







Atheroembolic Renal Disease

Nephrology Grand Rounds
October 12th, 2010
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Introduction

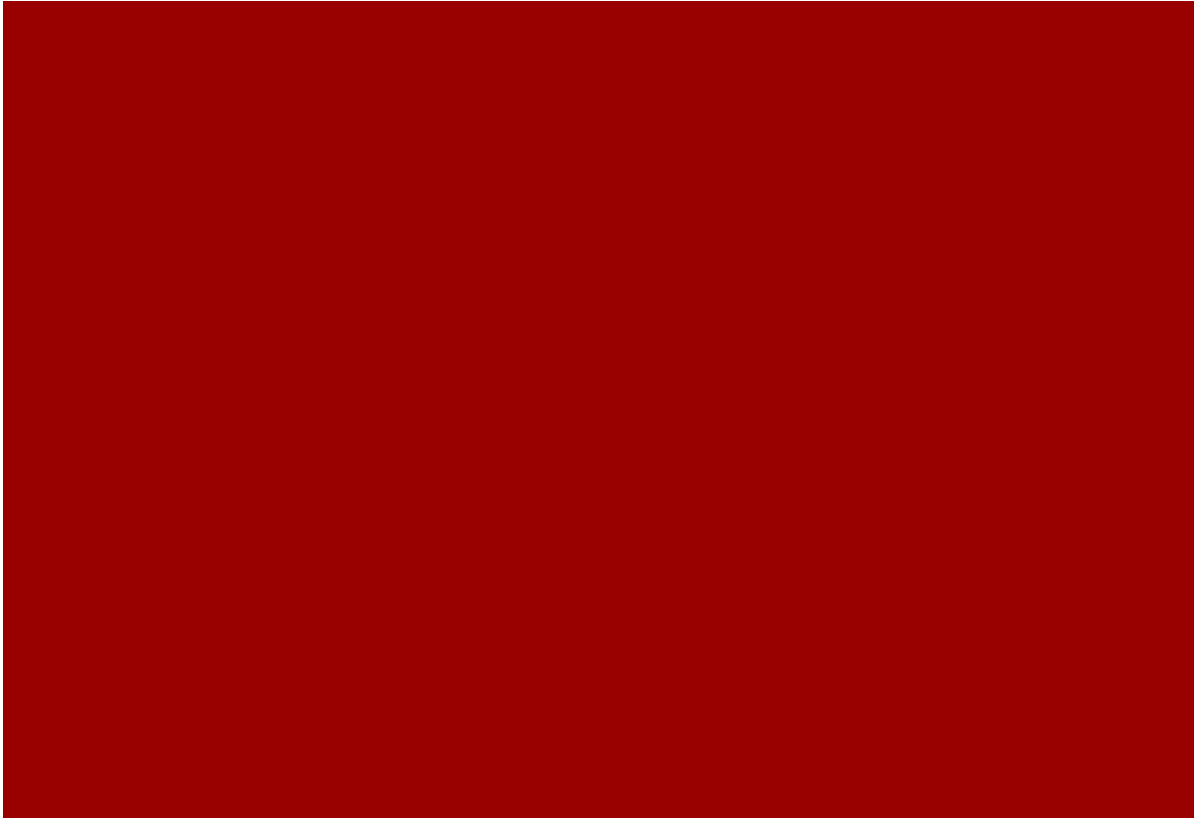
- Atheroembolic renal disease (AERD), sometimes referred to as renal cholesterol crystal embolization (CCE), is a form of renal failure that is secondary to occlusion and inflammation of renal arteries, arterioles, and glomerular capillaries with cholesterol crystals originating from atheromatous plaques of the aorta and other major arteries.
- Atheromatous material can be dislodged spontaneously or after intravascular trauma or anticoagulation.
- Typically, embolization affects the kidneys, skin, gastrointestinal system, and brain.

Background

- Panum 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 1945, Flory showed the embolic origin of cholesterol crystals from eroded aortic atheromatous plaques.
- 40 years later, Fine et al reviewed 221 cases of CCE, emphasizing the low rate of antemortem clinical diagnosis.
- In the past two decades, AERD has changed from being a pathological curiosity to a clinical syndrome.

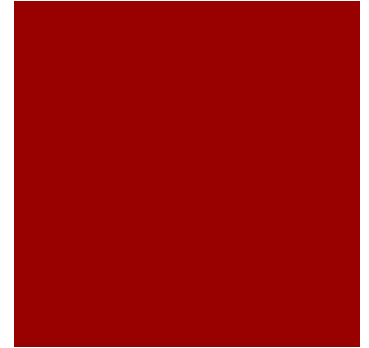


Panum PL. *Virchows Arch Pathol Anat Physiol*, 1862.
Flory CM. *Am J Pathol*, 1945.
Fine et al. *Angiology*, 1987.
Scolari et al. *Lancet*, 2010.



