Zenith abdominal aortic aneurysm endovascular graft

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Purpose: **The safety and efficacy of the Zenith (Cook Inc, Bloomington, Ind) endovascular graft was assessed based on the United States multicenter trial through 5 years of follow-up.**

Methods: **Between 2000 and 2003, the pivotal study enrolled patients to open surgery (control) or the Zenith endovascular graft (endovascular). A separate continued access study arm enrolled endovascular patients using the same inclusion/exclusion criteria. Both studies were designed for 2-year follow-up, and the pivotal endovascular patients had the option of extending the study follow-up through 5 years. All endovascular patients were stratified by physiologic risk into high-risk and standard-risk groups to assess overall mortality, rupture, conversion, endoleaks, secondary interventions, and sac enlargement. The entire endovascular cohort was pooled to assess device integrity, limb occlusion, component separation, and migration. The suboptimal endovascular result (SER) was established as an end point to assess late adverse outcomes. Statistical analyses included Kaplan-Meier estimations and Cox regression to assess factors contributing to sac enlargement and SER.**

Results: **The study enrolled 739 endovascular patients (352 pivotal, 387 continued access); 158 patients in the pivotal study reconsented to be followed up for 5 years. For the patients at standard and high risk at 5 years, the respective survival estimate was 83% and 61%, aneurysm-related death was 2% and 4%, and freedom from rupture was 100% and 99.6%, respectively. Cumulative risk of conversion, limb occlusion, migration >10 mm, or component separation was ≤3% at 5 years. Cumulative risk of late endoleak was 12% to 15%, representing the primary indication for secondary interventions which occurred in 20% of standard-risk patients and 25% of high-risk patients through 5 years. Sac enlargement was very rare and associated with advanced age and larger aneurysms. SER was predicted by advanced age and internal iliac artery occlusion.**

Conclusion: **These middle- and long-term data support long-term durability of the Zenith endovascular graft. Risk of aneurysm-related death or rupture was exceptionally low, and complications of migration, limb occlusion, and device integrity issues were uncommon. Incidence of late endoleaks and association of endoleaks with sac growth underscore the need for long-term follow-up of patients treated with endovascular grafts, although the sequelae of such events are unknown. (J Vasc Surg 2008;48:1-9.)**

Long-term results after endovascular aneurysm repair are essential to affirm durability of the intent to diminish risk of rupture and aneurysm-related death. The continuous evolution of implant design during the course of clinical trials may affect the relevance of long-term data. Unlike most other commercially available stent grafts, the Zenith device (Cook Inc, Bloomington, Ind) has undergone remarkably few changes since its introduction in 1997. Nevertheless, there is a paucity of published information on the long-term performance of the current device. Reports from Australia have included data on predicate designs,[1] and only two centers in the United States (US) had access to the Zenith stent graft before the US pivotal Zenith Multicenter Trial (ZMT) in 2000.[2] The primary end point of this study was a comparison of the morbidity between the surgical control arm and the standard-risk endovascular arm at 30 days and at 1 year. The initial analysis of the pivotal trial was reported in 2004, shortly after the device was approved for commercial use in the United States.[3]

In addition to the initial ZMT report, several analyses have further delineated the device performance in a variety of patient populations. These include an assessment of late complications,[4] the effects of the suprarenal stent on renal function,[5] stent graft oversizing on neck dilation,[6] gender on overall outcome,[7] large iliac limb diameters on iliac

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Competition of interest: Dr Greenberg has received grant and research support, consulting fees, and licensed intellectual property to Cook Inc. Dr Chuter has received research support, consulting fees, and licensed intellectual property to Cook Inc. Dr Sternbergh and Dr Cambria have received research support from Cook Inc for their Zenith and TX2 endograft trials. Dr Fearnot is employed by MED Institute, a Cook Group company.

Additional material for this article may be found online at www.jvascsurg.org.

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0741-5214/$34.00

doi:10.1016/j.jvs.2008.02.051

dilatation,[8] and the management of type II endoleaks.[9] The effect of physiologic risk and challenging anatomic factors were also evaluated with regard to morphologic outcomes,[10] and other reports assessed a variety of factors and late outcomes in the context of other endovascular grafts.[11-13]

The infrarenal device used in the ZMT construct has also become a platform to develop endovascular grafts to treat more complex aneurysms, including devices with fenestrations intended to allow the treatment of juxtarenal[14,15] and thoracic aneurysms,[16] and branched devices used to treat thoracoabdominal aneurysms.[17-19] Design modifications have allowed for the ability to preserve antegrade internal iliac arterial flow in the setting of common iliac aneurysms.[20-22] We analyzed later outcomes (up to 5 years) of infrarenal aneurysms treated in the US pivotal study with the initial infrarenal device construct and also in a continued access study that enrolled patients using identical inclusion/exclusion criteria and stratification regimen. Patients in the pivotal study were monitored for up to 5 years, and patients in the continued access study were monitored to 2 years. In this article we report the extended follow-up data from both the pivotal and continued access studies.

