Atheroembolic disease--a frequently missed diagnosis: results of a 12-year matched-pair autopsy study

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Results of a 12-year matched-pair autopsy study

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Abbreviations

AD = Atheroembolic disease
USZ = University Hospital Zürich
SD = standard deviation
CI = confidence intervals
OR = odds ratio
Abstract

Diagnosis of atheroembolic disease (AD) is challenging, since no specific test is available, and it often masquerades as other clinical conditions. The aim of this study was to investigate the relative frequency of autopsy-proven AD over time, to describe its clinical presentation and to identify risk factors for AD. We screened 2066 autopsy reports from the period of 1995 to 2006 for AD. For each AD case a control patient without AD was matched for age, sex and autopsy year. Diagnostic and therapeutic interventions (operations, catheter interventions and drug treatment) in the last 6 months before death, as well as clinical and laboratory parameters during the last hospitalization were retrieved from electronic charts. Fifty-one AD patients were identified. Among these only 6 (12%) had been diagnosed clinically. The organs most often affected were kidney (71%), spleen (37%) and lower gastrointestinal tract (22%). The relative AD frequency decreased over time from 3.5 to 0.5/100 autopsies, whereas the frequency of clinically suspected as well as biopsy-proven AD remained constant. Among clinical signs, skin lesions such as livedo reticularis and blue toe (33% vs. 14%, p=0.04) were significantly increased in AD patients compared with the matched controls. Furthermore a trend for higher incidence of eosinophilia and proteinuria in AD patients was observed. Vascular interventions within 6 months before death were highly associated with AD (55% vs. 29%, p=0.01), and in a multivariable analysis this remained the only significant risk factor for AD. Thus, the diagnosis of AD is frequently missed. Vascular interventions represent the most important risk factor for AD and should be performed restrictively in high-risk patients.
**Introduction**

Atheroembolic disease (AD), also referred to as cholesterol crystal embolization, cholesterol atheroembolism, or cholesterol atheromatous embolism, was first described by Flory (4) in 1944. He reviewed 267 autopsies and found 9 cases of AD. He described “cholesterol-crystal spaces”, where during tissue preparation the crystals had been dissolved in the arterial lumen and an empty crystal-shaped space remained. Kassirer described in 1969 two types of histological lesions found in AD: at an early stage “crystals surrounded by eosinophilic material” were found, whereas older lesions showed a thickened intima, macrophages and multinucleated foreign-body giant cells. He also described that fibrosis in the intima eventually obstructed the lumen completely. Only small vessels, mostly 150-200 µm in diameter were found to be affected (11).

The pathogenesis of AD has since been further analyzed: cholesterol crystals originate from the aorta in most cases (12), but can also be released from other major arteries, as long as severe atherosclerosis is present. To release the crystals into the bloodstream, the atheromatous plaque must be eroded, thus the soft core is exposed. The contents then are flushed into distal arterial beds and trigger an inflammatory reaction, which eventually occludes the artery. Eliot et al. (2) distinguished between an atheroembolus, that consists of a dislodged atheromatous plaque, big enough to clog a major artery, and a cholesterol embolus, which basically represents cholesterol crystals that occlude smaller arteries.

Cholesterol crystals can be released suddenly upon spontaneous rupture of an atheromatous plaque, but lately iatrogenic forms of the disorder have become the center of attention. Triggers are either mechanical trauma - usually surgery on arteries (27), catheter interventions such as angiography or angioplasty (22) or drug interventions in the coagulation system such as therapeutic anticoagulation (18) or thrombolysis (5, 8, 21).

The precise incidence of AD is not clear and varies in a large range depending on the risk profile of the patient group investigated. In a non-selected Dutch population, with an autopsy rate of 7%, 0.31% of autopsied patients were identified to have suffered from AD (20). In contrast, in high risk
patient groups the incidence can raise considerably. Thurlbeck and Castleman (27) found an astonishing 77% incidence in an autopsy population that had undergone aortic aneurysm repair. Mayo and Swartz (16), however, reported a 4% incidence among their inpatients in a renal care unit.

