion of renal arteries, arterioles, and glomerular capillaries with cholesterol crystals originating from atheromatous plaques of the aorta and other major arteries. Atheromatous material can be dislodged spontaneously or after intravascular trauma or anticoagulation. Typically, embolisation affects the kidneys, skin, gastrointestinal system, and brain. For this reason, atheroembolic renal disease is regarded as part of a multisystemic disorder.<sup>1-5</sup> Atheroembolic disease, like thromboembolism, can complicate severe atherosclerosis. However, thromboembolism develops when a thrombus overlying an ulcerated plaque embolises and lodges in medium or large arteries, causing localised ischaemia.

Panum<sup>6</sup> first described atheroembolism in 1862, in the autopsy report of the Danish sculptor, Thorwaldsen, who died from a heart attack. In a coronary artery, a ruptured atheroma was identified, with atheromatous material filling the lumen distally. In English records, the first report of atheroembolism was made in 1926 by Benson,<sup>7</sup> who reviewed three cases of coronary embolisation. In 1945, Flory<sup>1</sup> proved the embolic origin of cholesterol crystals from eroded aortic atheromatous plaques. 40 years

later, Fine and co-workers<sup>4</sup> reviewed 221 cases of cholesterol crystal embolisation, underlining the low rate of antemortem clinical diagnosis. In the past two decades, atheroembolic renal disease has changed from being a pathological curiosity to a clinical syndrome. Some studies<sup>8-12</sup> provided an accurate assessment of the main characteristics of the disorder, including risk factors, causal events, clinical and laboratory findings, and renal and patient outcomes. Thus, this disease can now be thought of as a recognisable cause of renal disease, with diagnosis before death possible in most cases.

## Epidemiology

Atheroembolic renal disease complicates widespread atherosclerosis in adults older than 60 years.<sup>8-12</sup> The disorder predominantly affects men and is rare in black people, possibly because of decreased recognition of the cutaneous lesions.<sup>13</sup> Incidence is unknown. In clinical series, prevalence varies, probably because of sampling bias. In unselected autopsy series,<sup>14-17</sup> the frequency of atheroemboli findings is low, ranging from 0.31% to 2.40%. However, in autopsy studies<sup>2,16-19</sup> done in elderly patients and those who died after aortic surgery or aortography, researchers have reported an increased frequency, from 12% to 77%. In two large renal biopsy studies,<sup>20,21</sup> frequency of 1% was reported. However, in people older than age 60 years, the prevalence was 4.0–6.5%.<sup>22,23</sup> In clinical practice, Mayo and Swartz<sup>9</sup> have estimated that 5–10% of all cases of acute renal failure could be due to atheroembolism.<sup>9</sup> Belenfant and colleagues<sup>10</sup> reported that 3% of patients admitted to a tertiary renal intensive care unit were diagnosed with atheroembolic renal disease.<sup>10</sup>

## Pathophysiology

Presence of diffuse aortic atherosclerosis is essential for development of atheroembolic renal disease.<sup>1-3</sup> The usual risk factors for atherosclerosis (age older than 60 years, male sex, diabetes, hypertension, and cigarette smoking) are also major risk factors for atheroembolic renal disease<sup>11,24,25</sup> (panel 1). The atherosclerotic plaque, which is the main pathological entity of atherosclerosis,

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### Search strategy and selection criteria

We searched Medline (January, 1950–July, 2009), the Cochrane Library (January, 1993–July, 2009), and Embase (January, 1966–July, 2009) with the search terms “atheromatous embolism”, “athero-embolism”, “atheroembolism”, “cholesterol crystals”, “cholesterol embolism”, “cholesterol embolization”, or “cholesterol emboli”. We also searched for these terms combined with “clinical trials”, “prevention”, “pathogenesis”, “pathophysiology”, “diagnosis”, and “epidemiology”. We had no language restrictions. We focused on original research, systematic reviews, and reviews or editorials. We also searched the reference lists of selected articles identified by the search strategy. The date of the last search was July 31, 2009.

**Panel 1: Population at risk for atheroembolic renal disease**

- Male sex
- Older than age 60 years
- White people
- Hypertension
- Tobacco use
- Diabetes mellitus
- Atherosclerotic vascular disease
  - Ischaemic cardiac disease
  - Cerebrovascular disease
  - Abdominal aortic aneurysm
  - Peripheral vascular disease
  - Ischaemic nephropathy

	n	Spontaneous AERD (%)		Iatrogenic AERD			
				All causes (%)	Angiography (%)	CV surgery (%)	Anticoagulation (%)
Fine <sup>4</sup>	221	153	(69%)	68 (31%)	39 (18%)	20 (9%)	30 (14%)
Lye <sup>5</sup>	129	50	(40%)	79 (60%)	55 (43%)	7 (5%)	17 (13%)
Thadhani <sup>8</sup>	52	0	(0%)	52 (100%)	50 (96%)	2 (4%)	19 (37%)
Belenfant <sup>10</sup>	67	3	(4%)	64 (96%)	57 (85%)	24 (36%)	51 (76%)
Scolari <sup>27</sup>	354	83	(24%)	271 (76%)	221 (81%)	69 (25%)	108 (40%)

AERD=atheroembolic renal disease. CV=cardiovascular.