MATERIAL AND METHODS

The US Zenith abdominal aortic aneurysm (AAA) Endovascular Graft pivotal study was a 2-year controlled trial that enrolled 432 patients who were treated with open surgery (control) or the Zenith endovascular graft (endovascular); the latter group was stratified by physiologic risk into high-risk and standard-risk groups. The details of the study design, high-risk criteria, and inclusion and exclusion criteria were previously published.[3] The primary study end point was a comparison of the morbidity between the surgical control arm and the standard-risk endovascular arm at 30 days and 1 year. The device received US Food and Drug Administration (FDA) approval in May 2003.

Patient enrollment after the pivotal cohort was allowed within a separate continued access study arm, within which patients were enrolled with the same inclusion and exclusion criteria and allocated into high- and standard-risk groups, in a manner identical to that in the pivotal study. However, sites participating in the continued access arm of the trial were not required to submit preoperative films for review and sizing to a centralized site, providing an avenue for greater implanting physician independence. After device approval, pivotal patients were given the option of extending the study follow-up through 5 years, whereas continued-access patients were monitored for only 2 years.

All participating patients were required to sign an informed consent document approved by the respective institutional review boards. A core laboratory was responsible for the independent assessment of all imaging studies, and a clinical events committee was responsible for review and adjudication of all events reported during the course of the trial. A data safety monitoring board reviewed the results according to an enrollment schedule and allowed the study to progress to completion.

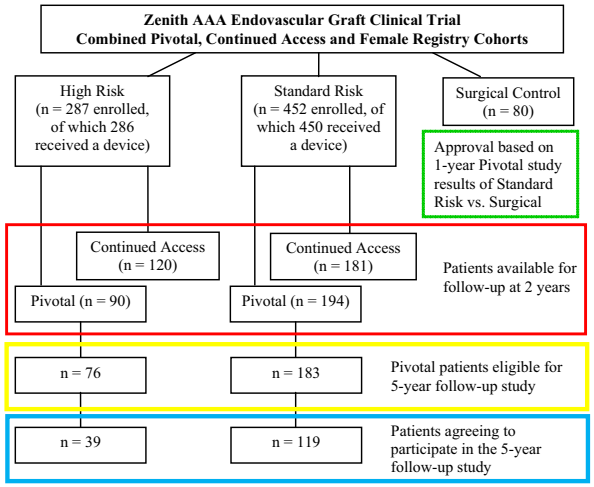

Fig 1. Enrollment in the United States Zenith Multicenter Trial (ZMT). The pivotal portion of the trial included 80 surgical controls, 200 standard-risk endovascular patients, 100 high-risk endovascular patients, and 52 patients allocated to the roll-in arm. After pivotal enrollment was completed, continued access was provided through a separate study arm. At the conclusion of the 2-year follow-up, pivotal patients were given the opportunity to participate in an extended follow-up study carrying out annual assessments through 5 years. The various categories of the trial resulted in three fundamental patient groups: surgical controls, standard-risk endovascular, and high-risk endovascular. For analysis purposes, the roll-in, pivotal study, and continued access groups were combined into conglomerate standard- and high-risk endovascular groups, with a variable degree of follow-up. This flow chart shows enrollment and follow-up details. *AAA,* Abdominal aortic aneurysm.

Enrollment criteria for the pivotal and continued access studies were identical. Moreover, a statistical analysis showed that data from the two studies were poolable (Table I, online only). Patients in both studies were categorized into standard- and high-risk groups by fitness for surgery (physiologic risk). For the purpose of data analysis, it was assumed that a patient's physiologic state would have no bearing on outcomes such as device integrity, limb occlusion, and component separation and migration, which definitively relate to long-term device performance. These outcomes were assessed using pooled data from both risk categories.

Outcomes considered physiologic risk–dependent included death, rupture, conversion, endoleak, secondary interventions, and sac enlargement. Indeed, differences in outcomes with this device between patients at high and standard physiologic risk have been previously published with respect to survival,[23] sac behavior, and endoleaks.[10] For risk-dependent outcomes, the standard- and high-risk groups were analyzed separately; however, data were still combined from the pivotal and continued access studies.

