PIVOTAL Trial Update

With enrollment more than half complete, the PIVOTAL trial aims to answer the question of the best treatment model for patients with small aneurysms.

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The prevalence of abdominal aortic aneurysms (AAAs) has tripled in the last 30 years, making it the 13th leading cause of death in the western world.[1,2] In the US, approximately 1.5 million people have a clinically recognized AAA, and 190,000 new cases are diagnosed each year.[3] Of this number, only 70,000 to 80,000 surgical repairs are performed worldwide annually. There are many other individuals with AAAs who cannot undergo conventional surgical procedures because their operative risks are greatly increased due to serious medical comorbidities, such as coronary and pulmonary disease, chronic renal failure, or chronic lung disease. The most significant complication of AAAs is rupture, from which more than 15,000 subjects die annually.

The current therapy to prevent rupture of AAAs is surgical repair of the aneurysm. Until recently, this procedure was performed via an open surgical technique requiring general anesthesia, an abdominal or retroperitoneal incision, and extensive operative dissection of the abdominal cavity.[4] The 30-day mortality rate for this procedure in centers of excellence is 3% to 5%, with major morbidity rates ranging from 15% to 40%. The recent introduction of catheter-based endovascular technology has led to the development and testing of minimally invasive procedures to treat AAAs and prevent rupture with the potential to reduce morbidity and mortality rates, shorten hospital stays, and provide a satisfactory treatment outcome.[5] Endovascular exclusion of AAAs has the potential to revolutionize the treatment of the disease. Juan Parodi, MD, in Buenos Aires, Argentina, pioneered the first endovascular repair of an AAA in 1990.[6] This event initiated intense investigations that have led to rapid technological enhancements of endograft devices.

Initial clinical results of prospective trials with endovascular grafts in subjects with AAA have shown a similar mortality rate and a lower morbidity rate compared to open surgery. In the last 5 years, there have been more than 30,000 endovascular graft devices implanted annually in patients to treat AAA disease, with generally favorable results.[7]

BACKGROUND

Traditional teaching dictates repair for aneurysms when they reach a diameter of 5 cm to 6 cm. Although smaller aneurysms were often offered repair when the patient was relatively healthy, there existed little objective data to justify repair of smaller aneurysms. Relatively recently, two randomized, prospective trials, the United Kingdom Small Aneurysm trial[7] and the US Veterans Administration (ADAM) trial,[8] compared early surgical repair with observation. Both trials concluded that little if any benefit accrued from early open surgical repair of aneurysms 4 cm to 5.5 cm in diameter. This conclusion was reached despite a statistically significant benefit in the primary endpoint of long-term survival in the UK trial.

The perioperative complication rates associated with open surgery were not insignificant for the two trials, and the mortality rate was high in the UK trial. The perioperative mortality rate was 5.42% after open repair (7.2% after open repair in the surveillance arm and 5.5% after open repair in the early surgery arm). Noting that two deaths occurred in 29 patients treated with procedures other than traditional open repair, the corrected perioperative mortality rate decreased slightly to 5.37%.

The late aneurysm-related death rate was .13% per year in the early surgery group and .95% per year after open repair in the surveillance group. The duration of follow-up was disparate in the two groups but can be estimated. There were 526 nonruptured aneurysms treated in the immediate repair group, followed for a mean of 4.9 years (526 X 4.9=2,577). Assuming 4,656

TABLE 1. ENDPOINTS

Primary Endpoints

- Aneurysm rupture
- Aneurysm-related death

Secondary Endpoints

- All-cause mortality and aneurysm-related mortality in smokers vs nonsmokers
- Aneurysm rupture
- Successful deployment and delivery of stent graft
- Migration of stent graft
- Loss of patency of the stent graft (via imaging)
- Endoleaks within the 1-year follow-up
- Aneurysm shrinkage or growth
- All-cause mortality and duration of hospital stay and institutional rehabilitation after hospital stay (in hospital or dedicated institution)
- Procedural success defined as successful exclusion of the aneurysm, without the occurrence of a secondary adverse event, up to the moment the skin of the patient has been closed
- Secondary endovascular procedures between the 30-day posttreatment and 1-year follow-up
- Conversion to open surgical repair for the test group
- Quality of life
- Occurrence of one or more secondary adverse events

