Factors Affecting Long-term Mortality After Endovascular Repair of Abdominal Aortic Aneurysms

Christian de Virgilio, MD; Julie Tran, MD; Roger Lewis, MD, PhD; Carlos Donayre, MD; Christine Dauphine, MD; Rodney White, MD; Hao Bui, MD

Hypothesis: Endovascular repair of abdominal aortic aneurysms has made considerable advancements with respect to perioperative mortality. However, fewer data are available regarding factors affecting long-term mortality, including the impact of adverse perioperative cardiac events. Perioperative clinical cardiac risk factors are significant predictors of long-term mortality.


Main Outcome Measures: Preoperative, intraoperative, and postoperative factors were analyzed using multivariate Cox proportional hazards models to identify statistically significant independent predictors of long-term survival (beyond 30 days and after discharge from the hospital).

Results: The mean age was 74 years, and 90% of the patients were male. Median follow-up was 2.57 years (interquartile range, 0.92-4.06 years). The leading cause of death was cardiac in nature. On multivariate analysis, the number of preoperative clinical cardiac risk factors ($P<.001$), spending 2 or more days in the intensive care unit ($P<.001$), and having an ST-segment elevation myocardial infarction ($P<.001$) were predictors of decreased long-term survival. Of note, having a perioperative non-ST-segment elevation myocardial infarction was not predictive of decreased survival ($P=.09$).

Conclusions: Adverse cardiac events are the leading cause of long-term mortality following endovascular repair of abdominal aortic aneurysms. Preoperative clinical cardiac risk factors are significant predictors of long-term mortality, as are a prolonged intensive care unit stay and a perioperative ST-segment elevation myocardial infarction. A perioperative non-ST-segment elevation myocardial infarction did not influence long-term outcome.

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IN THE PAST DECADE, ENDOVASCULAR abdominal aortic aneurysm (AAA) repair (EVAR) has rapidly evolved. Despite the increasing popularity of EVAR, some controversy remains regarding its long-term efficacy. Recent studies comparing open AAA repair and EVAR indicate that the 30-day mortality after EVAR is at least two thirds less than open repair. With at least a 2-year follow-up, however, patients in the EVAR group had a higher rate of reinterventions and there was no difference in cumulative survival rates. The EVAR Trial Participants confirmed this finding, noting that 4 years after randomization, there was no difference in all-cause mortality between open AAA repair and EVAR. Schouten et al demonstrated that adverse cardiac events remain a major source of long-term morbidity and mortality following EVAR, and outcomes in patients undergoing EVAR were not different from those in patients undergoing open AAA repair. The purpose of our study was to determine whether preoperative, operative, and immediate perioperative factors were predictive of long-term mortality in a large group of patients undergoing EVAR.

METHODS

STUDY DESIGN

This clinical investigation was undertaken to determine the perioperative, operative, and postoperative factors that affect long-term mortality after EVAR. The study was approved by the human subjects committee of the Los Angeles Biomedical Institute (the research arm of Harbor-UCLA Medical Center, Torrance, Calif). A retrospective analysis of a prospective database was conducted, and it included preoperative, intraoperative and immediate postoperative factors. Twenty-five variables that were thought to be important were selected for...
univariate analysis and were analyzed to determine whether they contributed to overall mortality on long-term follow-up.

**PATIENT POPULATION**

Consecutive patients who underwent elective endovascular repair of an infrarenal AAA between June 3, 1996, and January 31, 2005, were identified through an institutional database. Patients with thoracic, suprarenal, or ruptured aneurysms were excluded, as were those undergoing emergent repair.

**CLINICAL FACTORS**

The examined preoperative factors included age, sex, number of clinical cardiac risk factors (age >70 years, angina, diabetes mellitus, history of myocardial infarction or Q wave on an electrocardiogram as defined by Eagle and colleagues,5-7 and history of congestive heart failure [CHF]), size of the AAA, American Society of Anesthesiology class, serum creatinine level, and perioperative use of β-blockade.

Examined intraoperative factors included anesthetic type (local, general, or epidural), development of intraoperative hypotension (defined as systolic blood pressure <100 mm Hg), and length of anesthesia time.