Specific endovascular outcomes are reported in accordance with the most recent version of the endovascular

reporting standards document,[24] except when detailed. Aneurysm-related deaths included any patients who died ≤30 days of the primary procedure or any secondary procedure, and patients outside of that window whose deaths were considered by the clinical events committee to be potentially related to the procedure or device.

The methods for determining device migration are detailed in a previously published article.[25] For completeness, both 5-mm and 10-mm cutoffs are reported. Device integrity issues refer to holes in the fabric, separation (fracture) of the barbs, and fractures of the z-stents. Endoleaks were considered late occurring only if no endoleak had been identified on postprocedural cross-sectional imaging studies before the 6-month examination.

For this study, a conglomerate end point, termed the suboptimal endovascular result (SER), was created with the intention of assessing the risk that a potentially adverse outcome would develop after endovascular repair. This end point was intended to assess which patients derived any benefit from scheduled follow-up visits or interventions. This end point included AAA-related death, rupture, conversion, migration >10 mm, limb thrombosis, the development of a late endoleak, or the need for any aneurysm-related secondary intervention. The early identification of patients who are at risk for reaching this end point has significant implications on the optimal follow-up protocols.

Data were managed by MED Institute, a Cook Group company. All statistical analyses were performed using SAS 8.2 software (SAS Institute, Cary, NC). Standard tabulations of data included means, standard deviations, and percentages, where applicable. Poolability was determined by comparing the continued access groups with the pivotal trial groups. Kaplan-Meier life-tables were constructed to assess for differences between the standard- and high-risk patient cohorts and, where appropriate, for clinical and imaging outcome variables.

Patients are censored at their last known date of follow-up. For outcomes other than death, the last known date of follow-up includes the date of death. A Cox regression model was developed to determine the relationship between the time and occurrence of maximum measured aneurysm enlargement and the relevant covariates of interest included in the standard- and high-risk patient cohorts. A similar Cox regression analysis was used to assess preoperative patient characteristics as potential predictors of the time and occurrence of an SER. For both Cox analyses, individual factors were first analyzed by a univariate model. Individual factors with a value of $P < .15$ from the univariate analysis were included in an additional multivariate step-wise Cox regression analysis. A significance level of $P = .05$ was used to identify significant results from both univariate and multivariate analyses.

RESULTS

The study began in January 2000 and was completed in June 2003 after the enrollment of 819 patients, of which 80 were standard-risk surgical controls. Of the 739 enrolled endovascular patients, 736 underwent successful implantation of a Zenith AAA stent graft, and three implantations were aborted due to iliac artery morphology not appreciated before the procedure. Two of these patients were successfully treated with open repair, and one patient elected to have no intervention for the AAA. At 2 years, 610 patients were alive and participating in the trial. Of the 88 patients who died, 7 had been converted, 1 did not receive the device, and 33 were lost to follow-up. From the survivors, 259 patients were candidates for the 5-year study, and 158 patients provided voluntary consent (Fig 1). The continued access group was considered to be poolable with the pivotal trial group based on statistical analyses that demonstrated only two differences between the groups, consisting of a slightly higher incidence of myocardial infarctions and lower incidence of prior aortic surgery in the pivotal study group (Table I, online version only).

Death, rupture, and conversion. Table II provides a detailed analysis of freedom from death, rupture, and conversion through 5 years of follow-up. Fig 2 depicts Kaplan-Meier plots for all-cause mortality. Not surprisingly, the all-cause mortality rate was significantly higher in the high-risk group ($P < .001$). This was the only outcome in Table II to show a significant difference between the physiologic risk groups, although it is possible that differences were obscured by the rarity of many of these events.

Only one rupture occurred in the entire study cohort. The patient was successfully converted, as previously reported.[3] There were seven other conversions in the study, two of which occurred after failed stent graft insertions (as described previously). Two more conversions were performed to treat infection detected between 1 and 2 years, one conversion was for an additional visceral aortic aneurysm, and one was done to address a persistent proximal endoleak at 6 months. The only conversion that occurred >2 years resulted from late proximal neck dilation at 4 years of follow-up.

Migration, component separation, limb occlusion, and device integrity. Given that these adverse events were considered to be independent of physiologic risk, all endovascular patients were viewed as a conglomerate group. Device migration was categorized into movement of 5 mm and 10 mm, the latter of which relates to the endovascular reporting standards and most other device trials.[24] These results are detailed in Table III. Only two cases of migration of >10 mm occurred, both in the continued access group at their concluding follow-up of 2 years. No migrations >10 mm occurred in the pivotal study throughout the 5 years. Of the 19 patients where migration between 5 and 10 mm was noted at any time point, none underwent secondary procedures associated with the migration, continued to have migration, or had associated adverse events.