**Table 1: Precipitating factors of atheroembolic renal disease**

is characterised by a fibrous cap overlying a core containing necrotic cellular debris, foam cells, and lipids, including cholesterol crystals. Haemodynamic stress, inflammation, and haemorrhage can destabilise the plaque, which becomes friable and prone to erosion and rupture.<sup>26</sup> The disease develops when the fibrous cap is denuded and portions of its core components break off, reaching the arterial bloodstream.<sup>1-5</sup> Plaque disruption caused by shear stress or intrinsic mechanisms leads to spontaneous atheroembolism—the most common form in the 1980s.<sup>4</sup>

Nowadays, atheroembolic renal disease tends to be iatrogenic, accounting for as many as 76–77% of cases in recent series,<sup>10-12,27,28</sup> suggestive of the increased use of vascular procedures, anticoagulation, or thrombolysis<sup>4,11,24</sup> (table 1). Thurlbeck and Castleman<sup>2</sup> first recognised embolisation as a complication of vascular surgery causing plaque disruption during vessel incisions, cannulation, manual manipulation, or clamping. Embolisation can develop with any vascular procedure, such as abdominal aortic aneurysm resection and endovascular surgery, and aortoiliac, aortofemoral, and coronary artery bypass surgery.<sup>11,24</sup> Angiography is the most common iatrogenic cause, accounting for up to 80% of cases.<sup>8,10,27</sup> The disorder has been reported after aortography, renal, mesenteric, or coronary angiography, and percutaneous transluminal angioplasty with and without stenting. Mechanical trauma has a key role.

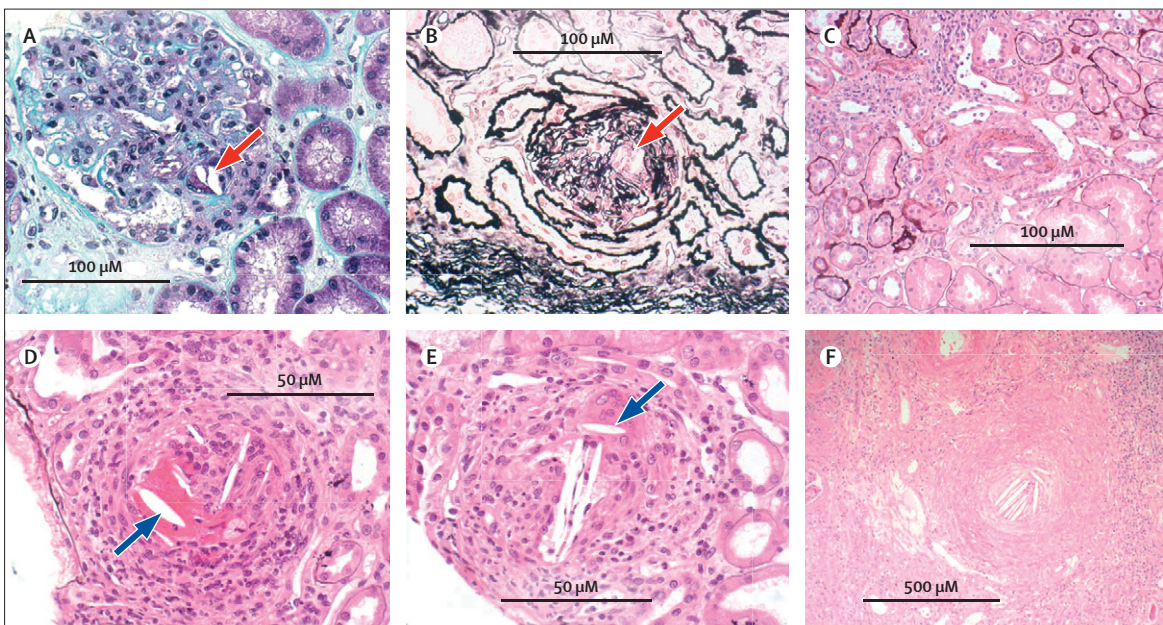
Guidewires and catheters can scrape aortic walls and disrupt atherosclerotic plaques.

Coronary angiography is the most common procedure causing embolism.<sup>24,27</sup> However, the risk associated with coronary angiography might be underestimated in some study designs. Large retrospective studies reported incidence rates of one to two new cases per 1000 procedure-years.<sup>15,29,30</sup> Conversely, incidence of the disease after coronary angiography was several times higher than this rate, at 18–24 new cases per 1000 procedure-years in two prospective studies.<sup>31,32</sup> Failure to search systematically for the disease in retrospective studies might be one possible explanation for this discrepancy. Since use of angiographic and endovascular procedures has increased exponentially during the past decades, and these procedures are now liberally extended to patients older than 60 years and with increasingly severe disease, the frequency of atheroembolic renal disease could reasonably be expected to rise in patients at risk.

Atheroembolic renal disease is an uncommon complication that is reported in patients given anti-coagulants (warfarin, heparin, and low-molecular-weight heparin) or after thrombolytic therapy.<sup>3-5,8-12</sup> These therapies can undermine the stabilising protective effects of thrombi on ulcerated plaques.<sup>33-36</sup> In studies of patients with biopsy-proven atheroembolic renal disease, anticoagulation was regarded as a precipitating factor in 13–76% of cases.<sup>4,5,8-12</sup> However, in the absence of preceding invasive vascular procedures, anticoagulation was the sole triggering factor in only 7% of patients.

Once in the bloodstream, emboli lodge in small arteries of 150–200 µm in diameter.<sup>1-4</sup> In studies<sup>20,21,37-40</sup> in people and animals, results suggest that emboli produce a microcrystalline angiitis, characterised by an endothelial inflammatory reaction developing in a stepwise pattern. Shortly after lodging, polymorpho-nuclear leukocytes and eosinophils infiltrate the affected arterioles, preceding mononuclear-cell infiltration and giant-cell formation. Thrombus formation then takes place, with endothelial proliferation and intimal fibrosis, leading to arterial obstruction. This final late phase occurs within 2–4 weeks. These processes generally result in ischaemia, sometimes in infarction, and rarely in necrosis. Because the crystals are insoluble in body fluids and not removable by phagocytosis, they persist indefinitely.