Postoperative data were divided into 2 categories: perioperative events (within 30 days or during the same index hospitalization) and death from any cause beyond that time. Perioperative factors included length of intensive care unit (ICU) stay, total length of stay, adverse cardiac events, cardiac death, and death from all causes. An adverse perioperative event was defined as an event that occurred either within 30 days after the surgery or during the same index hospitalization. Cardiac events included ST-segment elevation myocardial infarction (MI) (STEMI), non-STEMI, and CHF. A non-STEMI was defined as a peak creatinine kinase-MB fraction to more than 5% and a troponin level of 2 ng/mL in the absence of changes on the electrocardiogram. A STEMI was defined as one of the following factors: (1) same elevations of cardiac enzymes; (2) addition of new Q waves or persistent ST-segment changes on the electrocardiogram; and (3) characteristic ischemic symptoms lasting more than 20 minutes. Congestive heart failure was defined as signs or symptoms of pulmonary congestion, new left or right ventricular failure, or abnormal chest radiographic findings. A major arrhythmia was defined as one necessitating ICU care or resulting in a decrease in systolic blood pressure to less than 90 mm Hg. Cardiac death was defined as death secondary to a cardiac complication. The primary endpoint of the study was death due to any cause beyond 30 days and after hospital discharge.

**STATISTICAL ANALYSIS**

All of the statistical analyses were performed using SAS version 8.2 software (SAS Institute, Cary, NC). Data were translated from the database format to native SAS format. Numeric data are described using means and medians with interquartile ranges. Kaplan-Meier survival curves were used to describe the survival curves for defined subpopulations, and the log-rank test was used to make univariate comparisons of these survival curves. Multivariate Cox proportional hazards models were used to determine the independent associations of potential predictors with survival time.

Because of the finite number of patients included in the database and because we used all available data, no power or sample size calculation was performed. However, given the medically important and statistically significant differences observed, we believe that the study was adequately powered to detect meaningful differences in median survival between groups of patients.

**RESULTS**

**PATIENT CHARACTERISTICS**

During the 11-year period, 468 patients underwent elective infrarenal AAA repair. The mean ± SD age was 74 ± 8 years, and 90% of the patients were male. The mean ± SD AAA size was 55.8 ± 10.5 mm. Median follow-up was 936 days (interquartile range, 335-1479 days). Patient variables including clinical cardiac risk factors, intraoperative factors, and immediate postoperative events are presented in Table 1. Eighty-five percent of the patients had at least 1 clinical cardiac risk factor, and 36% had 2 or more risk factors. Local anesthesia with intravenous sedation was the mode of anesthesia in 62% of the patients. Forty patients (9%) had a perioperative MI, including 27 non-STEMIs (6%) and 13 STEMIs (3%). Twenty patients (4%) developed perioperative CHF.

**CAUSES OF DEATH**

Twenty deaths occurred in the perioperative period and were thus excluded from the long-term analysis. Of these 20 deaths, 11 (55%) had causes determined to be cardiac or pulmonary. On long-term follow-up, an addi-
tional 120 patients died. The leading cause of death on long-term follow-up was cardiac in nature (34 patients [28%]), followed closely by malignant disease (30 patients [25%]), then pulmonary complications (8 patients [7%]), and lastly, late rupture (6 patients [5%]). Other causes of long-term death included renal failure (4 patients [3%]), sepsis (4 patients [3%]), dissecting aortic aneurysm (2 patients [2%]), and mesenteric thrombosis (1 patient [1%]). The cause of death was unknown in 31 cases (26%). The mean ± SD overall 5-year survival was 62.4% ± 3.7% (95% confidence interval, 55.2%-69.5%).

UNIVARIATE ANALYSIS

Preoperative factors associated with decreased long-term survival included history of Q wave on an electrocardiogram, being older than 70 years, history of CHF, and an American Society of Anesthesiology class of 4 or higher. Angina approached significance (P = .05). Intraoperative hypotension was associated with decreased long-term survival whereas length of anesthetic time and anesthetic type were not. Immediate postoperative factors associated with decreased long-term survival included a prolonged ICU stay (≥2 days), long length of stay (≥5 days), perioperative STEMI, and perioperative CHF. Non-STEMI was not associated with decreased long-term survival. Median survival for patients with and without these variables is shown in Table 2.

MULTIVARIATE ANALYSIS

Multivariate analysis revealed that only the number of clinical cardiac risk factors (hazard ratio, 1.38; 95% confidence interval, 1.17-1.62), a longer ICU stay (hazard ratio, 2.11; 95% confidence interval, 1.38-3.24), and the development of a STEMI in the perioperative period (hazard ratio, 3.54; 95% confidence interval, 1.35-9.30) were associated with decreased long-term survival. Survival curves by the number of clinical cardiac risk factors are shown in the Figure.