Component separation was rare, and only three patients experienced graft limb separation through 5 years. In two cases, disconnection of the uncovered top stent from the graft material necessitated placement of proximal extensions with new uncovered proximal fixation systems.

Limb occlusions were also rare, with a cumulative risk of 2.6% throughout the study course. Of note, all limb

Table II. Freedom from adverse endovascular events categorized by physiologic risk group (standard vs high risk) and expressed as Kaplan-Meier estimates, with standard errors listed in the parentheses

	Freedom from adverse event		
Group/exam period	*Rupture*	*Conversion*	*AAA-death*
High risk			
1-month	1.000 (0) (n = 283) (e = 0) (c = 4)	0.997 (0.003) (n = 283) (e = 1) (c = 3)	0.990 (0.006) (n = 283) (e = 3) (c = 1)
12-month	0.996 (0.004) (n = 252) (e = 1) (c = 34)	0.993 (0.005) (n = 252) (e = 2) (c = 33)	0.968 (0.010) (n = 252) (e = 9) (c = 26)
24-month	0.996 (0.004) (n = 210) (e = 1) (c = 76)	0.988 (0.007) (n = 210) (e = 3) (c = 74)	0.964 (0.011) (n = 210) (e = 10) (c = 67)
36-month	0.996 (0.004) (n = 39) (e = 1) (c = 247)	0.988 (0.007) (n = 39) (e = 3) (c = 245)	0.964 (0.011) (n = 39) (e = 10) (c = 238)
48-month	0.996 (0.004) (n = 39) (e = 1) (c = 247)	0.988 (0.007) (n = 39) (e = 3) (c = 245)	0.964 (0.011) (n = 39) (e = 10) (c = 238)
60-month	0.996 (0.004) (n = 26) (e = 1) (c = 260)	0.988 (0.007) (n = 26) (e = 3) (c = 258)	0.964 (0.011) (n = 26) (e = 10) (c = 251)
Standard risk			
1-month	1.000 (0) (n = 447) (e = 0) (c = 4)	0.998 (0.002) (n = 447) (e = 1) (c = 3)	0.993 (0.004) (n = 447) (e = 3) (c = 1)
12-month	1.000 (0) (n = 422) (e = 0) (c = 29)	0.993 (0.004) (n = 422) (e = 3) (c = 26)	0.989 (0.005) (n = 422) (e = 5) (c = 24)
24-month	1.000 (0) (n = 375) (e = 0) (c = 76)	0.991 (0.005) (n = 375) (e = 4) (c = 72)	0.984 (0.006) (n = 375) (e = 7) (c = 69)
36-month	1.000 (0) (n = 119) (e = 0) (c = 332)	0.991 (0.005) (n = 119) (e = 4) (c = 328)	0.978 (0.009) (n = 119) (e = 8) (c = 324)
48-month	1.000 (0) (n = 116) (e = 0) (c = 335)	0.991 (0.005) (n = 116) (e = 4) (c = 331)	0.978 (0.009) (n = 116) (e = 8) (c = 327)
60-month	1.000 (0) (n = 79) (e = 0) (c = 372)	0.982 (0.010) (n = 79) (e = 5) (c = 367)	0.978 (0.009) (n = 79) (e = 8) (c = 364)

n, patients at risk; *e*, cumulative events; *c*, cumulative censored; *n/a*, not applicable.

occlusions occurred ≤2 years of insertion; no new events were seen between 2 and 5 years of follow-up.

Endoleaks, sac enlargement, and secondary interventions. Endoleak rates were analyzed separately for the standard- and high-risk groups owing to potential differences between the physiologic risk groups[10] and the potential for physiologic risk to influence the likelihood that a patient would undergo a secondary intervention. The reported incidence of primary endoleaks was exceptionally low, and most were resolved by the 2-year time point.[3] Details regarding late endoleaks are listed in Table II and Fig 3. Most of these were type II endoleaks, and no difference existed between the groups at standard and high physiologic risk.

Kaplan-Meier estimates were used to assess the likelihood of freedom from sac enlargement and freedom from