Clinical diagnosis of AD remains challenging, since a multitude of different symptoms have been observed and only a few and unspecific laboratory findings can help to make the diagnosis. Therefore this study aimed to investigate the relative frequency of autopsy-proven AD over a 12-year period, to identify risk and precipitating factors and to facilitate diagnosis of AD through identification of clinical and laboratory features of the disease.
Patients and Methods

Data Collection

We reviewed 2066 autopsy reports from autopsies performed between January 1995 through December 2006 as a retrospective single center case-case-control study on patients of the Department of Internal Medicine at the University Hospital in Zürich, Switzerland (USZ). The search was performed manually as well as through an electronic database search. A central database for patient charts exists in this hospital since 1995 and includes not only medical reports, but also laboratory values, imaging studies, ECGs and other specialized examinations. To enter the case group [group 1], patients had to meet the following criteria: 1) Cholesterol emboli were found in at least one vital organ; thereby clinical and subclinical cases were not differentiated; cholesterol emboli were defined as “cholesterol-crystal spaces”, where during tissue preparation the crystals had been dissolved in the arterial lumen and an empty crystal-shaped space remained. 2) Treatment before death was received at the Department of Internal Medicine at USZ, therefore all clinical and laboratory data were available there in digital or in printed form; 3) Autopsy was performed in the Department of Pathology at USZ.

Criteria to enter the control group [group 2] were the following: 1) No cholesterol emboli had been found at autopsy. Criteria 2) and 3) from above were also applied for group 2. Furthermore, control patients were matched to case patients for sex, age and autopsy year in a 1:1 ratio. Two patients with AD were not matched to a control patient, because they arrived in cardiac arrest to the emergency room, so that very few clinical data and no laboratory features were available for analysis. Pathologists performed all autopsies according to a standardized procedure, and all organs were systematically examined and analyzed by histology.

For all case and control patients we systematically recorded data about demography, comorbidities, clinical manifestations of AD and precipitating factors during the last six months before death (23, 25). These data were retrieved from an electronic chart database and manually checked where ne-
cessary. Data on the highest recorded laboratory values were collected for the period of the last hospital stay before death. The cause of death was determined by the clinical and pathology reports. Presence of risk factors for atherosclerosis such as hypertension, hypertriglyceridemia or hypercholesterolemia and diabetes were assumed when either a respective medication was prescribed or the diagnosis appeared in the medical history. In addition we checked laboratory records for information on blood lipids. Hypercholesterolemia was defined by total cholesterol levels >190 mg/dL, and hypertriglyceridemia by total triglyceride levels >150 mg/dL (6). Tobacco abuse was recorded, without making a difference between current, recent or earlier tobacco use, when a history of smoking of a minimum of 5 pack years was known. Acute renal failure was registered when the serum creatinine level doubled from baseline, according to an adapted classification of the Acute Kidney Injury Network (17). Chronic kidney failure was defined as either kidney damage or decreased kidney function for at least 3 months (14).

We also collected data for calculation of relative AD frequency per year in autopsies, biopsies and clinical cases observed in the Department of Internal Medicine at USZ. Information on total number of autopsies and biopsies with and without AD was retrieved from the electronic database of the Department of Pathology, whereas the total number of clinically suspected cases and the total number of inpatient discharges at the Department of Internal Medicine were retrieved from an electronic chart system by full text searches of discharge reports.

The ethical committee for clinical studies of the Canton of Zürich approved of this study.

**Statistical analysis**

Descriptive Statistics were computed. Results are presented as means ± standard deviation (SD) and relative frequency. To skewed continuous variables such as blood serum creatinine, blood urea nitrogen, C-reactive protein, lactate dehydrogenase and pancreatic amylase, logarithmic transformation was applied. First, univariable and multivariable logistic regression for case/control was computed. Next, univariable and multivariable conditional logistic regression analysis was performed in
order to control for matching in the data. A p-value of $\leq 0.05$ was considered statistically significant. For comparison of relative frequencies, the Wilson method was used for the computation of 95% confidence intervals (CI) for the difference of true proportions. All data were analyzed with SPSS version 16.0 for Macintosh. Conditional logistic regression was performed with STATA Version 10 for Macintosh. Graphs were generated in Power Point and Excel.
**Results**

Among 2066 autopsies performed between 1995 and 2006, we found 51 patients with autopsy-proven AD, resulting in a relative frequency of 2.5% in this particular population. Interestingly, of those 51 patients only 6 (12%) had been diagnosed before death.