Epidemiology

Epidemiology – Autopsy Series



- In unselected autopsy series, the frequency of CCE findings is low, ranging from 0.31% to 2%.
- However, in autopsy studies done in elderly patients who died after aortic surgery or aortography, researchers have reported an increased frequency of CCE, ranging between 12-77%.

Moolenaar W. Arch Intern Med, 1996.
Cross S. J Clin Pathol, 1991.
Flory CM. Am J Pathol, 1945.
Thurlbeck WM. NEJM, 1957.

Epidemiology – Renal Biopsy Series



Biopsy Study	Number of Biopsies	Incidence
Jones and Innaccone	755	1.1%
Greenberg	500	1.6%
Lie	4589	1.1%
Preston (age > 65)	334	4.25%

Greenberg A et al. *Am J Kidney Dis*, 1997.
Lie JT et al. *Pathol Annu*, 1992.
Preston RA et al. *J Am Geriatr*, 1990.



Risk Factors

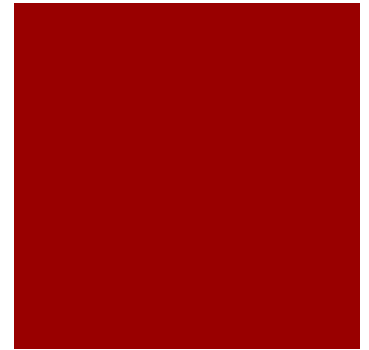
Predictors

Table 5. Univariate Analysis of Predictors for Postprocedure CES

Variables	No CES (n = 1,761) n (%)	CES (n = 25) n (%)	p Value
Age (yrs), mean ± SD	65 ± 10	69 ± 7	NS
>75 years old	310 (18%)	4 (16%)	NS
Male gender	1,152 (65%)	17 (68%)	NS
Coronary artery disease	1,470 (83%)	20 (80%)	NS
Acute coronary syndrome	354 (20%)	10 (40%)	0.02
Multivessel coronary artery disease	503 (28.5%)	13 (52.0%)	0.01
Atrial fibrillation	68 (3.9%)	1 (4.0%)	NS
Left ventricular ejection fraction <45%	129 (7.3%)	2 (8.0%)	NS
Hypercholesterolemia	662 (38%)	7 (28%)	NS
Diabetes mellitus	550 (31%)	10 (42%)	NS
Hypertension	867 (49%)	18 (75%)	0.03
Smoking	668 (38%)	14 (70%)	0.02
Cerebrovascular disease	112 (6%)	5 (20%)	0.01
Aortic aneurysm	54 (3%)	3 (12%)	0.01
Arteriosclerosis obliterans	75 (4%)	1 (4%)	NS
Chronic renal failure with hemodialysis	46 (3%)	1 (4%)	NS
Baseline serum creatinine (mg/dl), mean ± SD	1.1 ± 1.4	1.6 ± 2.0	NS
≥2.0 mg/dl	60 (3%)	2 (8%)	NS
C-reactive protein (mg/dl), mean ± SD	0.7 ± 1.7	2.4 ± 3.0	0.01
≥1.0 mg/dl	202 (12%)	9 (36%)	0.01
Femoral approach	1,238 (70%)	20 (80%)	NS
Coronary intervention	418 (24%)	8 (32%)	NS
Anticoagulation	331 (19%)	5 (20%)	NS

Abbreviation defined in Table 1.

