Anemia is associated with abdominal aortic aneurysm (AAA) size and decreased long-term survival after endovascular AAA repair

Nicolas Diehm, MD,[a,b] James F. Benenati, MD,[a] Gary J. Becker, MD,[c] Ramon Quesada, MD,[d] Athanassios I. Tsoukas, MD,[e] Barry T. Katzen, MD,[a] and **Margaret Kovacs, EdD, RNC,[a]**
Miami, Fla; Bern, Switzerland; and Phoenix, Ariz

Objective: **Anemia is a common comorbid condition in various inflammatory states and an established predictor of mortality in patients with chronic heart failure, ischemic heart disease, and end-stage renal disease. The present study of patients with abdominal aortic aneurysm (AAA) undergoing endovascular repair (EVAR) assessed the relationships between baseline hemoglobin concentration and AAA size, as well as anemia and long-term survival.**

Methods: **Between March 1994 and November 2006, 711 patients (65 women, mean age 75.8 ± 7.8 years) underwent elective EVAR. Anemia was defined as a hemoglobin level <13 g/dL in men and <12 g/dL in women. Post-EVAR mean follow-up was 48.3 ± 32.0 months. Association of hemoglobin level with AAA size was assessed with multiple linear regression. Mortality was determined with use of the internet-based Social Security Death Index and the electronic hospital record. Kaplan-Meier survival curves of anemic and nonanemic patient groups were compared by the log-rank method. Multivariable logistic regression models were used to determine the influence of anemia on vital status after EVAR.**

Results: **A total of 218/711 (30.7%) of AAA patients undergoing EVAR had anemia at baseline. After adjustment for various risk factors, hemoglobin level was inversely related to maximum AAA diameter (β: − .144, 95%-CI: −1.482 − .322, $P = .002$). Post-EVAR survival was 65.5% at 5 years and 44.4% at 10 years. In long-term follow-up, survival was significantly lower in patients with anemia as compared to patients without anemia ($P < .0001$ by log-rank). Baseline hemoglobin levels were independently related to long-term mortality in multivariable Cox regression analysis adjusted for various risk factors (adjusted HR: 0.866, 95% CI: .783 to .958, $P = .005$). Within this model, statin use (adjusted HR: .517, 95% CI: .308 to .868, $P = .013$) was independently related to long-term survival, whereas baseline AAA diameter (adjusted HR: 1.022, 95% CI: 1.009 to 1.036, $P = .001$) was an independently associated with increased mortality.**

Conclusions: **Baseline hemoglobin concentration is independently associated with AAA size and reduced long-term survival following EVAR. Thus, the presence or absence of anemia offers a potential refinement of existing risk stratification instruments. (J Vasc Surg 2007;46:676-81.)**

Abdominal aortic aneurysm (AAA) is a potentially fatal condition as its propensity to rupture increases as maximum AAA diameter increases.[1] Aneurysm formation and progression is associated with chronic transmural aortic wall inflammation.[2,3]

Endovascular AAA repair (EVAR), a minimally-invasive treatment option, has proven advantages over open surgical AAA repair in the perioperative period.[4,5] Protection from AAA-related death, a crucial end-point after EVAR,[6] has been shown to be as high as in 96% at 5 years and 93% at 9 years.[7-9] However, the cumulative 5-year survival of 49% highlights the increased mid-term mortality risk of these often medically frail patients.[7,8]

Besides the devastating consequences of AAA rupture, the systemic implications of aneurysmal disease have recently increasingly been acknowledged.[7,8,10-13] In particular, AAA patients were shown to be at significant risk for cardiovascular complications[5,7,8,14,15] and AAA is now considered a coronary heart disease risk equivalent.[16] Furthermore, AAA size is independently associated with inflammatory markers[10-13] as well as with an increased risk of perioperative complications[17] and cardiovascular mid-term mortality after open surgical[18] and endovascular[19,20] AAA repair.