Histologically, cholesterol crystal emboli are identified in the lumen of arcuate and interlobular arteries as biconvex, needle-shaped, and empty clefts, referred to as ghost cells, because they dissolve during specimen processing. Rarely, small crystals lodge in the afferent arterioles and glomerular capillaries. The tissue damage caused by these crystal emboli is usually patchy. Glomerular and interstitial changes are mainly ischaemic, with a varying extent of glomerular obsolescence and interstitial fibrosis. In the early phases, areas of acute tubular necrosis can be identified. Cholesterol crystal



**Figure 1: Renal cholesterol crystal emboli**

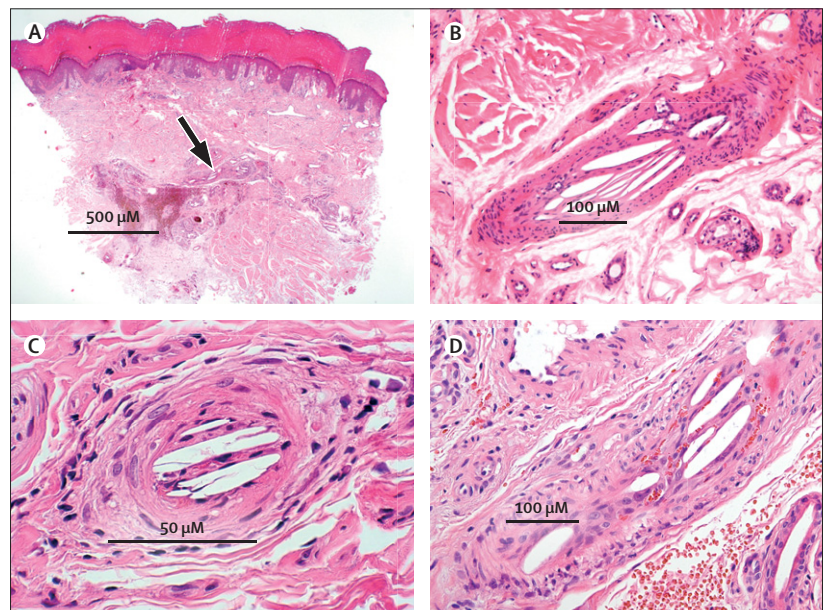
Intraglomerular cholesterol crystals (arrows, A–B); cholesterol crystals in a renal arteriole (C); crystals in an arcuate artery with a pseudovasculitis inflammatory reaction (arrow, D); crystals in an arcuate artery, and encasement of a crystal by a giant cell (arrow, E); and organised occlusive crystals in a renal arteriole (F).

emboli are also identified in the skin, gastrointestinal tract, and muscle<sup>11,20,21</sup> (figures 1 and 2).

### Clinical features

Clinical presentation of atheroembolic renal disease depends on the location and size of the embolising plaque, lodging sites, intensity and recurrence of the showering process, and pre-existing atherosclerotic disease. The ascending aorta and proximal aortic arch are the major sources of emboli to the cerebral and retinal arteries. Emboli to the visceral and renal arteries and to arteries of the legs and feet come from the descending thoracic and abdominal aorta.<sup>1–4</sup> Subclinical or mild episodes can go completely unrecognised. However, massive embolisation can lead to a fulminant clinical picture, with multi-system involvement.<sup>8–12</sup> (panel 2, table 2).

Kidney function can be affected acutely, subacutely, or in a chronic but slow, progressive way.<sup>8–12,24,25</sup> A pronounced renal impairment with acute onset, arising within 1 week of a clear causal event, affects 20–30% of patients.<sup>24,27</sup> This abrupt renal impairment is due to massive migration of crystals, and is associated with evidence of embolisation elsewhere, affecting gastrointestinal and cutaneous systems in most cases. The most common form of atheroembolic renal disease is a subacute presentation, with progressive renal failure developing in a stepwise way during several weeks after an inciting event. Frock and co-workers<sup>41</sup> reported that the mean interval between the arteriographic procedure and diagnosis of disease was 5.3 weeks.<sup>41</sup> This long delay between the triggering event and the onset of renal insufficiency suggests a



**Figure 2: Cholesterol crystal emboli in derma arterioles**

Low-power view of cholesterol crystals (arrow, A); and high-power showing clusters of cholesterol crystals (B–D).

causal role of recurrent emboli showers and inflammatory endothelial reaction. Another presentation is a chronic, slowly progressive renal impairment, often ascribed to nephroangiosclerosis or ischaemic nephropathy, which frequently co-cluster with cholesterol emboli. This mild form, with low-grade, clinically silent crystal migration is frequently underdiagnosed because extrarenal signs are absent and renal biopsy samples are not taken.<sup>42</sup>

The clinical course of renal failure can be variable. Dialysis is needed in 28–61% of patients with acute or subacute disease, with 20–30% partly recovering kidney function after a variable period of dialytic support.<sup>8–12</sup> Recovery can be due to reversal of inflammation and resolution of concurrent acute tubular necrosis in

ischaemic areas. Finally, atheroembolic renal disease can be associated with severe, uncontrolled hypertension. Renal infarction is a rare finding.<sup>20,21</sup>

Skin lesions are the most common extrarenal manifestations. Incidence of skin lesions is about 35%.<sup>43</sup> However, in most recent studies,<sup>8–12,44–46</sup> the frequency ranged from 75% to 96%. The classic skin lesions of this disease are blue toe syndrome and livedo reticularis. Affected toes are blue, cyanotic, painful, and cool to touch. The lesion might progress to ulceration, digital infarcts, or gangrene needing amputation. Patients often have palpable distal pulses. Livedo reticularis is a net-like, mottled red-blue discolouration usually on the lower legs and feet but sometimes on the buttocks and trunk. Blue toes and livedo reticularis are most evident on physical examination when the patient is upright. Rarely, the skin lesions are erythematous painful nodules or palpable purpura, requiring exclusion of leukocytoclastic vasculitis<sup>44–46</sup> (figure 3).