*Autopsy findings in AD cases*

We first analyzed the number of affected organs in each patient (Fig. 1A). Among the 51 patients with AD, 22% (11/51) showed involvement of more than two organs, with up to 5 organs in 2% (1/51). If we further assume that clinically typical skin manifestations were indeed symptoms of AD (even without histological confirmation), the percentage of patients with more than one organ affected rose to 61%. Thus, AD was a multisystem disorder in the majority of cases.

When we analyzed the type of organs involved (Fig. 1B), the kidneys were most often affected, namely in 36/51 patients (71%), confirming earlier findings (13). The kidney was followed by spleen, lower gastrointestinal tract and pancreas. The group named “Others” in Fig. 1B includes various organs which were rarely affected by AD. Among those 6 patients, we found cholesterol emboli in the brain (2 patients), the adrenal glands (2 patients), thyroid gland (1 patient), and penis (1 patient). The last patient presented with balanitis. As this was clinically a persisting problem, at autopsy a sample of the penis was taken, revealing an atheroembolus.

*Baseline characteristics and risk factors of AD patients and controls*

In our series of AD patients, 75% were male, all of them but one were aged above 53 (mean age was 71 ± 11 years). One patient, who was younger than 30, had suffered from congenital heart disease. All patients were Caucasian, with the exception of one Asian female. The mean body mass index was 25.5 ± 4 kg/m².

For further analysis of risk factors, 49 AD patients were matched to a control group for age, sex and autopsy year (Table 1). Two AD patients were not matched, since they arrived dead in the hospital.
In both groups 98% had atherosclerosis documented by autopsy. The autopsy of the 27-year-old patient did not reveal any generalized atherosclerosis of major arteries, but one area on the aortic root, where atherosclerotic changes were found. We must assume this was the source of the emboli.

Group 1 included 51% (25/49) diabetics, whereas in the control group, only 33% (16/49) had diabetes. This resulted in an insignificant p-value of 0.07.

Angiography with or without angioplasty turned out to be a highly significant risk factor for AD in univariable analysis (Odds’ ratio [OR]=3.5, 95%CI(OR)=1.30-9.36, p=0.01), and even in conditional multivariable logistic regression when controlling for matching it remained significantly associated with AD (OR=3.2, 95%CI(OR)=1.02-9.98, p=0.05). In addition, extensive surgery (joint replacement or opening of a body cavity) also represented a major risk factor for AD in univariable analysis as well as in conditional univariable logistic regression (OR=3, 95%CI(OR)=1.19-7.56, p=0.02), revealing no matching influence.

In 22% (11/49) of patients neither angiography, angioplasty, surgery on arteries, nor therapeutic anticoagulation had taken place in the last six months before death. In these patients AD probably occurred spontaneously. However, we can not exclude that either one of these interventions had taken place in the time beyond 6 months before death, i.e. before the recording of our data.

**Presentation of AD I: clinical signs and symptoms (Table 2)**

In our series of AD patients, involvement of the skin occurred in 33% (16/49) of cases. At examination either livedo reticularis or “blue toe” was found. Skin manifestations were significantly associated with AD in univariable analysis (OR=2.91, 95%CI(OR)=1.07-7.90, p=0.04). Results of the univariable conditional logistic regression were no longer significant (p=0.07).

Acute onset of renal failure was documented in 45% (22/49) of AD patients, but this number was even slightly higher in the control group, in which 55% (27/49) were affected. In contrast, pre-existing chronic renal failure was slightly more common among AD patients (61% [30/49] vs. 47% [23/49]), although this difference was not statistically significant (p=0.16).
Cholesterol emboli in retinal arteries, the so-called Hollenhorst plaques, were found in one patient. Unfortunately, only 6% (3/49) of AD patients underwent examination of the eye fundi. Taking all the charts into consideration, eye examination was reported on 5% (5/98) of the patients only.