Anemia is an important predictor of mortality in hemodialysis patients and in those with chronic heart failure and ischemic heart disease.[21-26] Anemia of chronic disease (ACD) is second most prevalent after anemia of iron deficiency.[23,27-29] The prevalence of ACD increases with age.[23,27-29] ACD is typically normochromic, normocytic, and hypoproliferative, and it is particularly encountered in the setting of chronic inflammatory conditions.[21,23,27,29] Thus, the pathophysiology of both AAA and ACD has recently been linked to chronic inflammation.[10,11,13,21,23,29,30]

From the Baptist Cardiac and Vascular Institute, Division of Interventional Radiology, Miami,[a] the Swiss Cardiovascular Center, Division of Clinical and Interventional Angiology and Vascular Research, Inselspital, University Hospital, Bern,[b] the Department of Radiology, Vascular & Interventional Section, University of Arizona College of Medicine, Phoenix,[c] the Baptist Cardiac and Vascular Institute, Division of Clinical and Interventional Cardiology, Miami,[d] and the Baptist Cardiac and Vascular Institute, Division of Vascular Surgery, Miami.[e]

Competition of interest: none.

Correspondence: James F. Benenati, MD, Baptist Cardiac and Vascular Institute, 8900 North Kendall Drive, Miami, FL 33176 (e-mail: jamesb@baptisthealth.net).

0741-5214/$32.00

doi:10.1016/j.jvs.2007.06.027

Table I. Demographics, risk factors, comorbidities, and cardiovascular medications of 711 consecutive patients undergoing elective endovascular abdominal aortic aneurysm repair

Baseline factor	*No anemia N = 493*	*Anemia n = 218*	P
Female gender, n (%)	51 (10.3%)	14 (6.4%)	.1198*
Age, mean ± SD (years)	74.6 ± 7.5	78.5 ± 7.5	<.0001†
Maximum AAA diameter mean ± SD (mm)	57.0 ± 9.7	60.8 ± 12.2	<.0001†
Height, mean ± SD (inches)	68.9 ± 3.5	68.9 ± 3.1	.9955†
Weight, mean ± SD (pound)	186.4 ± 37.0	174.7 ± 31.2	<.0001†
Baseline hemoglobin, mean ± SD (g/dl)	14.4 ± 1.0	11.6 ± 1.1	<.0001†
Baseline hematocrit, mean ± SD (%)	42.8 ± 3.1	35.3 ± 3.2	<.0001†
Postprocedural hemoglobin, mean ± SD (g/dl)	11.8 ± 1.7	10.1 ± 1.3	<.0001†
Postprocedural hematocrit, mean ± SD (%)	35.2 ± 3.8	30.6 ± 3.6	<.001†
White blood cell count, mean ± SD (cells/mcl)	7.4 ± 6.9	7.4 ± 6.7	.9550†
Creatinine clearance, mean ± SD (ml/min)	56.7 ± 18.9	44.9 ± 17.8	<.0001†
History of cancer, n (%)	121 (24.5%)	62 (28.4%)	.3062†*
Arterial hypertension, n (%)	388 (78.7%)	185 (84.9%)	.0640*
Hyperlipidemia, n (%)	269 (54.6%)	96 (44.0%)	.0116*
Diabetes mellitus, n (%)	69 (14.0%)	38 (17.4%)	.2558*
Smoking, n (%)	388 (78.7%)	164 (75.2%)	.3293*
COPD, n (%)	163 (33.1%)	65 (29.8%)	.4331*
History of cerebrovascular disease, n (%)	72 (14.6%)	45 (20.6%)	.0488*
History of PAOD, n (%)	127 (25.8%)	78 (35.8%)	.0072*
History of coronary artery disease, n (%)	208 (42.2%)	112 (51.4%)	.0272*
History of atrial fibrillation, n (%)	61 (12.4%)	38 (17.4%)	.0785*
Cardiac risk, n (%)			
0	186 (37.7%)	56 (25.7%)	.0020†
1	61 (12.4%)	20 (9.2%)	.2499†
2	233 (47.3%)	122 (55.9%)	.0346*
3	13 (2.6%)	20 (9.2%)	.0003*
Renal risk, n (%)			
0	422 (85.6%)	134 (61.5%)	<.0001*
1	60 (12.2%)	54 (24.7%)	<.0001*
2	10 (2.0%)	24 (11.0%)	<.0001*
3	1 (0.02%)	6 (2.8%)	.0041
Pulmonary risk, n (%)			
0	279 (56.6%)	104 (47.7%)	.0338*
1	124 (25.2%)	68 (31.2%)	.0997*
2	60 (12.1%)	33 (15.1%)	.2800*
3	30 (6.1%)	13 (6.0%)	.0000*
Betablocker, n (%)	200 (40.6%)	107 (49.1%)	.0400*
Statin, n (%)	217 (44.0%)	86 (39.4%)	.2851*
Antiplatelet therapy, n (%)	211 (42.8%)	113 (51.8%)	.0276*
ACE inhibitor, n (%)	113 (22.9%)	63 (28.9%)	.0908*

COPD, Chronic obstructive pulmonary disease; *PAOD,* Peripheral arterial occlusive disease.
*from Fisher exact test.
†from Student t-test.