The gastrointestinal system is the third most often affected system (18–48% of patients), leading to substantial morbidity.<sup>8–12</sup> Gastrointestinal tract involvement can take many forms. Patients can develop symptoms such as occult or frank blood loss and abdominal pain. Bleeding originates from any site, including the stomach, and results from superficial mucosal ulcerations or infarcts. Abdominal pain is caused by ischaemia of the bowel wall, potentially creating malabsorption and diarrhoea. Frank bowel infarction and perforation usually arise in the setting of catastrophic multi-organ disease. The liver, gallbladder, and pancreas are less commonly affected.<sup>47–51</sup> Gastrointestinal effects are often overlooked. Diagnosis can be established by pathological examination, because the endoscopic appearance is non-specific.<sup>52</sup> Patient outcomes in the presence of gastrointestinal disease are very poor.<sup>24,27</sup>

The true incidence of neurological embolisation is unknown and difficult to estimate, because the definitive diagnosis depends on evidence of embolisation to other organs. In the largest studies, neurological manifestations occurred in 4–23% of the patients with atheroembolic renal disease.<sup>8–12,27</sup> Mental confusion, transient ischaemic attack, focal neurological deficits, and amaurosis fugax are common findings.<sup>53–55</sup> Retinal emboli can affect 6–25% of patients,<sup>56</sup> representing a key to diagnosis (figure 4).<sup>8–12</sup> Rarely, spinal cord infarction with leg paralysis develops.<sup>57–60</sup>

Myositis and splenic infarcts are rare manifestations.<sup>61</sup> Emboli deriving from the aortic root or the proximal segments of the coronary arteries are often associated with angina and sudden cardiac death.<sup>62,63</sup> Pulmonary involvement proven by biopsy sample, characterised by diffuse alveolar haemorrhage mimicking systemic vasculitis, has been described in a few patients. The pathogenetic mechanisms of pulmonary haemorrhage remain poorly understood—a local inflammatory reaction elicited by emboli might have a role.<sup>64–67</sup> In autopsy studies, subclinical involvement of adrenals, testes, prostate,

### Panel 2: Clinical manifestations of atheroembolic renal disease

#### Kidney

- Acute, subacute, and chronic renal failure
- Severe uncontrolled hypertension
- Renal infarction

#### Skin

- Livedo reticularis
- Blue toe syndrome
- Ulceration and gangrene
- Purpura

#### Gastrointestinal system

- Abdominal pain
- Gastrointestinal bleeding
- Bowel ischaemia, infarction, and obstruction
- Pancreatitis, cholecystitis, and abnormal liver tests
- Splenic infarcts

#### Heart

- Myocardial ischaemia
- Myocardial infarction

#### Central nervous system

- Transient ischaemic attacks
- Amaurosis fugax
- Altered mental status
- Cerebral infarction
- Spinal cord infarction

#### Eye

- Retinal emboli (Hollenhorst plaques)

#### Systemic signs

- Fever
- Weight loss
- Malaise
- Myalgia
- Anorexia

	n	Skin lesions	GI tract	CNS	Retinal emboli	Eosinophilia
Fine <sup>4</sup>	221	75 (35%)	21 (10%)	0	14 (6%)	22 (73%)
Lye <sup>5</sup>	129	55 (43%)	16 (10%)	15 (12%)	12 (10%)	57 (71%)
Thadhani <sup>8</sup>	52	26 (50%)	15 (29%)	12 (23%)	13 (25%)	11 (22%)
Belenfant <sup>10</sup>	67	60 (90%)	22 (33%)	3 (4%)	15 (22%)	39 (59%)
Scolari <sup>27</sup>	354	266 (75%)	43 (12%)	35 (10%)	24 (7%)	238 (67%)

GI=gastrointestinal. CNS=central nervous system.

Table 2: Clinical findings in atheroembolic renal disease



**Figure 3:** Skin lesions in atheroembolic renal disease  
Blue toe syndrome of variable severity (A–G); and purpuric lesions (H).

thyroid, and virtually any organ has been reported<sup>4,17</sup> (figure 5). Finally, several non-specific findings can accompany the course of atheroembolic renal disease, such as fever, weight loss, myalgias, and headache, suggesting the systemic nature of the disease.<sup>4,8–12,20,21</sup>

### Laboratory findings

Laboratory test findings are non-specific, such as anaemia, leukocytosis, thrombocytopenia, and raised concentrations of inflammatory markers (ESR or C-reactive protein). Results of urinalysis are typically benign, with few cells and a minimum amount of proteinuria—a finding consistent with ischaemic damage.<sup>4,8–12</sup> Nephrotic-range proteinuria has been described<sup>11,68,69</sup> in a few patients with superimposed biopsy-proven focal glomerulosclerosis or diabetic nephropathy. Eosinophilia is an abnormal laboratory finding that frequently occurs during the acute phase of the disease, thereby showing immunological activation at the surface of the exposed emboli.<sup>8–12</sup> In a previous review, Kasinath and co-workers<sup>70</sup> described eosinophilia in 80% of cases of atheroembolic renal disease. Eosinophilia was typically transient, ranging from

6% to 18% in a recent study.<sup>70</sup> 67% of 354 patients had an eosinophil count higher than 500 cells per  $\mu\text{L}$ , confirming that eosinophilia can help establish the diagnosis.<sup>27</sup>

Other features can include hypocomplementaemia,<sup>71</sup> which has been reported in 39% of patients in one study.<sup>5</sup> However, this finding was not consistent with results of other studies.<sup>8–12</sup> Abnormal laboratory findings can implicate specific organs: increased concentrations of hepatic enzymes suggest liver disease, and raised amylase and lipase concentrations pancreatic disease; raised creatinine phosphokinase concentration are suggestive of myositis, and increased serum aspartate aminotransferase and lactate dehydrogenase concentrations are suggestive of renal infarction.<sup>4,10,11</sup> Finally, a few studies<sup>9,27,72</sup> reported proportions of cholesterolaemia in patients with atheroembolic renal disease, with total cholesterol higher than 5.2 mmol/L ranging from 23% to 27%, and 64%.