*Presentation of AD II: Laboratory findings (Table 2)*

Only 59% (58/98) of all reviewed charts contained urinalysis results. Hematuria was classified positive with ≥2+ by dipstick. In univariable analysis hematuria was significantly associated with the control group (OR=0.26, 95%CI(OR)=0.08-0.88, p=0.03). However, in conditional logistic regression when controlling for matching, it was no longer significant (p=0.14). Proteinuria was graded positive if the dipstick showed ≥1+. It showed a tendency for association with AD, although it did not reach significance (p=0.07) in univariable analysis. Overall kidney function did not differ between the two groups: the mean value of the peak serum creatinine was 3.04±2.22 mg/dl in AD patients and 2.94±1.83 mg/dl in controls.

Eosinophilia was reported to be frequently associated with AD (1, 7, 10, 16, 23). In our patient population, absolute eosinophil counts were available for 64 patients. Eosinophil counts above 500/µL were found in 17% (7/41) of AD patients, but only 6% (2/32) of controls. This yielded an OR >3, which however was not significant (p=0.18). Thus, we conclude that presence of eosinophilia should raise a high clinical suspicion of AD, although its absence cannot exclude it.

The optimal multivariable logistic regression was found to have 2 predictors: C-reactive protein (OR=0.995, 95%CI(OR)=0.991-0.999, p=0.019), which was available for all cases and controls, and angiography (OR=4.1, 95%CI(OR)=1.46-11.75, p=0.007). Conditional logistic regression also revealed that C-reactive protein (OR=0.996, 95%CI(OR)=0.99-1, p=0.09) and angiography (OR=3.2, 95%CI(OR)=1.02-9.98, p=0.045) were significantly associated with AD, therefore excluding any matching influence. Based on the OR’s among these two parameters only angiography was considered clinically significant.
Causes of death

One patient clearly died from extensive atheroembolic disease: 5 of his organs were affected in addition to typical skin lesions, and the disease led to acute renal failure. Overall, 69% (35/51) of the patients in group 1 died from cardiovascular causes, and AD may have played a role to a variable extent. The main other causes of death were sepsis in 16% (8/51) and neoplasia in 12% (6/51). In comparison, the causes of death in group 2 were cardiovascular in 49% (24/49), sepsis in 29% (14/49) and neoplasia in 22% (11/49). Thus, a tendency for a higher incidence of cardiovascular death was found in the AD group (OR = 2.28, p = 0.05)

Relative frequency of AD over time in autopsy, biopsy and clinical diagnosis

We first analyzed the relative frequency of AD per 100 autopsies in each year of the 12-year period from 1995 to 2006 and surprisingly found a decrease from 3.5 to 0.5 /100 autopsies (Fig. 2A). This however, was not statistically significant: the 95%CI for the difference of true proportions between years 1995 and 2006 is (-0.018, 0.06) revealed no difference in the relative frequencies between both years. During the same time, the overall number of autopsies had also declined. However, the median age of autopsied patients for the years 1995, 2000, and 2006 remained stable at 64.5 years, therefore not indicating any severe selection bias over time. Furthermore, differences in autopsy techniques could be excluded, as those standards have not changed over the years.

To evaluate whether this decline of AD in autopsy represents a real decline of the occurrence of disease in our observation period, we analyzed the relative frequency of biopsy-proven AD (Fig. 2B) and of clinical AD diagnoses (Fig. 2C) during the same time period in the Department of Internal Medicine at USZ. The former was normalized to the total number of biopsies, the latter to the total number of discharges of the respective year. For both analyses the relative frequency was stable over time.

One possible explanation for the difference between autoptic and clinical diagnoses of AD could be a better prognosis of AD due to an increased use of potentially protective medications such as sta-
tins and aspirin. Therefore we retrieved available data of the use of statins and aspirin from the records of the hospital pharmacy and found that indeed between 2000 and 2008 the delivery of statins to the wards at USZ has increased from 18’800 to 41’000 tablets a year, whereas during that same period of time delivery of aspirin remained stable.
Discussion

AD occurred at a frequency of 2.5% in a large autopsy series from patients deceased in the Department of Medicine of a major Swiss university hospital between 1995 and 2006. Due to a possible selection bias in the patient population of a tertiary care hospital, which admits a higher percentage of severely ill patients compared to other hospitals, this frequency may not be extrapolated directly to the general population. Of interest, AD was frequently missed clinically, since only 12% of the AD cases detected by autopsy were diagnosed ante mortem. The relative frequency of autopsy-proven AD had a tendency to decrease over time, whereas diagnoses of AD on biopsies and clinical diagnoses remained constant.