TABLE 2. INCLUSION CRITERIA

- Meet all indications for use as stated in the Medtronic Vascular AAA Stent IFU, including meeting one of the following indications (see IFU, Indications):
  - Aneurysm diameter of 4 cm to 5 cm that has also increased in size by .5 cm in the last 6 months, or
  - Aneurysm that is twice the diameter of the normal infrarenal aorta
- Infrarenal, nonaneurysmal neck length of greater than 1 cm at the proximal and distal ends of the aneurysm and an inner vessel diameter approximately 10% to 20% smaller than the labeled diameter
- Candidates must be low to moderate risk (categories 0, 1, and 2) except for age and hypertension that is controlled (diastolic pressure <90 mm Hg) with up to four drugs per the SVS/ISCVS comorbidity scoring system at time of enrollment
- AAA (4 cm to 5 cm) is confirmed by diagnostic computerized tomography within the previous 3 months before screening that will identify patient meets Medtronic Vascular AAA Stent Graft IFU criteria

patient-years of follow-up, the overall late aneurysm-related death rate was 19 out of 4,656, or .41% per year.[7] Excluding the 12 thoracic aneurysm deaths, there were three deaths from rupture and four deaths from aortoduodenal fistulae (seven aneurysm-related deaths over 4,656 patient-years of follow-up), or .15% per year.

The perioperative mortality rate was lower in the ADAM study, estimated at 2% in the combined groups (2.1% early surgery vs 1.8% surveillance; *P*=not significant). Aneurysm-related death occurred in 17 of 569 (3%) of the patients in the immediate repair group, exclusive of the two patients (.4%) who died as a result of thoracic aneurysms. Among these 17 patients, 11 patients died within 30 days, leaving six patients who died after the perioperative period. Given the total follow-up of 2,577 patient-years, the risk of late aneurysm-related death was six out of 2,577, or .23% per year without the thoracic aortic deaths and .31% (8/2,577) including these cases.

The relatively high complication rates associated with open surgery raise the question of whether a trial of early endovascular repair versus serial surveillance might demonstrate benefits from early repair. The perioperative mortality rate was 1.8% (22 out of 1,193) in the AneuRx (Medtronic CardioVascular, Endovascular Innovations, Santa Rosa, CA) database. Both in-hospital and perioperative mortality rates with endovascular repair have been proven to be lower with endovascular repair as compared with open repair in studies evaluating the two methods of aneurysm repair.[9-11] With respect to late deaths in the AneuRx database, assuming a mean duration of follow-up of approximately 2.8 years, the total exposure was 2.8 X 1,193, or 3,340 patient-years. With eight aneurysm-related deaths after 30 days, the risk was .24% per year, inclusive of stiff-body devices. These observations suggest that the perioperative mortality rate of endovascular repair may be lower than that following open surgery. In fact, these calculations were derived from endovascular repair of large and small aneurysms, while the corresponding data for open repair are from small aneurysms only. Noting the evidence for a lower mortality rate for endovascular repair of smaller versus larger aortic aneurysms,[12] it is likely that endovascular repair of small aneurysms may be substantially safer than open surgical repair of similarly sized aneurysms. If this assumption is true, it is quite possible that a trial of endovascular repair versus ultrasound surveillance of smaller aortic aneurysms may demonstrate benefit in the early repair group.

THE TRIAL

Based on this information, the PIVOTAL trial was designed to assess the merits of early endovascular repair