### Diagnosis

Because atheroembolisation is ubiquitous, atheroembolic renal disease can mimic several different clinical syndromes.<sup>21,73</sup> Knowledge of the risk factors and

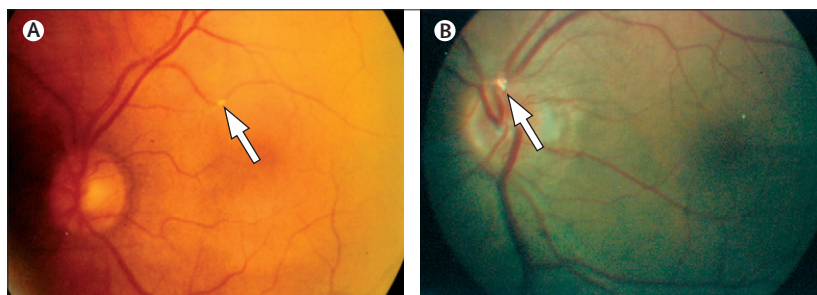


Figure 4: Retinal cholesterol crystal emboli

recognition of the variable clinical presentations can heighten the likelihood of making a premortem diagnosis.<sup>8-12,27</sup> The typical patient at risk is a man older than age 60 years with known atherosclerotic disease presenting with a clinical triad of a precipitating event, acute or subacute renal failure, and typical skin findings. Presence of eosinophilia should raise the level of suspicion. Renal biopsy is regarded as the definitive

method for diagnosis. Renal samples yield a positive diagnosis in more than 75% of patients with acute or subacute renal failure.<sup>74</sup> However, taking a renal biopsy sample is not always feasible, especially in sick patients. Taking a biopsy sample of skin lesions, a straightforward, and relatively non-invasive procedure, has a high diagnostic yield approaching 92%.<sup>41</sup> Feet and lower legs are also the best sites for biopsy.<sup>74,75</sup> Occasionally, histological confirmation can be made from biopsy samples from less likely target organs, such as gastrointestinal tissues.<sup>24</sup>

Tissue biopsy sampling is not necessary when cholesterol crystals are seen in the retinal vessels (Hollenhorst plaques), which can be identified in 10–25% of cases.<sup>8-12</sup> For this reason, funduscopy examination should never be omitted. Diagnosis by tissue sample is not needed in the presence of the classic triad. For patients with the classic triad, atheroembolic renal disease can be diagnosed solely on a clinical basis.<sup>8-12,27</sup> Thus, renal biopsy sampling can be avoided in some patients. Conversely,