Table II. Continued

Freedom from adverse event			
Death	*Late endoleak*	*Secondary intervention*	*Aneurysm enlargement*
0.990 (0.006)	n/a	0.972 (0.010)	1.000 (0)
(n = 283)		(n = 276)	(n = 210)
(e = 3)		(e = 8)	(e = 0)
(c = 1)		(c = 3)	(c = 0)
0.912 (0.017)	0.964 (0.013)	0.906 (0.018)	0.990 (0.007)
(n = 252)	(n = 172)	(n = 230)	(n = 195)
(e = 25)	(e = 7)	(e = 26)	(e = 2)
(c = 10)	(c = 92)	(c = 31)	(c = 13)
0.815 (0.023)	0.959 (0.014)	0.867 (0.021)	0.959 (0.015)
(n = 210)	(n = 111)	(n = 151)	(n = 120)
(e = 51)	(e = 8)	(e = 35)	(e = 7)
(c = 26)	(c = 152)	(c = 101)	(c = 83)
0.682 (0.039)	0.959 (0.014)	0.836 (0.031)	0.877 (0.041)
(n = 39)	(n = 26)	(n = 30)	(n = 29)
(e = 66)	(e = 8)	(e = 37)	(e = 12)
(c = 182)	(c = 237)	(c = 220)	(c = 169)
0.682 (0.039)	0.920 (0.040)	0.752 (0.054)	0.784 (0.063)
(n = 39)	(n = 22)	(n = 27)	(n = 22)
(e = 66)	(e = 9)	(e = 40)	(e = 15)
(c = 182)	(c = 240)	(c = 220)	(c = 173)
0.612 (0.048)	0.859 (0.070)	0.752 (0.054)	0.784 (0.063)
(n = 26)	(n = 13)	(n = 18)	(n = 14)
(e = 70)	(e = 10)	(e = 40)	(e = 15)
(c = 191)	(c = 248)	(c = 229)	(c = 181)
0.993 (0.004)	n/a	0.971 (0.008)	1.000 (0)
(n = 447)		(n = 434)	(n = 372)
(e = 3)		(e = 13)	(e = 0)
(c = 1)		(c = 4)	(c = 0)
0.964 (0.009)	0.972 (0.008)	0.900 (0.014)	0.997 (0.003)
(n = 422)	(n = 344)	(n = 381)	(n = 354)
(e = 16)	(e = 11)	(e = 44)	(e = 1)
(c = 13)	(c = 88)	(c = 26)	(c = 17)
0.908 (0.014)	0.947 (0.012)	0.876 (0.016)	0.972 (0.009)
(n = 375)	(n = 251)	(n = 282)	(n = 257)
(e = 40)	(e = 19)	(e = 54)	(e = 9)
(c = 36)	(c = 173)	(c = 115)	(c = 106)
0.860 (0.020)	0.917 (0.019)	0.822 (0.024)	0.952 (0.014)
(n = 119)	(n = 94)	(n = 98)	(n = 104)
(e = 51)	(e = 23)	(e = 62)	(e = 13)
(c = 281)	(c = 326)	(c = 291)	(c = 255)
0.853 (0.021)	0.907 (0.022)	0.805 (0.026)	0.933 (0.019)
(n = 116)	(n = 76)	(n = 93)	(n = 90)
(e = 52)	(e = 24)	(e = 64)	(e = 15)
(c = 283)	(c = 343)	(c = 294)	(c = 267)
0.830 (0.024)	0.879 (0.029)	0.805 (0.026)	0.922 (0.022)
(n = 79)	(n = 46)	(n = 61)	(n = 48)
(e = 55)	(e = 26)	(e = 64)	(e = 16)
(c = 317)	(c = 371)	(c = 326)	(c = 308)

any secondary intervention and are listed in Table II. The presumed causes of sac enlargement and the indication for any secondary intervention are listed in Table IV. Certain differences were noted with respect to morphologic outcome stratified by physiologic risk. A log-rank test showed a greater risk of late sac enlargement in high-risk patients. Specific factors that may have contributed to this effect were then assessed with a Cox regression model (Table V, online version only). Individual factors conducive to increased risk of sac enlargement ($P < .05$) included advanced age, lower body weight, female sex, larger initial aneurysm size, presence of cancer, and inclusion in the high-risk cohort. Anticoagulation status (aspirin, clopidogrel or warfarin) was not a factor associated with an increased risk of enlargement. An additional analysis with a multivariate step-wise Cox regression model revealed that

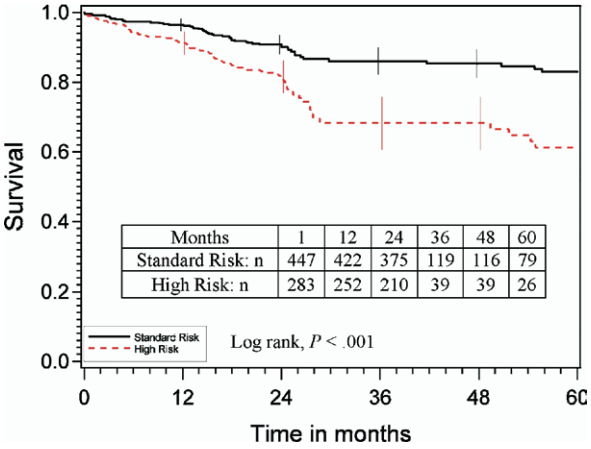

Fig 2. Kaplan-Meier graph shows mortality stratified by standard-risk *(black line)* and high-risk *(red line)* physiologic groups. Error bars represent 95% confidence intervals at each time point.

advanced patient age and larger initial aneurysm size are joint predictors of an increased risk of sac enlargement.