The purposes of this study were to evaluate the relationship between hemoglobin concentration and AAA size and between baseline anemia and long-term survival after EVAR.

PATIENTS AND METHODS

Between March 1994 and November 2006, 711 consecutive patients underwent elective EVAR for infrarenal AAA at a single center and were entered in a prospectively maintained database. EVAR was carried out by a dedicated interdisciplinary team consisting of interventional radiologists, vascular surgeons, and anesthesiologists as described previously.[31,32]

Definitions. Anemia was defined according to the World Health Organization as a hemoglobin level <13 g/dL in men and <12 g/dL in women.[33] General definitions[34] as well as classification of cardiovascular risk factors[35] followed the standards proposed by the Society of Vascular Surgery/International Society for Cardiovascular Surgery (SVS/ISCVS).

Patient treatment. A total of 326/711 (45.9%) patients were treated within five multicenter clinical trials of specific endografts. The results of several of these trials have recently been published.[36-39] The study protocols were in accordance with the Declaration of Helsinki and approved by the local ethics committee. Each patient gave written informed consent prior to participating in the trial. Furthermore, 385/711 (54.1%) patients were treated with use of commercially available endografts. Ethics committee approval was not obtained for these patients, since they were treated on a regular clinical basis using FDA-approved devices.

Patients with anatomically suitable AAAs were eligible for EVAR if they had an infrarenal aortic aneurysm that was 50 mm or larger in maximum transverse diameter or if they had documented imaging evidence of 1.5 times the reference aortic diameter and expansion rate >10% per year. Exclusion criteria for the present investigation were a life expectancy of <1 year, pregnancy, systemic infection, inflammatory aneurysm, AAA associated with connective tissue disease, or Marfan's syndrome and an untreatable bleeding diathesis or hypercoagulable state.

All patient baseline characteristics and laboratory data were collected preoperatively and are described in Table I.

Follow-up. Mean follow-up was 48.3 ± 32.0 months. The Social Security Death Index (SSDI, http://ssdi.rootsweb.com/) was used to ascertain mortality as of November 30, 2006.

Statistical analysis. Continuous data are presented as mean ± standard deviation (SD). Categorical data are given as absolute numbers and percentages. For univariable comparison of unpaired continuous data, the Student *t* test was used. For univariable comparison of paired continuous data, the paired *t* test was utilized. Categorical data was compared with use of the Fisher exact test. Multiple linear regression (adjusted for all baseline variables with significant difference in univariable comparison and for factors with potential impact on baseline AAA size and cause of anemia) was performed to assess the association between hemoglobin concentration and AAA size. Survival rates according to presence or absence of anemia at baseline are presented as Kaplan-Meier curves and compared by means of the log-rank test. Multivariable Cox proportional hazards analysis (adjusted for all baseline variables with significant difference in univariable comparison and for factors with potential impact and cause of anemia[23] as well as for factors with impact on decreased patient survival) was applied to assess the effect of hemoglobin concentration on survival. Results of the Cox regression model were presented as the hazard ratio (HR) and the 95% confidence interval (95% CI).

A *P* value <.05 was considered statistically significant. All calculations were performed using SPSS (Version 13.0, SPSS, Chicago, Ill).

RESULTS

Anemia was present in 218/711 (30.7%) of patients undergoing EVAR. Table I outlines patient demographic data, risk factors, comorbidities, and cardiovascular medications of patients contained in the present study. Patients with anemia were significantly older, had a larger maximum AAA diameter, as well as a lower body weight and creatinine clearance compared to patients without anemia. Hyperlipidemia was less prevalent, whereas history of symptomatic atherothrombosis as well as betablocker and antiplatelet therapy was more frequent in patients with anemia compared with patients without anemia. Furthermore, patients with anemia were less likely to have favorable cardiac, renal, and pulmonary risk scores than were patients without anemia.