TABLE 3. EXCLUSION CRITERIA

- Meet any of the contraindications stated in the Medtronic AAA Stent Graft IFU
- Mycotic, symptomatic, ruptured, or traumatic aneurysm
- Myocardial infarction without revascularization ≤6 months or with revascularization ≤1 month
- Cerebrovascular accident or transient ischemic attack within 30 days
- Peripheral white blood cell count <3 X 103/µL or platelet counts <100 X 103/µL, or >1,000 X 103/µL (≤3 months before randomization)
- Degenerative connective tissue disease (eg, Marfan's or Ehlers-Danlos syndrome)
- Evidence of diffuse distal embolization
- Inflammatory aneurysm
- Known bleeding or symptomatic hypercoagulable state
- Major surgical or interventional procedures (vascular and/or nonvascular) within 30 days before study enrollment
- Planned surgical or interventional procedure (vascular and/or nonvascular) within 30 days following enrollment into the study. However, subjects enrolled into the test group may receive the assigned treatment (any FDA-approved Medtronic AAA Stent Graft System) within 30 days of study enrollment
- Candidates are considered severe risk (category 3) except for age and number of drugs for controlled hypertension per the SVS/ISCVS comorbidity scoring system at time of enrollment
- Iliac artery with circumferential calcium
- Bilateral iliac artery <7-mm diameter
- Iliac artery aneurysm ≥3 cm
- Known thoracic aortic aneurysm ≥5 cm
- Planned conduit procedure for introduction of endograft

of infrarenal AAAs. This multicenter, prospective, randomized study will compare endovascular repair with an FDA-approved Medtronic Vascular AAA Stent Graft System as compared with surveillance for management of small (4-cm to 5-cm) AAAs. Subjects are enrolled into either the test group (endovascular repair with an FDA-approved Medtronic Vascular AAA Stent Graft System) or the control group (aneurysm imaging every 6 months).

STUDY OBJECTIVES

The primary objective of the study is to determine whether the repair of small aneurysms using an FDA-approved Medtronic Vascular AAA Stent Graft System is superior to surveillance with respect to the frequency of rupture or aneurysm-related deaths over the length of the study—until the last patient enrolled meets the 3-year follow-up time point.

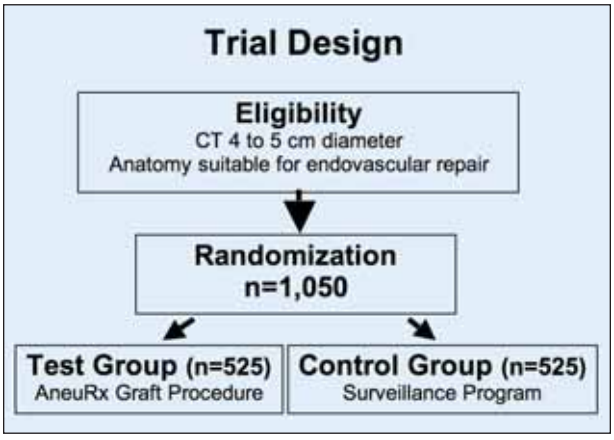

Figure 1. PIVOTAL trial design.

The secondary objectives of the study include assessment of all-cause and aneurysm-related mortality in smokers versus nonsmokers, the rate of aneurysm rupture, successful deployment of the stent graft, loss of patency of the stent graft, endoleaks within 1 year of graft placement, aneurysm shrinkage or growth, procedural variables, secondary procedures, quality of life, and occurrence of serious adverse events. Additionally, an economic substudy will be performed to compare medical resource use patterns and associated medical costs for the endovascular repair arm versus the surveillance arm, and a cost-effectiveness analysis will be performed. Secondary endpoints for the trial are noted in Table 1.

STATISTICAL METHODS

The primary analysis will be to compare the early endovascular intervention using an FDA-approved Medtronic Vascular AAA Stent Graft System to surveillance on time to either rupture or aneurysm-related death (composite outcome). This will be performed using Cox proportional hazards regression adjusting for clinical site and any significant baseline covariates. Interactions between the treatment effect and the baseline covariates will be assessed. The randomized groups will be compared with the log-rank test.

Secondary analyses will be performed on all variables listed as items to be assessed in the secondary objectives. Variables measured over time will be analyzed with mixed-effects models, including the subject and study site as random effects and the treatment and other baseline covariates as fixed effects. Treatment effects on early postoperative analyses will be assessed with logistic regression for categorical outcomes and analysis of