Suboptimal endovascular result analysis. Individual factors related to increased risk of SER were evaluated with a Cox regression model (Table VI, online only). The factors predictive of increased risk of SER ($P < .05$) included advanced age, presence of iliac involvement in the aneurysm, internal iliac artery occlusion, and smaller neck diameter. An additional multivariate step-wise Cox regression model showed that advanced age and internal iliac artery occlusion are joint predictors of an increased risk of SER.

DISCUSSION

The initial report of the ZMT provided evidence that endovascular repair of AAA with amenable anatomy was superior to open surgery for both associated morbidities and aneurysm-related death.[3] The conclusions were tempered by the expectation that endovascular repair would require more detailed follow-up than open repair and might not provide as durable a result. The data presented in this article extend our confidence regarding longer-term durability of endovascular repair with the Zenith AAA device through 5 years. The observation in 736 implants of only a single rupture (at 6 months), a freedom from open surgical conversion of >98%, and freedom from aneurysm-related death of 98% in standard-risk patients and 96% in high-risk patients support the long-term durability of this device. Yet as with most evaluations of endovascular treatments, it is the detailed analysis that will provide clues of whether a sustained benefit can be expected.

Regretfully, we have no data on the surgical control group beyond 1 year, precluding any long-term comparisons against surgical controls. Several previously reported adverse endovascular outcomes, such as limb thrombosis, stent fracture, and component separation, were so uncommon that further statistical analyses seeking causative factors or effect were not fruitful. However, other observa-

Table III. Pooled data (standard- and high-risk groups) for complications relating to the stent graft expressed as Kaplan-Meier estimates, with standard errors listed in the parentheses

	Freedom from event					
Exam period	*Limb occlusion*	*Migration >5 mm*	*Migration >10 mm*	*Barb separation*	*Stent fracture*	*Component separation*
1-month	0.988 (0.004) (n = 721) (e = 9) (c = 9)	n/a	n/a	1.000 (0) (n = 705) (e = 0) (c = 26)	1.000 (0) (n = 705) (e = 0) (c = 26)	1.000 (0) (n = 705) (e = 0) (c = 26)
12-month	0.981 (0.005) (n = 662) (e = 14) (c = 63)	0.995 (0.003) (n = 568) (e = 3) (c = 145)	0.999 (0.001) (n = 568) (e = 1) (c = 147)	0.994 (0.003) (n = 583) (e = 4) (c = 144)	1.000 (0) (n = 587) (e = 0) (c = 144)	1.000 (0) (n = 587) (e = 0) (c = 144)
24-month	0.974 (0.006) (n = 494) (e = 18) (c = 227)	0.977 (0.007) (n = 400) (e = 12) (c = 304)	0.999 (0.001) (n = 400) (e = 1) (c = 315)	0.980 (0.006) (n = 402) (e = 11) (c = 318)	0.998 (0.002) (n = 410) (e = 1) (c = 320)	0.994 (0.03) (n = 408) (e = 3) (c = 320)
36-month	0.974 (0.006) (n = 155) (e = 18) (c = 566)	0.955 (0.012) (n = 128) (e = 17) (c = 571)	0.996 (0.003) (n = 128) (e = 2) (c = 586)	0.965 (0.010) (n = 132) (e = 15) (c = 584)	0.993 (0.006) (n = 137) (e = 2) (c = 592)	0.991 (0.04) (n = 137) (e = 4) (c = 590)
48-month	0.974 (0.006) (n = 152) (e = 18) (c = 569)	0.955 (0.012) (n = 110) (e = 17) (c = 589)	0.996 (0.003) (n = 110) (e = 2) (c = 604)	0.935 (0.018) (n = 115) (e = 19) (c = 597)	0.985 (0.010) (n = 123) (e = 3) (c = 605)	0.977 (0.011) (n = 123) (e = 6) (c = 602)
60-month	0.974 (0.006) (n = 106) (e = 18) (c = 615)	0.935 (0.019) (n = 71) (e = 19) (c = 626)	0.996 (0.003) (n = 71) (e = 2) (c = 643)	0.918 (0.021) (n = 69) (e = 21) (c = 641)	0.968 (0.015) (n = 72) (e = 5) (c = 654)	0.977 (0.011) (n = 72) (e = 6) (c = 653)

n, patients at risk; *e*, cumulative events; *c*, cumulative censored; *n/a*, not applicable.