Table II. Thirty-day outcomes of 711 consecutive patients undergoing elective endovascular abdominal aortic aneurysm repair

30-day outcomes	*All patients n = 711*	*No anemia n = 493*	*Anemia n = 218*	P*
Procedural conversion	7 (0.09%)	5 (1.0%)	2 (0.09%)	1.0000
Procedural death	0 (0.0%)	0 (0%)	0 (0%)	N/A
Procedural rupture	0 (0%)	0 (0%)	0 (0%)	N/A
30-day conversion	10 (1.4%)	8 (1.6%)	2 (0.09%)	.7316
30-day death	10 (1.4%)	6 (1.2%)	4 (1.8%)	N/A
30-day rupture	0 (0%)	0 (0%)	0 (%)	N/A

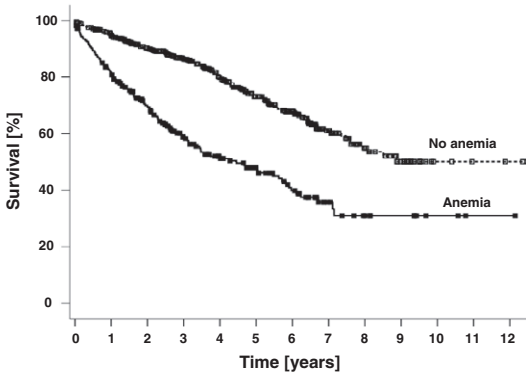
*from Fisher exact test.

Postprocedural hemoglobin concentration and hematocrit were significantly lower in patients diagnosed with anemia at baseline as compared to patients without anemia ($P < .0001$ and $P < .001$, Table I). Postprocedural hemoglobin concentrations as well as hematocrit were significantly lower compared with preprocedural values in both patients with and without anemia at baseline ($P < .0001$). With use of cell savers, transfusion was necessary in a total of 48/711 (6.8%) patients: 15/493 (3%) of patients without anemia at baseline and 30/218 (14%) of patients with anemia at baseline received blood products ($P < .0001$).

Hemoglobin level was inversely related to maximum AAA diameter (β: −.144, 95% CI: −1.482 to −.322, $P = .002$) within a linear regression model adjusted for age; weight; height; creatinine clearance; hyperlipidemia; diabetes mellitus; smoking; antiplatelet and beta blocker use; cerebrovascular disease; PAOD; coronary artery disease; cardiac, pulmonary and renal risk score. Conversely, maximum AAA diameter was inversely related to hemoglobin concentration (β = −.172, 95% CI: −1.947 to −.214, $P = .015$) in this model.

Post-EVAR 30-day rates of surgical conversion, AAA rupture, and death did not differ between both groups ($P > .05$, Table II). Survival was 65.5% after 5 years and 44.4% after 10 years (Fig 1). Long-term survival was significantly lower in patients with anemia as compared to patients without anemia ($P < .0001$, Fig 1).

Multivariable Cox proportional hazards analysis adjusted for age; maximum AAA diameter; weight; creatinine clearance; history of cancer; hyperlipidemia; diabetes mellitus; smoking; COPD; cerebrovascular disease; PAOD; coronary artery disease; cardiac, pulmonary and renal risk score; beta blocker, statin, antiplatelet, and ACE inhibitor use confirmed baseline hemoglobin levels to be independently associated with long-term mortality post-EVAR (adjusted HR: .866, 95% CI: .783 to .958, $P = .005$; Table III). Additionally, patient age (adjusted HR: 1.040, 95% CI: 1.015 to 1.065, $P = .002$), maximum AAA diameter (adjusted HR: 1.022, 95% CI: 1.009 to 1.036, $P = .001$), diabetes mellitus (adjusted HR: 1.819, 95% CI: 1.216 to 2.720, $P = .004$) as well as pulmonary (adjusted HR: 1.398, 95% CI: 1.157 to 1.689, $P = .001$) and renal risk score (adjusted HR: 1.595, 95% CI: 1.234 to 2.062,