Risk Factors



Panel 1: Population at risk for atheroembolic renal disease

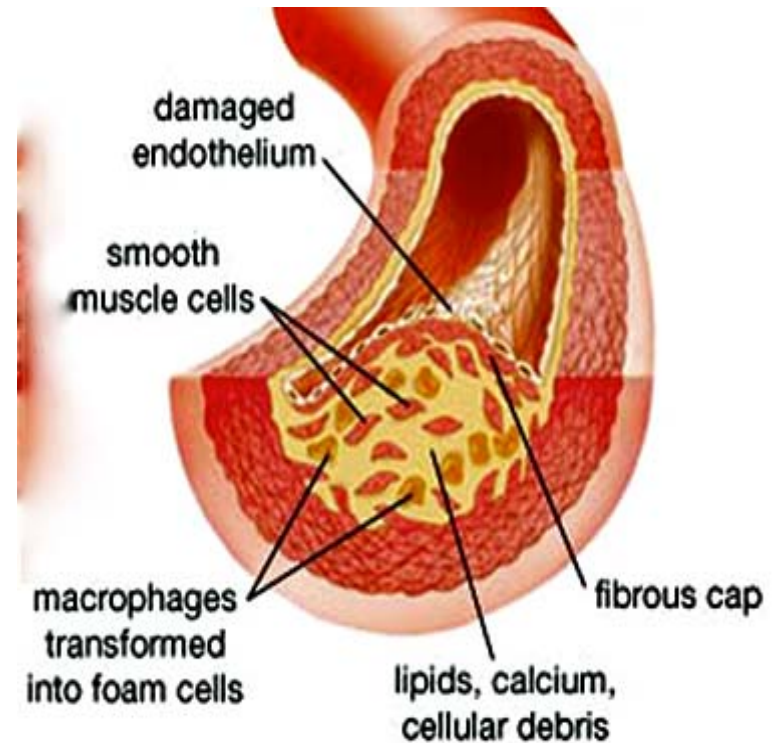
- Male sex
- Older than age 60 years
- White people
- Hypertension
- Tobacco use
- Diabetes mellitus
- Atherosclerotic vascular disease
 - Ischaemic cardiac disease
 - Cerebrovascular disease
 - Abdominal aortic aneurysm
 - Peripheral vascular disease
 - Ischaemic nephropathy



Pathogenesis

Pathogenesis

- The atherosclerotic plaque is characterized by a fibrous cap overlying a core containing necrotic cellular debris, foam cells, and lipids, including cholesterol crystals.
- Hemodynamic stress, inflammation, and hemorrhage can destabilize the plaque, which becomes friable and prone to erosion and rupture.
- Plaque disruption caused by shear stress or intrinsic mechanisms leading to spontaneous atheroembolism was the most common form of AERD up until the 1980s.
- Now, the vast majority of AERD is iatrogenic, owing to the increased use of endovascular procedures, anticoagulation, and/or thrombolytics.



Pathogenesis - Iatrogenesis



- Scolari et al retrospectively reported that 15 of 16,223 (0.09%) vascular procedures were complicated with atheroembolic disease (AED).
- In contrast, the autopsy study reported that the overall prevalence of AED was 25% to 30% of patients after cardiac catheterization.
- Multicenter prospective study of 1786 consecutive patients undergoing left heart catheterization reported twenty-five patients (1.4%) diagnosed as having AED.

Pathogenesis



	n	Spontaneous AERD (%)	Iatrogenic AERD			
			All causes (%)	Angiography (%)	CV surgery (%)	Anticoagulation (%)
Fine ⁴	221	153 (69%)	68 (31%)	39 (18%)	20 (9%)	30 (14%)
Lye ⁵	129	50 (40%)	79 (60%)	55 (43%)	7 (5%)	17 (13%)
Thadhani ⁸	52	0 (0%)	52 (100%)	50 (96%)	2 (41%)	19 (37%)
Belenfant ¹⁰	67	3 (4%)	64 (96%)	57 (85%)	24 (36%)	51 (76%)
Scolari ²⁷	354	83 (24%)	271 (76%)	221 (81%)	69 (25%)	108 (40%)

AERD=atheroembolic renal disease. CV=cardiovascular.

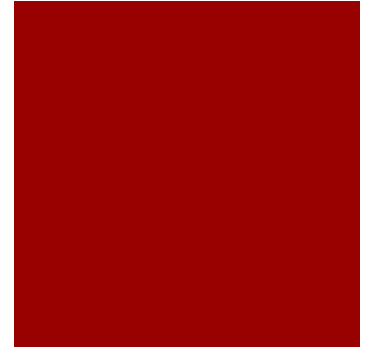
Table 1: Precipitating factors of atheroembolic renal disease

Fine et al. Angiography, 1987.
 Lye WC et al. Am J Nephrol, 1993.
 Thadhani R et al. Medicine, 1995.
 Scolari F et al. NDT, 1996
 Belenfant X et al. AJKD, 1999.