In table 3 our study cohort is compared to the cohorts of 4 previous studies. The table reveals a high variability in frequency of risk factors and symptoms of AD, which may partially reflect the use of different selection criteria, but also the high variability of clinical presentation of this disease.

Angiography and major arterial surgery are reported as two major risk factors for AD, especially in elderly patients with suspected atherosclerosis (22, 27). Our study confirmed this for angiography with a high significance even in multivariable analysis. During either of these two interventions, mechanical manipulation of blood vessels causes atheroembolic plaques to disrupt, and subsequently this debris might clog smaller peripheral arteries. In case of extensive extra-arterial surgery, such as a joint replacement or the opening of a body cavity, stress or pain-related hypertension cause shear forces which can promote atheromatous plaque rupture. In addition anticoagulants, which are given to prevent postoperative thrombosis, are also known to favor atheroembolic disease (18). However, the prophylactic dosage given after surgery, was found to be statistically insignificant in our study population.

Not every histological finding of cholesterol crystals in tissues leads to a clinically relevant disease manifestation. Therefore retrospective data derived from autopsy or biopsy studies may exaggerate
AD frequency (24). But still AD remains highly under-diagnosed and remains a marker of high atherosclerotic burden and therefore cardiovascular risk. In our autopsy collective, 88% were clinically missed, although almost all presented with typical risk factors and 33% had either livedo reticularis or blue toe as common skin symptoms. In our study cutaneous manifestations were significantly associated with AD. With 33% they are similar to earlier studies (3). In contrast, recently published studies report skin manifestations in 88-96% (1, 9, 24), most likely because lesions were systematically looked for and even subtle signs were recorded. Skin symptoms can first appear within a month after the intervention (15, 25), and might be better visible, if the patient is in an upright position (9). Biopsy confirms the diagnosis. If biopsy specimens are not taken too superficially (18), sensitivity reaches 86% (9).

Besides a variety of symptoms, which often are not conclusive, few laboratory features help to make the diagnosis of AD. Eosinophilia has been pointed out to be present for 2-3 days in early stages of the disease, and therefore can be easily missed (10). In contrast, Thériault et al. (26) stated that eosinophilia was present more than 1 month after AD diagnosis. This leads to the assumption that the presence of eosinophilia is alternating over a long period of time. The fact that this finding has been reported in several other studies with varying percentages between 44-100% (1, 7, 10, 16, 23) reinforces this theory. In our series, we must assume that eosinophilia was missed in several other cases, because our study did not include long term surveillance, nor were eosinophil counts collected regularly, both measures necessary to comply with the episodical appearance of eosinophilia.

The kidney is often targeted in AD. Scolari et al. (24) suggested that the proximity to the abdominal aorta, and the large renal blood supply are the reason for the frequent involvement. In our series, 71% of the examined kidney samples, showed the typical crystal shaped clefts. This could have led to the higher percentage of chronic renal disease and proteinuria in group 1. Indeed, urinalysis might give helpful clues towards diagnosis of AD. Search for proteinuria should be performed, as this has regularly been observed in AD patients (7, 25). Greenberg et al. stated in their study, that
two distinct populations among AD patients exist and that in those patients with heavy proteinuria (38% in their series) focal segmental glomerulosclerosis with capillary loop collapse was found in 78% (7).

Although incidence of AD is reported to be less than 5% (13, 16, 20), mortality and especially morbidity, as well as the economic impact of the disease are considerable (9, 13). Thus timely diagnosis is required and can be achieved with a high level of clinical suspicion. White men, older than 50 years, who present with classical symptoms and risk factors of advanced atherosclerosis, are prone to suffer from this medical condition (23). When undergoing any kind of intervention on arteries, monitoring for AD should take place. Common findings of AD are blue toe, livedo reticularis, or renal failure. But AD can also cause pancreatitis, muscle pain, gastrointestinal bleeding, hypertension, peptic ulcer, inflammatory bowel disease (19), as well as prostatitis, and hemorrhagic cystitis (20). Therefore AD often masquerades as presumed other clinical conditions. Even the balanitis in one of our patients might have occurred as a consequence of AD. Molinari et al. reported to have “observed singular reports of cholesterol crystal embolization in connection with skin hyperplasia and atrophy, […], lichen ruber planus, preputial ulcer, and basalioma” (20).