Patients at risk, n													
No anemia	493	443	381	320	255	194	149	73	42	23	5	3	2
Anemia	218	171	127	89	66	53	37	16	10	7	3	1	1
Cumulative survival, %													
No anemia	100	94.8	90.3	86.3	79.5	78.2	73.1	66.4	60.1	53.6	50.1	50.1	50.1
Anemia	100	81.7	70.0	58.8	51.2	47.9	39.8	35.7	31.0	31.0	31.0	31.0	31.0
Standard error, %													
No anemia	0	1.0	1.4	1.6	2.0	2.3	2.6	3.0	3.6	4.3	4.3	4.3	4.3
Anemia	0	2.7	3.2	3.7	3.8	3.9	4.2	3.0	4.4	4.9	4.9	4.9	4.9

Fig 1. Cumulative survival of patients with and without anemia undergoing elective endovascular abdominal aortic aneurysm repair ($P < .0001$ by log-rank).

$P < .001$) were independently associated with reduced survival, whereas statin use was associated with greater survival (adjusted HR: .517, 95% CI: .308 to .868, $P = .013$) in this model (Table III).

DISCUSSION

Mediation by elevated pro-inflammatory cytokines is common to the pathophysiology of both AAA and ACD.[40-42] In the present study, decreased hemoglobin concentration, as a marker of chronic disease, was shown to be independently associated with AAA size and reduced long-term survival after EVAR.

In the present series, 30-day mortality after EVAR was 1.4%, whereas 5-year and 10-year survival were 65.5% and 44.4%, respectively. As more long-term follow-up data on patients undergoing treatment for AAA becomes available,[7,8] the systemic implications of abdominal aortic aneurysmal disease are becoming more apparent. Still, long-term survival of AAA patients compares well with patients with symptomatic cerebrovascular disease[43,44] and various types of malignancies such as colon cancer[45] and is substantially higher as compared to patients with intermittent claudication.[46] Considering the fact that AAA patients are at significant risk for cardiovascular complications,[7,8,17,18,20] AAA is now considered a CHD risk equivalent.[16]

Maximum AAA diameter as a potential marker of systemic inflammatory burden has been shown to directly correlate with inflammatory markers such as interleukin-6 and C-reactive protein.[10-13] Furthermore, maximum AAA diameter as an expression of AAA size was shown to influence on rates of perioperative cardiovascular complications,[17] and cardiovascular midterm mortality after open surgical AAA repair[18] and after EVAR.[7,8,20] The present study confirms the highly significant inverse relationship between AAA size and long-term survival, underlining previous observations regarding mid-term survival after EVAR.[7,8,20]

Anemia has traditionally been viewed as an "innocent bystander" and accepted as an abnormality associated with chronic diseases.[22] However, the presence of anemia has recently been identified as an important predictor of increased mortality in patients with end-stage renal disease, chronic heart failure and ischemic heart disease.[21-26] In inflammatory states, increased hepcidin concentrations cause iron sequestration in macrophages, resulting in hypoferremia and anemia.[21,23,29,47] Furthermore, pro-inflammatory cytokines induce hypoferremia by modulating macrophage iron metabolism via induction of ferritin biosynthesis.[48] In the present series, anemia was highly prevalent and was independently associated with AAA size and increased mortality during long-term follow-up after multivariable adjustment of a multitude of clinical baseline factors. Given these associations, we speculate that there may be a role for anemia as an inflammatory surrogate marker and risk stratification tool in patients with AAA, although no direct link between anemia and inflammatory markers was established in the present study.

Although the effect of statins in reducing the risk of cardiovascular disease is well established, robust data on its dedicated use in patients with AAA is scarce. Statins are associated with greater long-term survival after open AAA surgery[49] and after EVAR.[50] Besides their well-studied lipid-lowering and anti-inflammatory properties associated with improved cardiovascular outcomes, statins reduce levels of enzymes involved in aortic wall degeneration in cell culture[51,52] and in human AAA tissue.[53] The present series confirms statin use to be an independent predictor of decreased long-term mortality in AAA patients, thereby underlining important observations from the EUROSTAR registry.[50] Fewer than 50% of patients in the present series were prescribed statins prior to EVAR. The fact that treatment of cardiovascular risk is currently still suboptimal in patients with AAA has recently been highlighted by others.[15] Despite the fact that AAA has been recognized as a coronary heart disease risk equivalent,[16] dedicated recommendations regarding drug treatment are currently lacking.