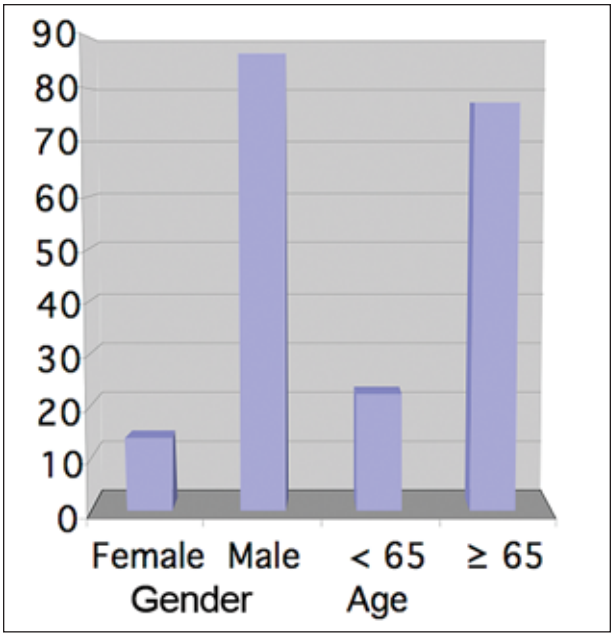

Figure 2. Demographics of enrolled PIVOTAL patients.

covariance for continuous outcomes, again adjusting for site and other baseline covariates. All tests will be two-tailed with a significance level of .05.

INCLUSION/EXCLUSION CRITERIA

The major inclusion criteria for this study are designed to allow enrollment of patients with small aneurysms (4 cm to 5 cm in diameter) who are candidates for endovascular aneurysm repair with an FDA-approved Medtronic Vascular AAA Stent Graft System and who are at low to moderate risk for repair of their AAA. The patients should meet the indications for use of the device as stated in the instructions for use (IFU) and a life expectancy of at least 3 years. Specific inclusion criteria are noted in Table 2.

The major exclusion criteria are designed to inhibit the enrollment of individuals with complicated aneurysms or whose anatomy is not amenable to treatment with an endograft. In addition, it is significant that patients with medical problems that would complicate repair or increase perioperative risk are excluded from the trial. Specific exclusion criteria are noted in Table 3.

SAMPLE SIZE CONSIDERATIONS

The sample size is based on the primary outcome of time to rupture or aneurysm-related death. Using data from previous studies,[7,8] we estimate that the hazard rate for the composite outcome in our surveillance group will be approximately 1.7% per year. This is based on an estimated 5.1% Kaplan-Meier event rate at 3 years. From our Cleveland Clinic Foundation data on early endovascular repair, we estimate the 3-year Kaplan-Meier composite event rate to be about 2.1%, corresponding to a yearly hazard rate of about .71% per year. These estimates correspond to a hazard ratio of .42 (.71/1.7) for surveillance versus early endovascular repair. For power calculations, we assume a constant hazard over time. This may not be the case, and the actual analyses would account for nonconstant hazard in either or both groups. We are interested in