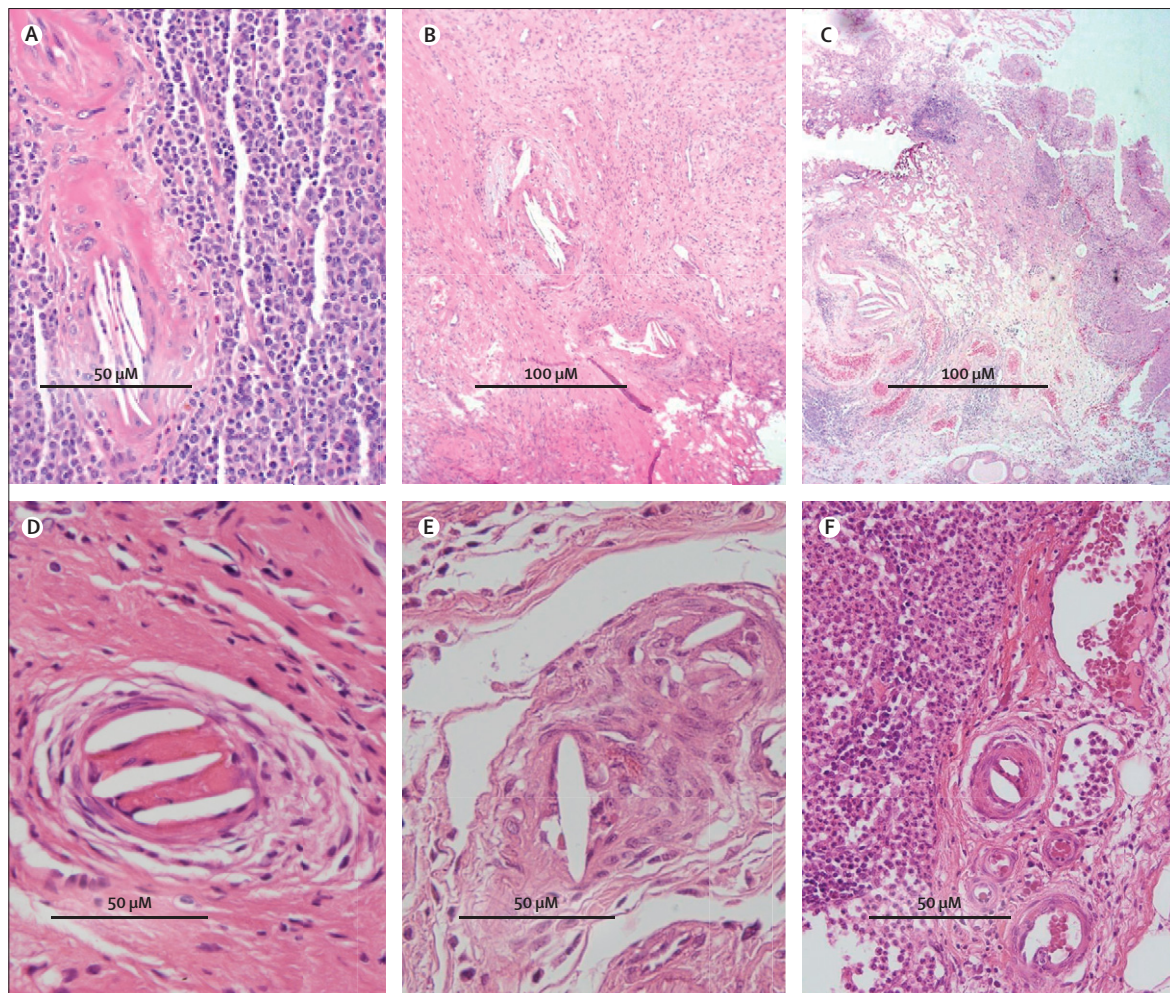


Figure 5: Cholesterol crystal in extrarenal sites  
Spleen (A); prostate (B); bladder (C); stomach (D); ileum (E); and lymph node (F).

renal biopsy is crucial for diagnosis of cases with chronic, smouldering forms of this disease, which are frequently spontaneous and usually develop in the absence of evident extrarenal signs<sup>11,24,27</sup> (panel 3 and table 3).

Differential diagnoses are contrast nephropathy, small-vessel vasculitis, drug-induced interstitial nephritis, and subacute bacterial endocarditis. In contrast nephropathy, the rise in plasma creatinine concentrations happens immediately after the radiographic study, and the course is different—creatinine concentration peaks within a few days after exposure and returns to or near baseline after 10–14 days.<sup>11,20,21,24</sup> Extrarenal emboli, if present, enable diagnosis of atheroembolic renal disease. The disease can be distinguished from systemic vasculitis by urinalysis, typically characterised by the absence of proteins and blood cells in atheroembolic renal disease as opposed to the nephritic sediment of vasculitis, and by an autoimmune screening including antineutrophil cytoplasmic antibodies testing.<sup>11,24</sup> The temporal relation between use of an offending drug and occurrence of fever, skin rash, eosinophilia, and acute renal failure strongly suggests acute tubulointerstitial nephritis, a diagnosis that should be confirmed by renal biopsy. Presence of subacute bacterial endocarditis needs to be ruled out, especially if hypocomplementaemia is present. Signs of systemic infection and echocardiographic findings exclude atheroembolic renal disease.

### Embolic disease in renal allografts

Atheroembolic renal disease in renal allografts is rare, with a frequency ranging from 0·39% to 0·47%.<sup>76,77</sup> So far, only 45 cases have been reported—too few to define the natural history of the disorder.<sup>76–85</sup> Such disease is probably underestimated because of the use of small needles for taking biopsy samples and sampling error. Atheroemboli causing injury to the renal allograft can arise from either the donor or the recipient vessels. Two distinct clinical presentations have been described. The first is an early atheroembolic renal disease, with emboli frequently released from the donor's arteries before or during organ harvesting. More rarely, early embolisation originates from the recipient's atheromatous vessels during the anastomosis. The early form is usually associated with primary non-function, and the embolic disease is confined to the allograft. The second form is a late clinical presentation, which can arise years after transplantation in stable grafts. In this case, emboli originate from the recipient's vessels. The disease is usually associated with precipitating factors, and in some cases shows features of a systemic disorder.

Renal outcomes of early and late atheroembolic disease seem to differ. Graft loss is frequently associated with early disease, in which the emboli originate from the donor. Prognosis can be especially poor in the setting of primary non-function. Conversely, late manifestations usually have a good outcome, with graft recovery in most cases.<sup>11,76–78</sup> The reason for this difference could be

#### Panel 3: Diagnostic criteria for atheroembolic renal disease

##### 1 Patient at risk

- Men older than 60 years
- Longstanding hypertension
- Tobacco use
- Diffuse atherosclerotic disease

##### 2 Presence of classic triad

- Exposure to precipitating factor
- Acute or subacute renal failure
- Peripheral signs of embolisations (eg, blue toe syndrome)

##### 3 Gastrointestinal or neurological effects and eosinophilia

- Should raise the level of suspicion

##### 4 Histological confirmation

- Pathological specimens obtained from the kidney, skin, or muscle
- Skin biopsy sample
- Simple, low-invasive procedure with high diagnostic yield
- Tissue biopsy sample not necessary in presence of retinal emboli
- Tissue sample not needed in presence of classic triad
- Renal biopsy is crucial to diagnosis of chronic forms of atheroembolic renal disease

	n	Biopsy sample					Clinical	Postmortem
		Kidney	Skin	Muscle	GI tract	Other		
Fine <sup>4</sup>	221	15 (7%)	18 (8%)	18 (8%)	5 (2%)	13 (6%)	0	152 (69%)
Thadhani <sup>8</sup>	52	16 (31%)	9 (17%)	11 (21%)	0	0	5 (9%)	11 (22%)
Belenfant <sup>10</sup>	69	24 (36%)	15 (22%)	0	12 (18%)	0	16 (24%)*	0
Scolari <sup>27</sup>	354	63 (18%)	13 (37%)	0	4 (1%)	0	14 (42%)*	7 (2%)

\*Clinical diagnosis was confirmed by retinal emboli in some patients. GI=gastrointestinal.