The endovascular technique has emerged as a less invasive approach for the repair of infrarenal AAAs. Recent studies indicate that perioperative mortality for EVAR is significantly lower (1.2%) than for conventional open repair (4.6%). Fewer data are available regarding the long-term results of EVAR. Blankensteijn et al reported that the cumulative survival rates for EVAR and open repair were nearly identical after a 2-year follow-up, suggesting that nonaneurysm mortality continues to claim patients in the long term. As such, our study sought to determine whether perioperative factors were predictive of an increased risk of long-term mortality. In our large series of 468 patients undergoing EVAR, we found several perioperative factors associated with decreased long-term survival: the number of preoperative clinical risk factors, an ICU stay of 2 or more days, and a perioperative CHF.
ional cardiac risk factor (diabetes, history of MI, history of CHF, age > 70 years, and angina). Interestingly, a perioperative non-STEMI was not associated with decreased long-term survival.

Several studies have investigated the primary causes of death after AAA repair. Blankensteijn et al. found that in the immediate perioperative period, most deaths after open repair were aneurysm related, such as bleeding, multiple organ failure, and ischemic bowel, whereas cardiovascular events remained the leading cause of death after both open AAA repair and EVAR after hospital discharge. Cardiac and pulmonary events were the primary causes of death in the perioperative period in our study. Schouten et al. reported a higher rate of cardiac events in the perioperative period for open AAA repair (21.8%) as compared with EVAR (3.1%). However, on long-term follow-up, the cardiovascular event rate for EVAR significantly increased and was similar to that for open repair (16% vs 19%, respectively), offsetting some of the early benefit of EVAR. In a large single-center study of open AAA repair, Hertz et al. reported 5-year survival of 79% and 10-year survival of 49%. The primary causes of long-term mortality in their study were cardiac events (23%) and malignancy (20%). MeNard et al. reported cumulative 5-year survival of 68%, with cancer and cardiac events the primary causes of death as well. Similarly, in our study, 28% of the long-term deaths were cardiac and 23% were due to malignant disease, with 5-year survival of 62%.

Clinical cardiac risk factors have been found to be useful predictors of perioperative cardiac events following numerous types of vascular procedures. Eagle et al. reported a 3.1% adverse cardiac event rate for patients with 3 or more clinical markers following major vascular surgery. Focusing on EVAR, de Virgilio et al. found a 22% major perioperative cardiac event rate for patients with 2 or more clinical cardiac risk factors vs only 3.4% for those who had 1 or no risk factors. Other studies have similarly emphasized the important predictive value of multiple clinical cardiac risk factors for perioperative cardiac events. Our study sought to determine whether these same clinical risk factors were useful in predicting long-term survival after EVAR. Interestingly, median survival decreased from 2292 days in patients with 1 clinical risk factor to only 949 days in those with 5 risk factors (P < .001). To our knowledge, this is the first study that has demonstrated the correlation between these clinical risk factors and long-term survival after EVAR.

We found that a perioperative STEMI was a predictor of decreased long-term survival whereas a perioperative non-STEMI was not. Considerable controversy exists regarding the significance of a postoperative non-STEMI. Yeager et al. found that patients surviving a perioperative STEMI after peripheral vascular surgery had a higher incidence of subsequent adverse cardiac events and coronary artery revascularization than patients undergoing vascular surgery who did not experience a perioperative MI. However, the study found that both groups had similar survival rates at long-term follow-up. Patients who had an asymptomatic perioperative “chemical MI” had a long-term outcome similar to patients who had no MI, suggesting that a perioperative chemical MI may not be a significant clinical event. Our findings support the observations made by Yeager and colleagues regarding the significance of a non-STEMI and suggest that in the absence of postoperative symptoms, it is unnecessary to obtain serial cardiac enzyme levels after EVAR. Conversely, the impact of a STEMI on long-term survival was highly significant (hazard ratio, 3.54) in our study. Although this might argue for a more aggressive approach to preoperative coronary intervention, a recent prospective, randomized study showed no benefit to preoperative coronary revascularization prior to vascular surgery. Furthermore, only 13 patients (3%) in our study had a postoperative STEMI, and as such, it is doubtful that aggressive preoperative coronary intervention would help the group as a whole. On the other hand, once a patient develops a STEMI postoperatively, these patients need close cardiac monitoring. Whether patients with a postoperative STEMI after EVAR would benefit from postoperative coronary intervention remains unclear and is deserving of further investigation.