If a patient is diagnosed with this disease, early and aggressive therapy should be initiated, since the prognosis for renal and patient survival is dismal, when multivisceral involvement occurs (1). One therapy approach by Belenfant et al. (1) aimed to prevent the three major causes of death in AD according to earlier published studies: “recurrence of cholesterol crystal embolization, cardiac failure and cachexia”. They used a combination of blood pressure lowering agents, hemodialysis, nutritional support, corticosteroids, discontinuation of anticoagulation treatment, and no further use of any intra-arterial interventions. Corticosteroids were administered in low doses and improvements in clinical status, as well as pain relief, were reported (1). However, use of corticosteroids still re-
mains controversial. Scolari et al. when publishing their multicentre study on 354 patients in 2007, stated, that no difference in outcome was noted, when giving steroids (23). A surgical approach for the management of affected patients has also been discussed in the past. After surgical removal of the sources of atheroemboli, a lower morbidity and less recurrence of AD as well as better outcome considering limb loss was observed, but this finding did not apply to the suprarenal aorta, that is believed to be the main source of thrombi (12). However, with still limited therapy options, no causal treatment available, and high morbidity, prevention of atheroembolic disease must be the first priority.

Taken together, our matched-pair autopsy study demonstrated that AD is still frequently missed in over 80% of the cases. Typical skin lesions and a history of atherosclerosis or arterial interventions should raise a high level of clinical suspicion and lead to simple clinical exams (such as looking for Hollenhorst plaques in the eye fundi) and screening for organ dysfunction (such as renal failure).
Acknowledgements

The authors thank Ms. Jeannette Adank for her valuable data on drug dispensation to USZ wards.
References


27. Thurlbeck, WM, Castleman, B. Atheromatous emboli to the kidneys after aortic surgery. 

Figure Legends

Figure 1. Organ distribution of atheroemboli in autopsies

(A) Numbers of organs affected by atheroembolic disease. (B) Type of organs affected by atheroembolic disease. Multiple listings are possible. We divided the gastrointestinal tract (GI tract) into an upper tract including esophagus, stomach, and duodenum, and a lower tract including jejunum, ileum and colon.

Figure 2. Relative frequency of AD over time

(A) Atheroembolic disease (AD) in autopsy, normalized to the total number of autopsies/year. (B) In biopsy, normalized to the total number of biopsies/year. (C) In clinical diagnosis, normalized to the total number of hospital discharges/year. All numbers refer to patients hospitalized in the Department of Medicine at University Hospital Zurich (Switzerland).
Table 1. Risk factors for atherosclerosis and atheroembolism in cases versus controls