Table 3: Diagnosis of atheroembolic renal disease

attributable to extensive embolisation in an atherosclerotic donor during organ procurement. Because the tendency to accept donors and recipients older than age 60 years and to use marginal donors with advanced atherosclerosis has increased, atheroembolic renal disease in renal allografts will probably be encountered more often than previously. To reduce the risk of atheroemboli, an accurate assessment of organ donors should be done. At the time of organ procurement, manipulation of the aorta should be kept to a minimum, mobilising the kidneys without cross-clamping the aorta, as done for living-related donors. Finally, the number of invasive vascular work-up procedures should be kept to a minimum.<sup>11,77</sup>

### Treatment

For patients with atheroembolic renal disease, the aim of treatment is to restrict the extent of ischaemic damage and prevent recurrent embolisation. No definitive treatment has been established. Therapeutic measures are mostly preventive and supportive.<sup>8–12,24–27</sup> Mainstays of

**Panel 4: Treatment of atheroembolic renal disease**

- Major goal
  - Restrict extent of the ischaemic damage
  - Prevent recurrent embolisation
- No definitive treatment has been established
- Therapeutic modalities are mostly preventive and supportive
- Preventive treatment aims to avoid further precipitating factors
  - Withdrawal of anticoagulant therapy
  - Avoid any new radiological or aortic surgery procedure
- Medical intervention
  - Mostly symptomatic
  - Aggressive treatment of associated hypertension and cardiac and renal failure
  - Optimum type of dialysis (peritoneal dialysis vs haemodialysis) unknown
  - Adequate nutritional support when needed
  - Steroids in patients with multisystem involvement and recurrent, progressive disease
  - Statins should be offered to all patients with atheroembolic renal disease

No clinical trials of treatment for patients with atheroembolic renal disease have been done. However, results of some studies of steroids and statins suggest that they might have a potential role. Possible benefits of steroids have been reported in small series.<sup>88-90</sup> Belenfant and co-workers<sup>10</sup> used low-dose steroid (0.3 mg/kg) in 18 patients with relapsing disease who had improved symptoms and nutritional intake.<sup>10</sup> Results of other series<sup>72</sup> have shown beneficial effects with high doses of steroids. Conversely, other reports<sup>4</sup> have shown little or marginal benefit from steroid treatment. In a prospective study<sup>27</sup> of 354 patients with atheroembolic renal disease, steroids were not associated with improved renal or patient outcomes. Thus, steroid use is still controversial, although it could have a role in patients with multi-system involvement, recurrent and progressive disease, and systemic inflammation.

Interest has grown in the potential protective role of statins. Occasional cases of atheroembolic renal disease have responded to statins.<sup>91</sup> In a prognostic study,<sup>12</sup> patients assigned statin therapy had a lowered risk of development of endstage renal disease. A large prospective study<sup>27</sup> confirmed this finding. Statins had a beneficial effect even when statin therapy was started after diagnosis of atheroembolic renal disease. The protective effect of statins could be attributable to plaque stabilisation and regression through lipid-lowering and anti-inflammatory mechanisms. Plaque stabilisation might result in a lowered risk for further embolisation. However, the observational nature of these data precludes establishment of causality. Despite these limitations, use of statins could be justifiable (panel 4). Finally, there are isolated reports of successful therapy in small numbers of patients given iloprost, pentoxifylline, and LDL apheresis. These approaches have yet to be tested in controlled studies. Other drugs such as antiplatelet agents and low-molecular weight dextran do not provide any benefit.<sup>11,24</sup>

Surgical removal of the source of emboli could offer a definitive treatment option. However, surgical treatment is often not feasible and is associated with substantial morbidity. A clear embolic source is difficult to identify. Additionally, patients are frequently too weak for surgery. Finally, the necessary aortic clamping during surgery would induce major risk for recurrence. A surgical approach was assessed by Keen and colleagues<sup>92</sup> in a prospective study of 100 patients. They concluded that surgery can be an option when the emboli source is located in the infrarenal aorta. If supra-renal aorta is implicated, morbidity and mortality is increased because of the risk for visceral and renal atheroembolisation. Thus, surgical intervention should be regarded as a rescue therapy, and restricted to life-threatening situations. To eliminate the embolic source, percutaneous transluminal angioplasty and stent placement have been undertaken in a few patients with aortoiliac and femoral artery sources of embolisation.<sup>93,94</sup> These endovascular procedures could also be associated with a high risk of further embolisation,

	n	Renal failure needing dialysis	Recovery of dialysis-dependent renal failure	Maintenance dialysis (end of follow-up)	1-year mortality
Fine <sup>4</sup>	221	62 (28%)	13 (21%)	0	179 (81%)
Lye <sup>5</sup>	129	52 (40%)	13 (26%)	0	83 (64%)
Thadhani <sup>8</sup>	52	23 (44%)	7 (32%)	0	45 (87%)
Belenfant <sup>10</sup>	67	41 (61%)	16 (39%)	23 (35%)	9 (13%)
Scolari <sup>27</sup>	354	11 (33%)	33 (28%)	88 (25%)	60 (17%)

**Table 4: Renal and patients outcome in atheroembolic renal disease**

preventive treatment are based on restriction of exposure to precipitating factors, such as withdrawal of anticoagulant therapy after carefully considering the pros and cons of these drugs, and avoidance of any additional radiological or aortic surgery procedure. Medical intervention in established cases is mostly for symptom management, and should aim to provide optimum treatment of associated hypertension and cardiac and renal failure. Cardiac dysfunction and hypertension should be aggressively treated. In some cases, renal replacement therapy is needed for uraemia and fluid balance control in patients that are unresponsive to high-dose diuretic therapy.<sup>10-12,24,27,74</sup> The optimum type of dialysis is not known. Both peritoneal dialysis and haemodialysis have been used.<sup>10,11,86,87</sup> Peritoneal dialysis might improve the chances of renal recovery because it does not need anticoagulation. In the absence of intestinal ischaemia and malnutrition, peritoneal dialysis should be the preferred treatment modality. However, haemodialysis without or with only minimal anticoagulation is not contraindicated. In most severe cases, during the acute phase, adequate nutritional support can be provided by parenteral nutrition.<sup>10</sup>



possibly occurring as a consequence of vessel injury caused by catheters and guide wires within the aorta (type 1 embolisation) or by active plaque disruption during balloon dilation or stenting (type 2 embolisation).<sup>95</sup> Definitive recommendations for use of this approach cannot yet be made.