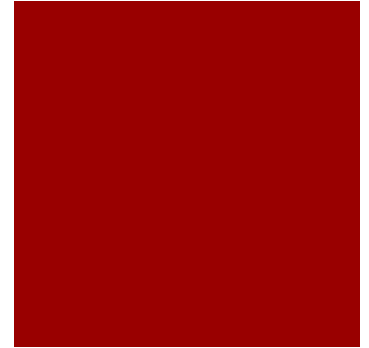
Histopathology

Histopathology



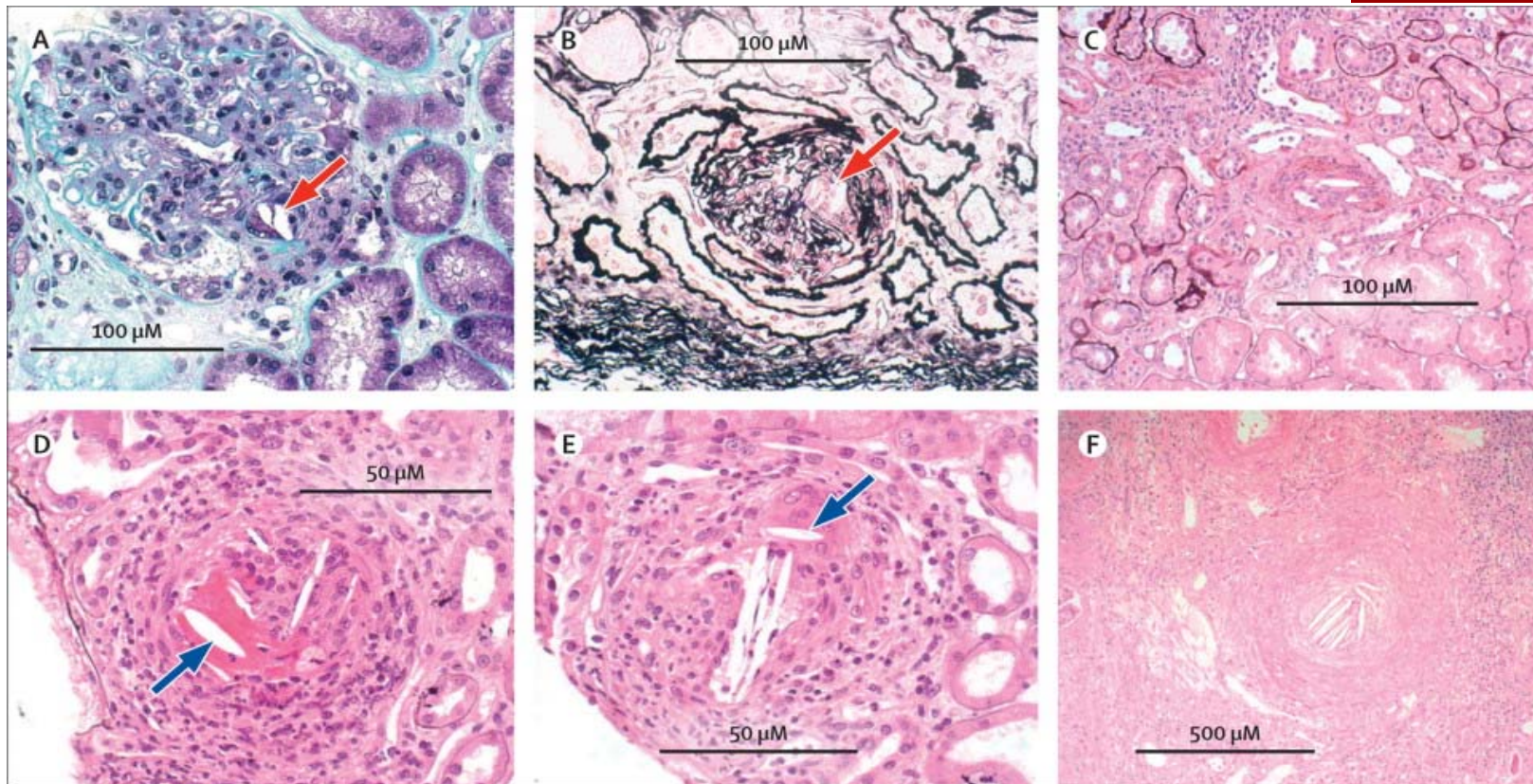
- Much has been learned from animal experiments in which cholesterol crystals were injected into the renal artery followed by serial observations of the vascular lesions.
- Cholesterol crystals are often too small and irregularly shaped to completely obstruct the artery in which they lodge, thus causing secondary ischemic atrophy rather than an acute renal infarction.
- Shortly after lodging, neutrophils and eosinophils infiltrate the affected arterioles.
- In time, the ensuing foreign body endothelial inflammatory reaction causes intimal proliferation, giant cell formation, and chronic fibrosis, narrowing of the vascular lumen over weeks to months in a stepwise pattern.