Three shortcomings of the present study must be addressed. First, since ACD can nowadays not be diagnosed even with specific laboratory tests directly aimed at differentiating anemia of inflammation from anemia resulting from other causes,[23,54] we cannot entirely rule out that causes for anemia other than chronic inflammation might have contributed to the above-described results. Nevertheless, three features of our analysis render the impacts of such artefacts less likely. By including age, creatinine clearance, and history of cancer in the multivariable analysis assessing factors contributing to reduced survival, the impact of these major causes of anemia was minimized.[23] Furthermore, the inverse relationship of hemoglobin levels and AAA size observed in this study further support assumptions for a link between anemia and chronic inflammation in this series. Second, the lack of available data to enable system-

Table III. Multivariable Cox regression analysis for prediction of mortality during long-term follow-up of 711 consecutive patients undergoing elective endovascular abdominal aortic aneurysm repair

	*Adjusted HR**	*95%-CI*	P
Age (per year)	1.040	1.015-1.065	.002
Maximum AAA diameter (per mm)	1.022	1.009-1.036	.001
Hemoglobin (per g/dl)	.866	.783-.958	.005
Diabetes mellitus	1.819	1.216-2.720	.004
Pulmonary risk score	1.398	1.157-1.689	.001
Renal risk score	1.595	1.234-2.062	.000
Statin use	.517	.308-.868	.013

*Adjusted for age; maximum AAA diameter; weight; creatinine clearance; history of cancer; hyperlipidemia; diabetes mellitus; smoking; chronic obstructive pulmonary disease; cerebrovascular disease; Peripheral arterial occlusive disease; coronary artery disease; cardiac, pulmonary and renal risk score; beta blocker, statin, antiplatelet and ACE inhibitor use.

atic and reliable determination of the causes of death in patients who underwent elective EVAR prevented an assessment of the direct relationship between anemia and cardiovascular events. Third, since anemia was diagnosed by a blood test prior to EVAR, the impact of anemia occurring during follow-up cannot be assessed utilizing this approach.

In summary, in the present series baseline hemoglobin concentration, as a marker of chronic disease, was shown to be independently associated with both AAA size and reduced long-term survival following EVAR. Thus, the presence or absence of anemia offers a potential refinement of existing risk stratification instruments. Since no direct link between inflammatory markers and anemia could be established in the present series, further investigations into the molecular linkage between anemia, inflammatory changes and AAA are warranted.

Part of this work was supported by the BCVI Cook Research Scholar Program.

AUTHOR CONTRIBUTIONS

Conception and design: GB, BK, MK
Analysis and interpretation: ND, JB, GB, RQ, AT, BK, MK
Data collection: JB, GB, RQ, AT, BK, MK
Writing the article: ND, JB, GB, MK
Critical revision of the article: GB, RQ, AT, BK
Final approval of the article: ND, GB, MK
Statistical analysis: ND, MK
Obtained funding: Not applicable
Overall responsibility: ND