There are certain limitations to our study. The study was a retrospective review of a prospective database, so complete follow-up for all of the patients could not be obtained. Causes of death were sometimes unclear, as they were determined by death certificates. For this reason, we analyzed all-cause mortality rather than attempting to limit long-term mortality to cardiac causes.

In summary, our results confirm that cardiovascular events remain a major source of mortality after EVAR. Long-term survival is influenced by several preoperative and immediate postoperative factors such as the number of clinical cardiac risk factors, the development of a perioperative STEMI, and a prolonged ICU stay. It is unclear whether more aggressive treatment of patients with a postoperative STEMI will improve survival, but this warrants further investigation. Finally, given the seemingly benign nature of a postoperative non-STEMI, postoperative cardiac enzyme screening may be unnecessary in asymptomatic patients.

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Correspondence: Christian de Virgilio, MD, Department of Vascular Surgery, 1000 W Carson St, Box 25, Torrance, CA 90509 (cdevirgilio@labiomed.org).

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REFERENCES


I have a number of questions for the authors.

You state that the cause of death was determined by a death certificate. How confident are you that the cause of death as gleaned from a death certificate is true? In many patients, the exact cause of death is unknown, and in patients with known CAD [coronary artery disease], many physicians just assume that the death is cardiac related. This is even more true in this present time when autopsies are rare.

How complete is your data set concerning CPK [creatine phosphokinase]–MB and troponin values? On univariate analysis, the P value was .09. Since the database used goes back to 1996 when the routine use of troponins was not practiced, are you sure that you did not miss clinically silent myocardial injury due to the early reliance on the less-sensitive CPK-MB? Would more troponin data have provided statistical significance? Have you looked at the predictability of troponins alone with regards to late cardiac death? Even if these markers are not helpful in predicting late cardiac death, do they still not have a role in the perioperative recognition of silent cardiac ischemia that may progress to clinically evident ischemia and lead to both early and late cardiac mortality?

It is impressive that over 50% of patients undergoing EVAR did so under local anesthesia with sedation. There was no difference in late deaths in patients undergoing local vs general anesthesia even though you would assume that the general anesthetic was more stressful and would lead to more perioperative STEMI events. Was there a difference in early perioperative deaths between the 2 anesthetic approaches, and what is your overall early mortality for EVAR in your experience? What is the primary cause of early death; is it cardiac as well?

One of the concerns with EVAR is delayed rupture, but this number is not mentioned in the manuscript as a cause of late death, although you state today that the delayed rupture rate and death was 5%. This rate of delayed rupture is significantly higher than what is reported by many other centers, including our own. Could you please clarify and provide us with the overall delayed rupture rate for EVAR at Harbor-UCLA?

You do not mention in the manuscript whether you routinely use perioperative β-blockade or statins, and you found that β-blockade was not an important factor in late death. Could you please comment on the use of β-blockade and statins in the EVAR patient population and vascular surgery in general, since others have shown these drugs may lower the incidence of both short- and long-term cardiac events?

Finally, now that you have established that you can identify a patient population following EVAR that is at risk for cardiac death, how will you use this information to minimize late cardiac mortality and increase the long-term benefit of EVAR? And, are these findings applicable to other reconstructive vascular surgical procedures as well?

In conclusion, this report and others suggest that the less stressful and less invasive nature of EVAR provides a decrease in fatal perioperative cardiac events, but in patients with critical cardiac disease, it only delays the inevitable. This is consistent with the observation that the perioperative management of cardiac risk using β-blockade and statins has a positive effect not only on short-term outcome but also on long-term survival. In fact, there is sufficient evidence to suggest that the real benefit of these perioperative maneuvers is the amelioration of the long-term manifestations of existing coronary artery disease. Therefore, in addition to the usual admonitions to patients to stop smoking and pay attention to the management of their hypertension and diabetes, we as vascular surgeons need to be proactive and interested in the medical management of atherosclerosis in order to maximize the long-term benefit of our operative interventions.