Histopathology



- Because the crystals are insoluble in body fluids and not removable by phagocytosis, they persist indefinitely.
- Histologically, cholesterol crystal emboli are identified as biconvex, needle-shaped, and empty clefts, referred to as ghost cells, because they dissolve during specimen processing.
- However, when specimens are snap-frozen with liquid nitrogen and the frozen specimen is examined under polarized light, one can demonstrate the birefringent character of the cholesterol crystals
- Crystals are mostly found in the lumen of arcuate and interlobular arteries. Rarely, small crystals lodge in the afferent arterioles and glomerular capillaries.

Histology



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 organized occlusive crystals in a renal arteriole (F).



Clinical Findings

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

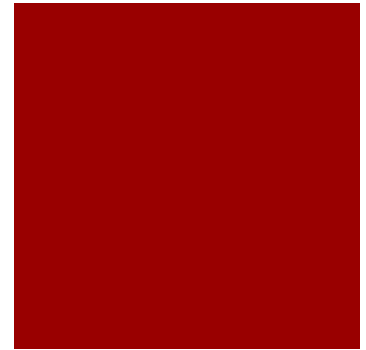
- Transient ischaemic attacks
- Amaurosis fugax
- Altered mental status
- Cerebral infarction
- Spinal cord infarction

Eye

- Retinal emboli (Hollenhorst plaques)

Systemic signs

- Fever
- Weight loss
- Malaise
- Myalgia
- Anorexia



Clinical Findings

Clinical Findings

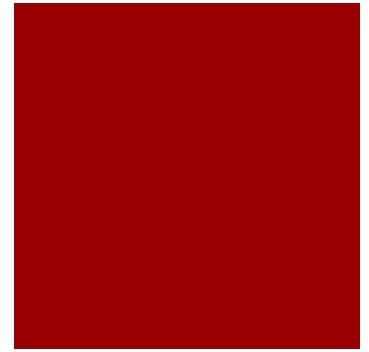


	n	Skin lesions	GI tract	CNS	Retinal emboli	Eosinophilia
Fine ⁴	221	75 (35%)	21 (10%)	0	14 (6%)	22 (73%)
Lye ⁵	129	55 (43%)	16 (10%)	15 (12%)	12 (10%)	57 (71%)
Thadhani ⁸	52	26 (50%)	15 (29%)	12 (23%)	13 (25%)	11 (22%)
Belenfant ³⁰	67	60 (90%)	22 (33%)	3 (4%)	15 (22%)	39 (59%)
Scolari ²⁷	354	266 (75%)	43 (12%)	35 (10%)	24 (7%)	238 (67%)

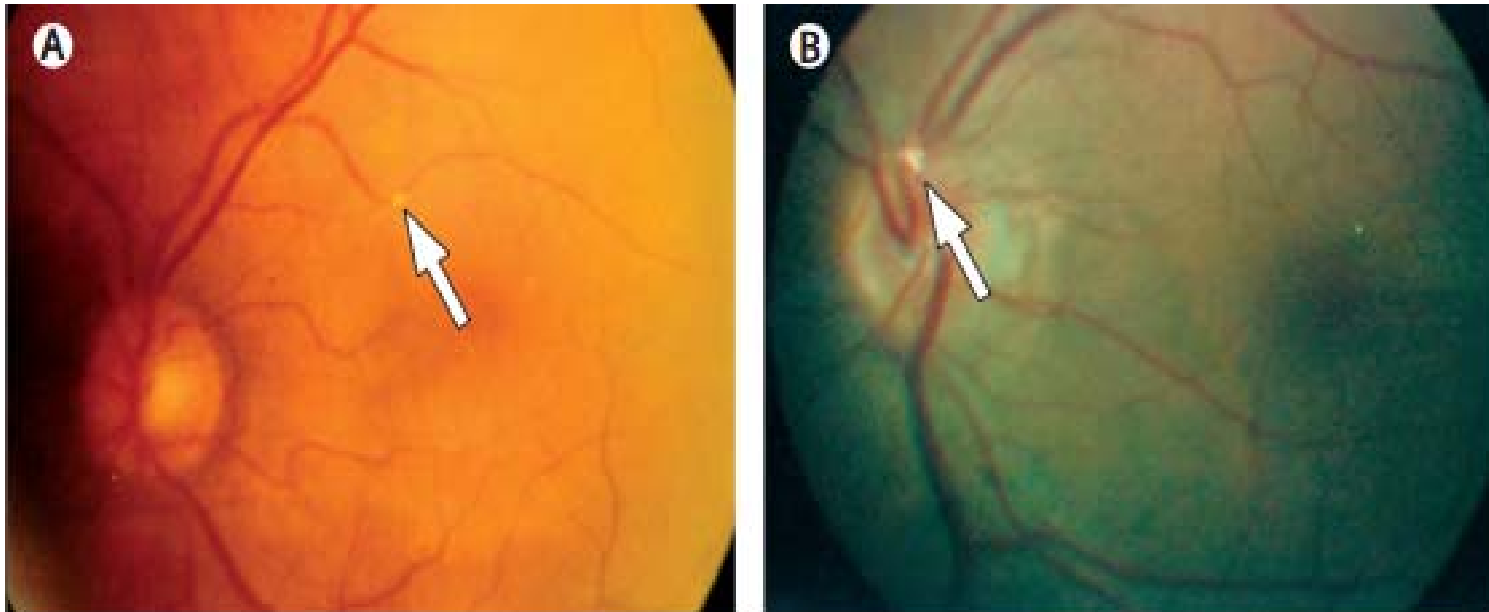
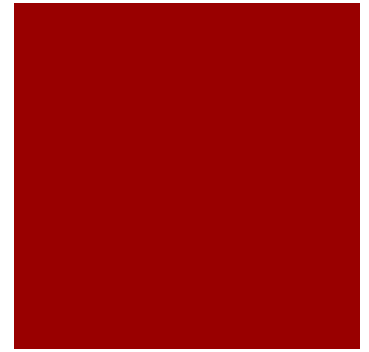
GI=gastrointestinal. CNS=central nervous system.