REFERENCES

1. Szilagyi DE, Smith RF, DeRusso FJ, Elliott JP, Sherrin FW. Contribution of abdominal aortic aneurysmectomy to prolongation of life. Ann Surg 1966;164:678-99.
2. Freestone T, Turner RJ, Coady A, Higman DJ, Greenhalgh RM, Powell JT. Inflammation and matrix metalloproteinases in the enlarging abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol 1995; 15:1145-51.
3. Diehm N, Schmidli J, Dai-Do D, Baumgartner I. Current evidence and prospects for medical treatment of abdominal aortic aneurysms. VASA 2005;34:217-23.
4. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomized controlled trial. Lancet 2004;364:843-8.
5. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med 2004;351: 1607-18.
6. Arko FR, Lee WA, Hill BB, Olcott Ct, Dalman RL, Harris EJ, Jr, et al. Aneurysm-related death: primary endpoint analysis for comparison of open and endovascular repair. J Vasc Surg 2002;36:297-304.
7. Zarins CK, Crabtree T, Bloch DA, Arko FR, Ouriel K, White RA. Endovascular aneurysm repair at 5 years: Does aneurysm diameter predict outcome? J Vasc Surg 2006;44:920-29.
8. Brewster DC, Jones JE, Chung TK, Lamuraglia GM, Kwolek CJ, Watkins MT, et al. Long-term outcomes after endovascular abdominal aortic aneurysm repair: the first decade. Ann Surg 2006;244:426-38.
9. Sicard GA, Zwolak RM, Sidawy AN, White RA, Siami FS. Endovascular abdominal aortic aneurysm repair: long-term outcome measures in patients at high-risk for open surgery. J Vasc Surg 2006;44:229-36.
10. Jones KG, Brull DJ, Brown LC, Sian M, Greenhalgh RM, Humphries SE, et al. Interleukin-6 (IL-6) and the prognosis of abdominal aortic aneurysms. Circulation 2001;103:2260-5.
11. Vainas T, Lubbers T, Stassen FR, Herngreen SB, van Dieijen-Visser MP, Bruggeman CA, et al. Serum C-reactive protein level is associated with abdominal aortic aneurysm size and may be produced by aneurysmal tissue. Circulation 2003;107:1103-5.
12. Rohde LE, Arroyo LH, Rifai N, Creager MA, Libby P, Ridker PM, et al. Plasma concentrations of interleukin-6 and abdominal aortic diameter among subjects without aortic dilatation. Arterioscler Thromb Vasc Biol 1999;19:1695-9.
13. Norman P, Spencer CA, Lawrence-Brown MM, Jamrozik K. C-reactive protein levels and the expansion of screen-detected abdominal aortic aneurysms in men. Circulation 2004;110:862-6.
14. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet 2005;365:2187-92.
15. Lloyd GM, Newton JD, Norwood MG, Franks SC, Bown MJ, Sayers RD. Patients with abdominal aortic aneurysm: are we missing the opportunity for cardiovascular risk reduction? J Vasc Surg 2004;40: 691-7.
16. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
17. Schouten O, Kok NF, Hoedt MT, van Laanen JH, Poldermans D. The influence of aneurysm size on perioperative cardiac outcome in elective open infrarenal aortic aneurysm repair. J Vasc Surg 2006;44:435-41.
18. Brady AR, Fowkes FG, Thompson SG, Powell JT. Aortic aneurysm diameter and risk of cardiovascular mortality. Arterioscler Thromb Vasc Biol 2001;21:1203-7.
19. Peppelenbosch N, Buth J, Harris PL, van Marrewijk C, Fransen G. Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR. J Vasc Surg 2004;39:288-97.
20. Schouten O, van Waning VH, Kertai MD, Feringa HH, Bax JJ, Boersma E, et al. Perioperative and long-term cardiovascular outcomes in patients undergoing endovascular treatment compared with open vascular surgery for abdominal aortic aneurysm or iliaco-femoro-popliteal bypass. Am J Cardiol 2005;96:861-6.
21. Stenvinkel P. The role of inflammation in the anaemia of end-stage renal disease. Nephrol Dial Transplant 2001;16:36-40.
22. Nissenson AR, Goodnough LT, Dubois RW. Anemia: not just an innocent bystander? Arch Intern Med 2003;163:1400-4.
23. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-23.

24. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002;13: 1928-36.
25. Langston RD, Presley R, Flanders WD, McClellan WM. Renal insufficiency and anemia are independent risk factors for death among patients with acute myocardial infarction. Kidney Int 2003;64:1398-405.
26. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12,065 patients with new-onset heart failure. Circulation 2003;107:223-5.
27. Matzner Y, Levy S, Grossowicz N, Izak G, Hershko C. Prevalence and causes of anemia in elderly hospitalized patients. Gerontology 1979;25: 113-9.
28. Salive ME, Cornoni-Huntley J, Guralnik JM, Phillips CL, Wallace RB, Ostfeld AM, et al. Anemia and hemoglobin levels in older persons: relationship with age, gender, and health status. J Am Geriatr Soc 1992;40:489-96.
29. Weiss G. Pathogenesis and treatment of anaemia of chronic disease. Blood Rev 2002;16:87-96.
30. Newman KM, Jean-Claude J, Li H, Ramey WG, Tilson MD. Cytokines that activate proteolysis are increased in abdominal aortic aneurysms. Circulation 1994;90:224-7.
31. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991;5: 491-9.
32. Katzen BT, Dake MD, MacLean AA, Wang DS. Endovascular repair of abdominal and thoracic aortic aneurysms. Circulation 2005;112: 1663-75.
33. World Health Organization. Nutritional anemias: Report of a WHO Scientific Group. Geneva, Switzerland; 1968.
34. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg 2002;35:1048-60.
35. Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg 1986;4:80-94.
36. Moore WS, Matsumura JS, Makaroun MS, Katzen BT, Deaton DH, Decker M, et al. Five-year interim comparison of the Guidant bifurcated endograft with open repair of abdominal aortic aneurysm. J Vasc Surg 2003;38:46-55.
37. Faries PL, Brener BJ, Connelly TL, Katzen BT, Briggs VL, Burks JA, Jr, et al. A multicenter experience with the Talent endovascular graft for the treatment of abdominal aortic aneurysms. J Vasc Surg 2002;35: 1123-8.
38. Najibi S, Steinberg J, Katzen BT, Zemel G, Lin PH, Weiss VJ, et al. Detection of isolated hook fractures 36 months after implantation of the Ancure endograft: a cautionary note. J Vasc Surg 2001;34:353-6.
39. Matsumura JS, Katzen BT, Hollier LH, Dake MD. Update on the bifurcated EXCLUDER endoprosthesis: phase I results. J Vasc Surg 2001;33:S150-3.
40. Jongen-Lavrencic M, Peeters HR, Wognum A, Vreugdenhil G, Breedveld FC, Swaak AJ. Elevated levels of inflammatory cytokines in bone marrow of patients with rheumatoid arthritis and anemia of chronic disease. J Rheumatol 1997;24:1504-9.
41. Newman KM, Jean-Claude J, Li H, Ramey WG, Tilson MD. Cytokines that activate proteolysis are increased in abdominal aortic aneurysms. Circulation 1994;90:II224-7.
42. Shteinberg D, Halak M, Shapiro S, Kinarty A, Sobol E, Lahat N, et al. Abdominal aortic aneurysm and aortic occlusive disease: a comparison of risk factors and inflammatory response. Eur J Vasc Endovasc Surg 2000;20:462-5.
43. Kragsterman B, Bjorck M, Lindback J, Bergqvist D, Parsson H. Long-term survival after carotid endarterectomy for asymptomatic stenosis. Stroke 2006;37:2886-91.
44. van Wijk I, Kappelle LJ, van Gijn J, Koudstaal PJ, Franke CL, Vermeulen M, et al. Long-term survival and vascular event risk after transient ischemic attack or minor ischemic stroke: a cohort study. Lancet 2005;365:2098-104.
45. Brenner H, Stegmaier C, Ziegler H. Long-term survival of cancer patients in Germany achieved by the beginning of the third millenium. Ann Oncol 2005;16:981-6.
46. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45:S5-S67.
47. Ganz T. Molecular control of iron transport. J Am Soc Nephrol 2007;18:394-400.
48. Konijn AM, Carmel N, Levy R, Hershko C. Ferritin synthesis in inflammation. II. Mechanism of increased ferritin synthesis. Br J Haematol 1981;49:361-70.
49. Kertai MD, Boersma E, Westerhout CM, van Domburg R, Klein J, Bax JJ, et al. Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. Am J Med 2004;116: 96-103.
50. Leurs LJ, Visser P, Laheij RJ, Buth J, Harris PL, Blankensteijn JD. Statin use is associated with reduced all-cause mortality after endovascular abdominal aortic aneurysm repair. Vascular 2006;14:1-8.
51. Nagashima H, Aoka Y, Sakomura Y, Sakuta A, Aomi S, Ishizuka N, et al. A 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, cerivastatin, suppresses production of matrix metalloproteinase-9 in human abdominal aortic aneurysm wall. J Vasc Surg 2002;6:158-63.
52. Steinmetz EF, Buckley C, Shames ML, Ennis TL, Vanvickle-Chavez SJ, Mao D, et al. Treatment with simvastatin suppresses the development of experimental abdominal aortic aneurysms in normal and hypercholesterolemic mice. Ann Surg 2005;241:92-101.
53. Wilson WR, Evans J, Bell PR, Thompson MM. HMG-CoA reductase inhibitors (statins) decrease MMP-3 and MMP-9 concentrations in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2005;3:259-62.
54. Schrier S. Anemia of chronic disease (anemia of inflammation). In: www.uptodate.com; accessed March 2007.

Submitted Apr 24, 2007; accepted Jun 10, 2007.