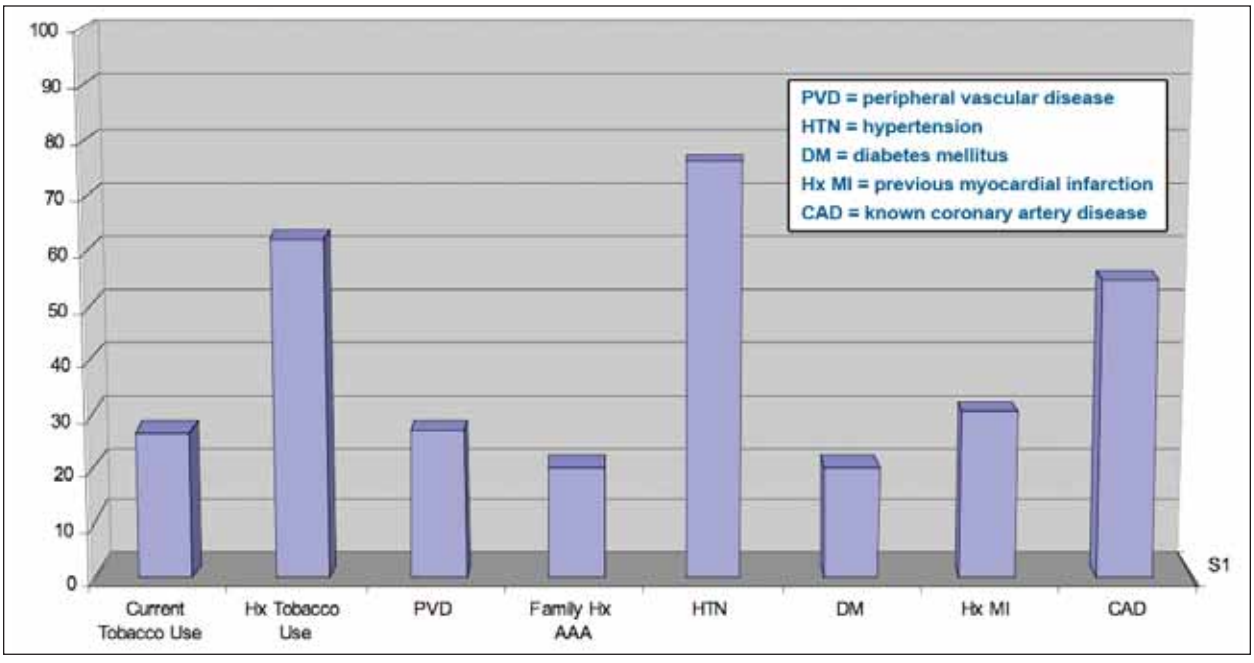

Figure 3. Medical comorbidities of enrolled PIVOTAL patients.

detecting a hazard ratio of .42 or smaller (further from no effect) with 80% power at the .05 significance level. Power calculations assume that the primary outcome will be evaluated 3 years after the last patient has been enrolled.

We conservatively assume 2.5 years of accrual time. Longer actual accrual time with the same 3-year follow-up after the last patient has been randomized would provide more power. We also assume that about 18% of patients will be lost to follow-up in each group over the 3-year follow-up period, that this loss will follow an exponential distribution, and that the reasons for being lost to follow-up will be unrelated to the treatment.

With the above assumptions, we would need approximately 1,050 total patients, or 525 per group. The trial design of the PIVOTAL trial is represented in Figure 1. Patients must have an assessment of their aneurysm morphology and anatomy before enrollment and randomization.

STUDY STATUS

To date, 70 sites have been initiated and begun enrolling patients. From March 2005 to August 2007, 487 patients have been enrolled in the PIVOTAL trial. Of these, 421 (86.4%) are men, 66 (13.6%) are women, and the mean age of enrollees is 70 (±7.9) years. Demographics for the group are listed in Figure 2, and medical comorbidities are listed in Figure 3. These demographics and associated comorbidities are representative of the larger population noted to have aneurysms.

DISCUSSION

The introduction of endovascular repair of AAAs has radically altered the treatment paradigm for individuals afflicted with this problem. In multiple assessments comparing the two treatment modalities, endovascular repair has proven to have lower morbidity rates,[9-11] and in those studies adequately powered, lower mortality rates as well.[10] Few would argue the point that this form of repair offers a significant advancement in the treatment of this disease process.

Importantly, outcomes from repair of aneurysms with endografts appear to be directly related to aneurysm size.[12-14] In these evaluations of outcomes related to aneurysm size from single institutions and the EUROSTAR registry collaborators, significant reductions in perioperative morbidity have been noted and in long-term follow-up as well. These studies document the benefit of endovascular aneurysm repair is potentially even more significant in individuals with small (<5 cm to 5.5 cm) aneurysms, making it even more important to assess the use of these devices, as opposed to open repair, in trials assessing the best form of therapy for patients with small aneurysms such as these.

In deciding whether to perform aneurysm repair, the clinician must weigh the relative risks and benefits of the proposed procedure and determine the method of treatment that offers the patient the best alternative. In the case of a patient who is noted to have a small aneurysm, the merits of open repair and surveillance have been assessed, but it is clear that there are distinct differences between open repair and endovascular repair. Extrapolation of conclusions based on data from the comparative trials of open repair to surveillance in decision making in the era of endovascular repair is unfounded.

The PIVOTAL trial has already passed the halfway point in its enrollment goal and is continuing to accrue patients. The completion of this trial should allow clinicians to determine the best treatment paradigm for patients diagnosed with small aneurysms. ■

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