Table 2: Clinical findings in atheroembolic renal disease

Clinical Findings



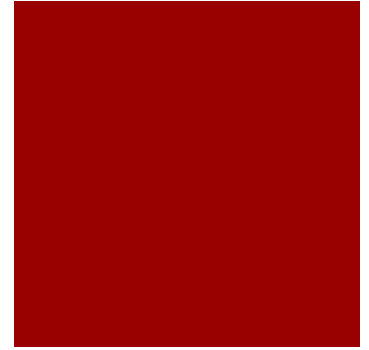
Clinical Findings – Hollenhorst Plaques





Laboratory Findings

Laboratory Findings - Urinalysis



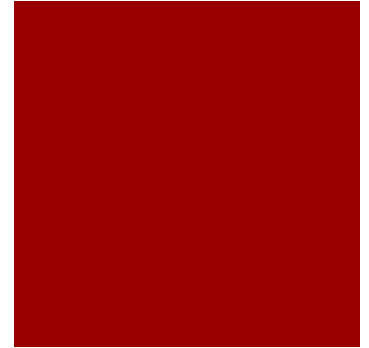
- The urinalysis may show bland urine, occasionally microscopic hematuria, or even red cell casts.
- The proteinuria is often minimal if present, rarely nephrotic range. Fine *et al* described proteinuria (1+ or more by dipstick) in 53% of patients with AERD.
- It has been suggested that the proteinuria and urinary sediment abnormalities are more likely to occur in patients who have glomerular capillary embolization than the more typical arterial involvement.

Laboratory Findings - Hypocomplementemia



- Hammerschmidt et al showed that the material extracted from human atheromatous plaques can trigger the complement pathway in vitro.
- Cosio et al noted hypocomplementemia in three patients with AERD.
- Subsequently, Cosio et al measured serum complement levels in six additional patients and found that two-thirds had decreased levels of serum complement in the absence of any other known cause of hypocomplementemia.
- Subsequent studies have reported hypocomplementemia in 30-40% of patients with AERD.

Laboratory Findings - Eosinophilia



- Eosinophilia is an abnormal laboratory finding that frequently occurs during the acute phase of the disease, thereby supporting immunological activation at the surface of the exposed emboli.
- In a previous review, Kasinath et al described eosinophilia in 80% of cases of AERD with 67% of 354 patients having an eosinophil count higher than 500 cells per μL .
- Subsequent studies have reported eosinophilia in 25-50% of cases of AERD.



Diagnosis

Diagnosis

- Diagnosis is often made on clinical grounds with classic triad of precipitating event, renal dysfunction and skin lesions.
- Taking a biopsy sample of skin lesions has a high diagnostic yield approaching 92%.
- Tissue biopsy sampling is not necessary when cholesterol crystals are seen in the retinal vessels (Hollenhorst plaques), which can be identified in 10–15% of cases.