Primary prevention of atheroembolic renal disease is important, restricting indications for angiography and surgical procedures in atherosclerotic patients. Non-invasive diagnostic methods, such as MR angiography or computer-assisted tomographic angiography, could in part obviate the risk for catheter-induced embolisation. During endovascular procedures, use of proper and cautious techniques, including a so-called no touch technique avoiding direct trauma of the catheter tip to the atheromatous vessel wall might reduce risk of embolisation. Finally, the potential application of embolic protection devices, which removes atheromatous debris, could help keep risk of embolisation to a minimum.

## Outcomes

### Renal survival

Few outcome studies have been done in patients with atheroembolic renal disease. Renal prognosis is poor. Lye and co-workers<sup>5</sup> reported that 40% of 129 patients needed dialysis, of whom only 21% recovered sufficient renal function to stop dialysis. In a series, Thadhani and colleagues<sup>8</sup> reported that 44% of 52 patients underwent dialysis. Belenfant and co-workers<sup>10</sup> reported that dialysis was needed in 61% of 67 patients, with 13 patients regaining sufficient renal function to be free of dialysis. In a prospective study,<sup>12</sup> 37% of 95 patients needed dialysis, 14 recovered sufficient renal function to stop dialysis, and 23 remained dialysis dependent (24%; table 4). The most important predictors of endstage renal disease needing permanent dialysis therapy were pre-existing chronic renal insufficiency and longstanding hypertension. Another major finding was a protective benefit of statins—patients given statin treatment had a significantly lower risk for development of end-stage renal disease than did those not given statins.<sup>12</sup>

### Patient survival

Atheroembolic renal disease is generally associated with high mortality. An 81% mortality rate was reported by Fine and co-workers at 1 year.<sup>4</sup> Lye and colleagues<sup>5</sup> reported a 64% mortality rate at 1 year. The major cause of death was cardiovascular. A favourable clinical outcome, with a 1-year mortality rate of 13%, was reported by Belenfant,<sup>10</sup> with an aggressive therapeutic approach. The protocol was based on avoidance of anticoagulation and aortic manipulating procedures, good control of hypertension and heart failure, dialytic therapy, and adequate nutritional support. Benefits of similar supportive care were confirmed in a prospective study<sup>27</sup> of 354 patients, with an 83% 1-year patient-survival rate (table 4). Predictors of increased risk for death were diabetes and heart failure,

baseline levels of renal function, acute or subacute renal failure, and development of extrarenal manifestations, especially affecting the gastrointestinal tract (relative risk [RR] 2.57, 95% CI 1.69–3.93). Finally, previous statin use was associated with improved patient survival (RR 0.44, 0.28–0.67). Notably, the same predictors were associated with an increased risk for endstage renal disease, suggesting a common underlying mechanism for renal and cardiovascular events.<sup>27</sup>

## Future research

Atheroembolic renal disease has become a recognisable cause of renal failure. However, its incidence in patients at risk remains unknown, and diagnosis depends on how much experience centres have had with this disease. Ideally, a systematic search for signs and symptoms of the disease in populations undergoing aortic procedures would provide information to answer this important question. In terms of prognosis of established cases, avoidance of known precipitating factors and individualised supportive measures could substantially improve clinical outcome.<sup>96,97</sup> However, the disorder greatly affects patient and renal survival, and further research is urgently needed to alter its clinical course. Three different areas of clinical investigation need to be explored.

The first is the potential benefit of specific therapies, such as steroids and statins. A reactive inflammation around the crystals is suggested by eosinophilia, a cytokine-mediated occurrence,<sup>98</sup> and has a role in causing or worsening ischaemia. However, anti-inflammatory benefits might be counterbalanced by harmful effects of steroids on the cardiovascular system. For this reason, benefits and harms of steroid treatment should be tested in clinical trials. The protective role of statins<sup>12,27</sup> should also be confirmed by intervention studies. Atheroembolic renal disease alone represents an indication for standard statin therapy. Intensive statin therapy seems to provide more cardiovascular protection than does standard therapy in patients with coronary disease,<sup>99,100</sup> and whether this effect applies to patients with atheroembolic renal disease needs to be tested.

The second area of research is the modality of renal replacement therapy in patients needing dialysis. Clinical trials are necessary to test whether standard haemodialysis needing anticoagulation is associated with worse patient and renal outcomes than is peritoneal dialysis. Last, the prognostic effect of antiembolic devices during endovascular procedures on the evolution of atheroembolic renal disease is unknown. This approach is the standard of care during carotid artery stenting because it reduces procedure-related embolic strokes.<sup>101</sup> Such protection devices have also been used during renal artery stenting with promising results.<sup>102</sup> Insufficient information is available to test the pros and cons of a broadened use to reduce short-term and long-term atheroembolic complications of endovascular procedures.

**Contributors**

Both authors contributed equally to the design and writing of this Seminar.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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