Cornelius Olcott, MD, Stanford, Calif: I suspect that the information Dr Tran gave us today is from the initial proce-
dure. As you know, many of these EVAR patients require more than 1 procedure in order to deal with endoleaks, migration, and the like. Did these multiple procedures influence the number of cardiac complications and/or the mortality rate?

Ronald G. Latimer, MD, Santa Barbara, Calif: To follow up on the smoking question: since there were late deaths, what was the percentage of patients who stopped smoking after their vascular procedures? Then, a question about malignancy: this seemed to be the second cause of death in these patients. What types of malignancies were there, and were there any indications that these patients needed to be screened for the malignancies?

G. Andrew Macbeth, MD, Stockton, Calif: I would be interested in knowing if they had a sense in those patients who were accepted as anatomic candidates for EVAR, how many had formal preoperative coronary artery evaluation in addition to the standard preoperative EKG? I would also be interested in knowing if you think that the advent of 64-slice CTA [computed tomographic angiography] will result in coronary CTA replacing the nebulous, equivocal persantine thallium studies in the preoperative cardiac workup.

Dr de Virgilio: Dr Weaver brings up some very important points with regards to the cause of death. As I mentioned before, the study was a retrospective review of a prospective database that was compiled by research nurses who made a diligent effort to obtain complete follow-up. However, the difficulty in determining the cause of death is the lack of autopsies, as pointed out by Dr Weaver, and the incomplete nature of death certificates. So admittedly, some of these deaths that were recorded as cardiac arrests may have been due to a ruptured aneurysm. For this reason, the primary endpoint of our study was death from any cause and not specifically cardiac mortality.

With regards to the troponins and the CPK-MBs, Dr Weaver brings up another good point that early on in our experience, we were using CPKs and this then shifted over to using troponins. As you are all aware, the troponin level is a more sensitive indicator of minor cardiac injury, and thus some patients with silent ischemia may have been missed in the earlier phase of our study. I doubt, however, that this would have altered our findings, which demonstrate that having a perioperative non-STEMI did not decrease long-term survival.

With respect to the perioperative mortality with the 2 anesthetic approaches, Dr Weaver mentioned that about 50% of our patients are done under local. I need to qualify that by stating that our center was 1 of the first centers in the US [United States] that performed EVAR, and for the first several years, we served as a referral base for patients who were considered too high risk to be done via the open approach, and these early deaths may have raised the mortality.

Another point that Dr Weaver brought up is the issue of late rupture. The slide we showed may have been misinterpreted. There were 6 late deaths due to rupture, which represents 5% of all late deaths. However, the overall late rupture rate was only 1.2%.

With respect to β-blockade, early on in the study, we were not using β-blockade routinely. It has now become our policy, with the more recent literature, that we use β-blockade routinely. There are numerous studies that demonstrate the use of statins and β-blockade can in fact reduce perioperative as well as long-term cardiac morbidity and mortality.

I think our study brings up the point that cardiac morbidity and mortality long term remain an important problem following AAA repair whether the repair is endovascular or open. I think the study emphasizes that we as vascular surgeons need to continue to follow our patients, and we need to focus on the long-term medical management of vascular disease. It is incumbent upon us to take the lead with respect to the medical management of our patients, including the long-term use of β-blockade, statins, and smoking cessation programs.

Dr Olcott brought up an important point, which is that the EVAR patients will frequently need more than 1 procedure. I believe that’s why when you look at the perioperative mortality for EVAR, it is significantly less than for open repair, but when you look at the long-term mortality, EVAR is the same as open. I think the explanation for this, as has been highlighted in other studies, is the EVAR patients often are going to need reinterventions, and each reintervention adds additional stress and anesthetic risk. However, we did not specifically, in this study, look at which patients needed additional procedures.

Dr Latimer brought up a very important point which is that the need for us, as vascular surgeons, to encourage smoking cessation. This is highlighted by the fact that lung cancer was the primary malignancy detected in our patients.

Another comment was made regarding the role of coronary revascularization in these patients. Our policy has been in fact not to pursue preoperative coronary revascularization. There is a recent randomized study from the New England Journal of Medicine last year indicating that preoperative coronary revascularization has no benefit with respect to lowering cardiac morbidity and mortality. So, we actually have a protocol in place now where we β-block patients, control the heart rate, and place them on statins, and then proceed directly to surgery without any revascularization. Our own prospective, blinded studies have indicated that thallium stress testing is of no benefit and has limited predictive value.