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



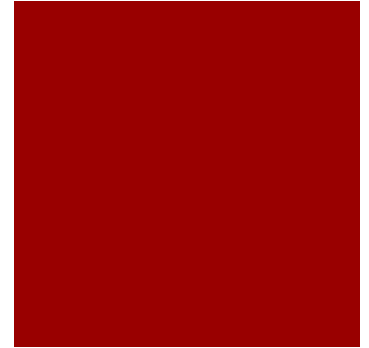
Diagnostic Criteria



Treatment (or lack thereof...)

Treatment

- There have been no prospective clinical trials of treatment for patients with AERD.
- Therapeutic measures are mostly preventive and supportive to restrict the extent of ischemic damage and prevent recurrent embolization.
- 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 interventional angiographic or vascular surgery procedures.



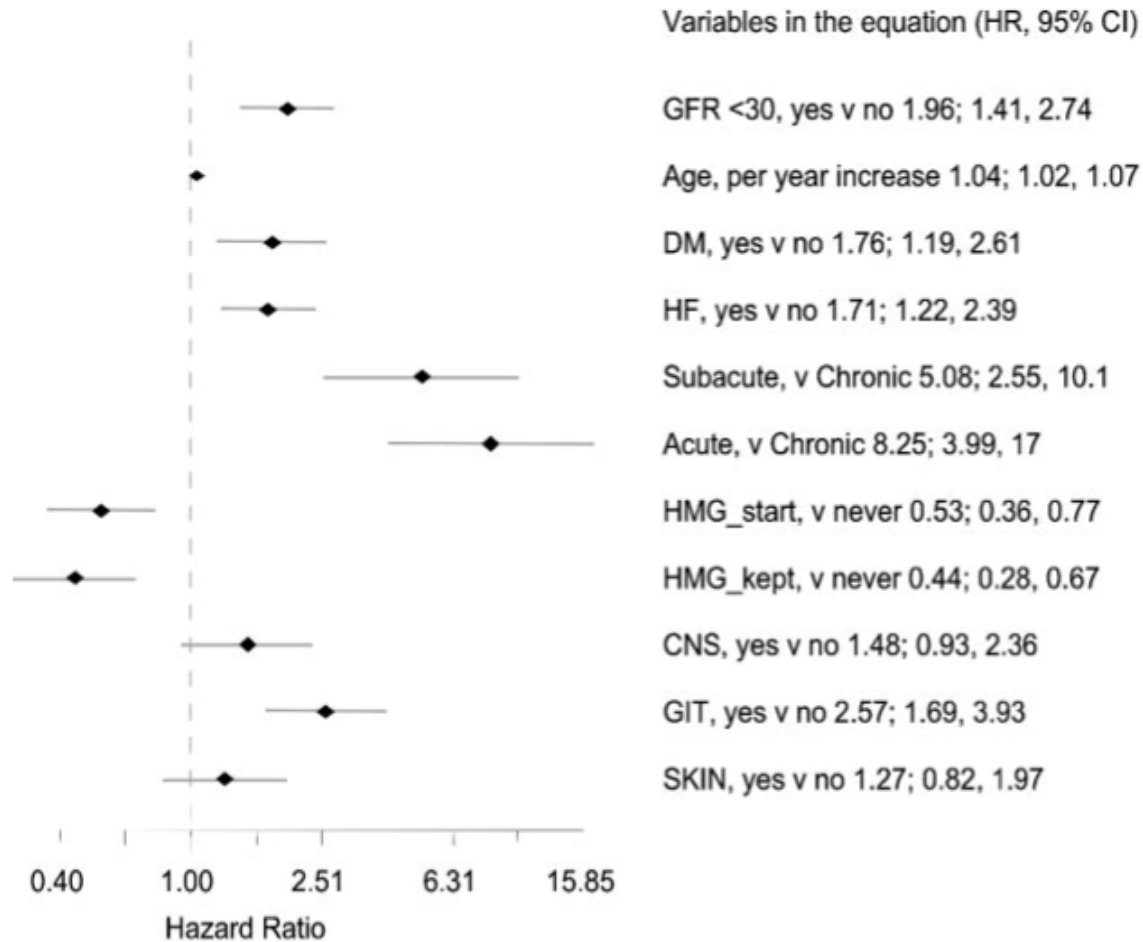
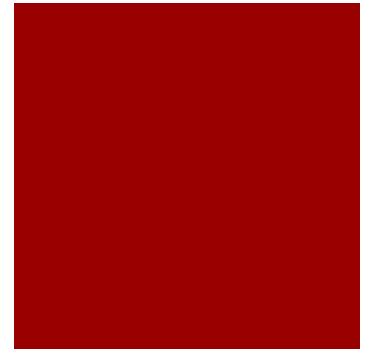
Treatment - Steroids