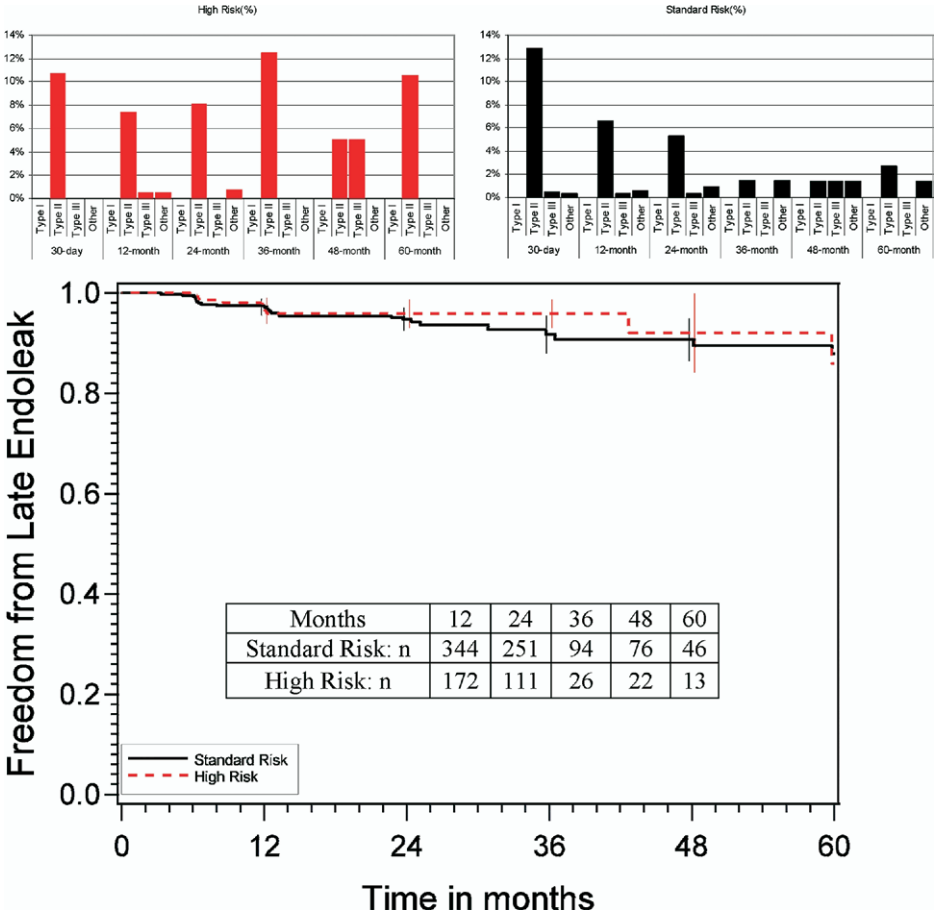

Fig 3. The incidence of both new and persistent endoleaks by type and time of onset is shown for high-risk *(red)* and standard-risk *(black)* groups. The Kaplan-Meier plot shows the cumulative risk for a late endoleak of any type. Error bars represent 95% confidence intervals at each time point. No statistical differences were noted between the high- and standard-risk groups, although the numbers of patients at late follow-up time points were relatively small.

tions such as endoleak, sac enlargement, and secondary interventions merit further discussion.

The Zenith endovascular graft has shown good long-term device durability in this study. Component separation was rare: Only three patients experiencing graft limb separation through 5 years. In two cases, the uncovered top stent had disconnected from the graft material, which required placement of proximal extensions with new uncovered proximal fixation systems. These occurrences, along with a small number of cases in Europe and Australia, were responsible for a design modification in 2002 to double the suture-mediated attachment between the top stent and the proximal margin of the graft. None of the modified devices in the continued access arm have shown signs of top stent disconnection.

Barb separations were also noted and previously reported[3] and still have not been associated with any clinical sequelae. Subsequent to this study, the barbs were increased in diameter—from 0.009 inches to 0.011 inches—to reduce the likelihood of separations.

Minor device changes occurred after the conclusion of the US trial and included an increased gap between the first three z-stents to improve neck conformability, the addition of a 36-mm-diameter device, and the implementation of a hydrophilic-coated sheath and a modified valve (Captor Valve, Cook) in an effort to improve delivery.