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Cases (N/N; %)</th>
<th>Controls (N/N; %)</th>
<th>OR</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI (OR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>(25/49) 51%</td>
<td>(16/49) 33%</td>
<td>2.148</td>
<td>0.067</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>(28/49) 57%</td>
<td>(25/49) 51%</td>
<td>1.280</td>
<td>0.543</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tobacco use (≥ 5 years)</td>
<td>(28/40) 70%</td>
<td>(20/31) 65%</td>
<td>1.238</td>
<td>0.677</td>
<td></td>
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</tr>
<tr>
<td>Hypertriglyceridemia or hypercholesterolemia</td>
<td>(21/25) 84%</td>
<td>(18/24) 75%</td>
<td>1.75</td>
<td>0.438</td>
<td></td>
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<tr>
<td>Symptomatic arterial disease</td>
<td>(47/49) 96%</td>
<td>(45/49) 92%</td>
<td>2.089</td>
<td>0.408</td>
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<td></td>
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<table>
<thead>
<tr>
<th>Therapeutic interventions</th>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>Therapeutic anticoagulation</td>
<td>(18/47) 38%</td>
<td>(10/48) 21%</td>
<td>2.359</td>
<td>0.065</td>
<td>2.8</td>
<td>1-7.77</td>
<td>0.048</td>
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<tr>
<td>Platelet aggregation inhibitors</td>
<td>(31/49) 63%</td>
<td>(22/49) 45%</td>
<td>2.114</td>
<td>0.07</td>
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<tr>
<td>Statin use</td>
<td>(7/49) 14%</td>
<td>(8/49) 16%</td>
<td>0.854</td>
<td>0.779</td>
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<tr>
<td>Angiography</td>
<td>(18/49) 37%</td>
<td>(7/49) 14%</td>
<td>3.5</td>
<td>0.01</td>
<td>3.75</td>
<td>1.2-11.3</td>
<td>0.019</td>
</tr>
<tr>
<td>Surgery on arteries</td>
<td>(9/49) 18%</td>
<td>(3/49) 6%</td>
<td>3.45</td>
<td>0.077</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive surgery (all but surgery on arteries) †</td>
<td>(34/49) 69%</td>
<td>(22/49) 45%</td>
<td>2.782</td>
<td>0.015</td>
<td>3.00</td>
<td>1.19-7.56</td>
<td>0.02</td>
</tr>
<tr>
<td>Angiography, angioplasty or surgery on arteries</td>
<td>(27/49) 55%</td>
<td>(14/49) 29%</td>
<td>3.068</td>
<td>0.009</td>
<td>3.17</td>
<td>1.26-7.93</td>
<td>0.014</td>
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</tbody>
</table>

OR = odds ratio  
CI = confidence intervals  
† Extensive surgery was defined as opening of a body cavity or prosthesis implantation; in this group we also included two patients who received an intraaortic balloon pump.
### Table 2. Symptoms and signs of atheroembolism in cases versus controls

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Descriptive statistics (N/N; %) or (Median±SD)</th>
<th>Univariable logistic regression</th>
<th>OR</th>
<th>P-value</th>
<th>OR</th>
<th>95%CI (OR)</th>
<th>P-value</th>
</tr>
</thead>
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<td><strong>Symptoms</strong></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Abdominal Symptoms*</td>
<td>(26/49) 53% (24/49) 49%</td>
<td></td>
<td>1.178</td>
<td>0.686</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Muscle pain</td>
<td>(6/49) 12% (3/49) 6%</td>
<td></td>
<td>2.140</td>
<td>0.303</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>(10/49) 20% (14/49) 29%</td>
<td></td>
<td>0.641</td>
<td>0.349</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin manifestation (Livedo reticularis, blue toe)</td>
<td>(16/49) 33% (7/49) 14%</td>
<td></td>
<td>2.909</td>
<td>0.036</td>
<td></td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria ◊</td>
<td>(19/22) 86% (23/36) 64%</td>
<td></td>
<td>3.580</td>
<td>0.073</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria Δ</td>
<td>(5/21) 24% (19/35) 54%</td>
<td></td>
<td>0.263</td>
<td>0.030</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic amylase (U/L) ∞</td>
<td>42±223.09 29±60.11</td>
<td></td>
<td>1.005</td>
<td>0.154</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood serum creatinine (mg/dl) ∞</td>
<td>2.17±2.22 2.44±1.83</td>
<td></td>
<td>1.00</td>
<td>0.793</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Urea Nitrogen (mg/dl) ∞</td>
<td>39.21±56.02 56.02±30.81</td>
<td></td>
<td>0.998</td>
<td>0.898</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L) ∞</td>
<td>851.5±6942 777±4145</td>
<td></td>
<td>1.00</td>
<td>0.993</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/dl) ∞</td>
<td>142±102.94 182±109.93</td>
<td></td>
<td>0.996</td>
<td>0.034</td>
<td>0.995</td>
<td>0.99-0.9995</td>
<td>0.031</td>
</tr>
<tr>
<td>Eosinophilia (&gt; 500/µL)</td>
<td>(7/41) 17% (2/32) 6%</td>
<td></td>
<td>3.09</td>
<td>0.179</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation  
OR = odds ratio  
CI = confidence intervals  
* Abdominal symptoms defined as: emesis, diarrhea or abdominal pain  
◊ Proteinuria defined as: dipstick indicating ≥1+  
Δ Hematuria defined as: dipstick indicating ≥2+  
∞ Laboratory data recorded: highest values during last hospitalization before death