- Belenfant et al, used low-dose prednisolone (0.3 mg/kg) in 18 patients with relapsing disease reporting a favorable effect on mesenteric ischemia, as evidenced by relief of abdominal discomfort and improvement of oral feeding.
- Similarly, Belenfant reported that patients with severe lower limb pain improved dramatically with corticosteroid treatment, allowing for the withdrawal of morphine.
- Conversely, Fine et al failed to demonstrate benefit of steroids in a review of 221 cases of CCE.
- In a prospective multicenter study by Scolari et al of 354 patients with AERD, steroid therapy (used in 154 patients) was not associated with improved renal or mortality outcomes.

Treatment - Statins

- The protective effect of statins is theoretically attributable to plaque stabilization and regression through lipid-lowering and anti-inflammatory mechanisms.
- In a prospective prognostic study (n = 95), Scolari et al reported that statin therapy was independently associated with a decreased risk of ESRD.
- In a larger follow up study (n=354), Scolari et al, confirmed this finding with a 50% reduction in dialysis and death among those receiving statins, even when statin therapy was started after diagnosis of AERD.

Treatment - Statins





Prognosis

Prognosis

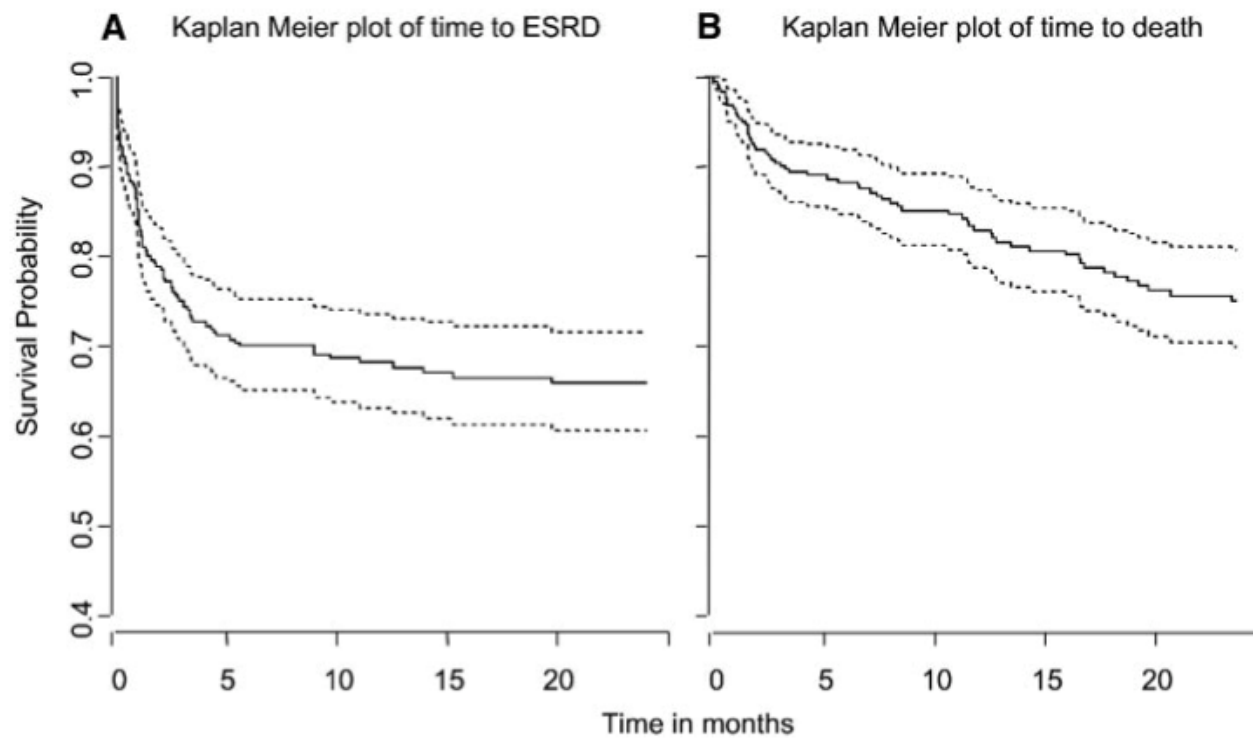


Figure 1. Kaplan-Meier survival curve and 95% CI of time to ESRD (A) and patient death from diagnosis (B).

Prognosis



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

Table 4: Renal and patients outcome in atheroembolic renal disease



Thank You