The overall incidence of endoleaks, sac enlargement, and migration were favorable in comparison with other multicenter device trials,[26,27] with a low incidence of primary endoleaks and an overall incidence of late endoleaks of $<4\%$ at every annual time point. The risk of sac enlargement was approximately 1.6% for the standard-risk patients at each annual time point, and the cumulative risk for migration was $<1\%$ for all patients.

Type I and III endoleaks were notably absent after correction of problems relating to the initial implantation. As calculated from life-table estimates, 12% to 14% of the patients are at risk for the development of late endoleaks ≤ 5 years of implantation. Reassuringly, most late leaks in this study were type II in nature, but the mechanism by which

Table IV. Data for patients that had evidence of aneurysmal sac size increase (>5 mm) or any secondary intervention

Event	*No.*
Aneurysm enlargement	
Potential cause	
Total patients, No.	31
Persistent endoleak	
Type II	20
Other	5
Graft infection	2
Proximal neck dilation	1
Unidentified	3
Secondary interventions	
Total	153
Conversion	8
Endoleak	96
Proximal type I	5
Distal type I	10
Type II[a]	67
Type III	11
Multiple	3
Graft kink, limb stenosis or occlusion	21
Top stent detachment	2
Renal (angiography, angioplasty or stenting)	14
Distal embolization	2
Other	10
Peripheral vascular	7
Thoracic dissection	1
Thrombosis of dialysis graft	1
Diagnostic Angiogram for Endoleak	1

[a]Type II endoleaks were the most frequent etiology of enlargement and the most common secondary intervention. The need for such interventions and method by which they were done was left to the discretion of the treating physician.

they occur is uncertain. It is possible that late endoleaks occurred in an intermittent manner or simply were not appreciated on earlier imaging studies, but those are unlikely explanations for all late leaks. Alternatively, late type II endoleaks may represent spontaneous recanalization of lumbar or the inferior mesenteric arteries.

Although many endovascular enthusiasts consider type II endoleaks entirely benign, ruptures relating to type II endoleaks[13] and the incontrovertible link between endoleaks and sac enlargement[11] cannot be ignored. Of the 31 patients who experienced sac enlargement during the trial, 25 were related to endoleaks (early or late), 80% of which were type II in nature. Not surprisingly, the treatment of early and late type II endoleaks accounts for about two-thirds of all secondary interventions. The association of sac enlargement with high physiologic risk has been previously noted[10] and is confirmed in this report. In addition, a multivariate Cox regression analysis identified advanced patient age and larger initial aneurysm size as predictive factors for sac size enlargement. These observations merit further investigation.

The establishment of a conglomerate end point (SER) representative of virtually any adverse late device event was established in an effort to determine whether a subset of patients could be identified requiring vigilant follow-up, while patients unlikely to present with events might have a more relaxed follow-up schedule. The freedom from a SER was then calculated, and factors contributing to the likelihood of a SER were assessed. Advanced age and internal iliac artery occlusion were noted to be significant preoperative factors linked to a SER.

The primary study weaknesses relate to the nonrandomized design, the limited number of patients consenting to 5 years of follow-up, and the lack of long-term follow-up for all control (open surgical) patients. These study design issues preclude firm conclusions regarding the superiority of endovascular repair compared with open repair. Furthermore, the limited number of patients followed up out to 5 years also restricts the power of our statistical analyses. It is possible that if detailed, monitored, core lab data were available on a greater number of patients, our assessment of SER could provide the ability to suggest scientifically supported follow-up paradigms. Consideration has been given to further studies in these areas.

CONCLUSIONS

Overall, the longer-term results reported in this study support the use of the Zenith AAA Endovascular Graft in patients amenable to open surgical repair, as well as those considered to be at high-physiologic risk. The lack of late ruptures, small number of conversions, and low risk of migration, limb thrombosis, component separation, and stent fracture relate to the integrity of the implant construct, proper patient selection, and the technical abilities of our investigators. Sac behavior and late endoleak incidence, although generally favorable, mandate continued follow-up. The occurrence of late endoleaks and persistent sac enlargement in a subset of patients treated with endovascular AAA repair will require further investigation. The application of the Zenith endovascular graft to infrarenal aneurysms with appropriate anatomy is associated with a very low risk of failure ≤5 years and thus provides a promising platform for future developments.

AUTHOR CONTRIBUTIONS

Conception and design: RG, TC, NF
Analysis and interpretation: RG, TC, NF
Data collection: RG, TC, RC, WS
Writing the article: RG, TC, RC, WS, NF
Critical revision of the article: RG, NF
Final approval of the article: RG, TC, RC, WS, NF
Statistical analysis: NF
Obtained funding: NF
Overall responsibility: RG

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Submitted Nov 27, 2007; accepted Feb 23, 2008.

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