INvestigation of STEnt grafts in patients with type B Aortic Dissection: Design of the INSTEAD trial—a prospective, multicenter, European randomized trial

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Purpose This study describes the design of an ongoing randomized trial initiated to compare the 2-year outcome of *uncomplicated* type B aortic dissection when treated by endovascular implantation of a Medtronic Talent stent graft adjunctive to best medical treatment versus best medical treatment alone.

Methods Patients older than 18 years with type B aortic dissection as diagnosed by computed tomography or magnetic resonance angiography are randomized to either a thoracic aortic endoprosthesis and antihypertensive treatment, called "stent grafting," or a tailored antihypertensive treatment, called "medical treatment." Only patients in a clinically stable condition and without spontaneous thrombosis of the false lumen after 14 days of the index dissection are considered eligible for study inclusion.

Results Primary outcome measure is all-cause mortality. Secondary outcome variables include conversion to stent and/or surgery, induced thrombosis of the false lumen, cardiovascular morbidity, aortic expansion (>5 mm/y of maximum diameter including true and false lumina), quality of life, and length of intensive care unit and hospital stay. The study design calls for 136 patients to be randomized and monitored for 24 months.

Conclusions The INSTEAD trial is the first randomized trial investigating the role of endoluminal treatment of uncomplicated type B aortic dissection. By the end of December 2004, 125 patients were randomized, accounting for 92% of the target. Final results of the INSTEAD trial should be available in 2006. (Am Heart J 2005;149:592-9.)

Early clinical experience with endografts focused on treatment of abdominal aortic aneurysms and was followed closely by management of descending thoracic aneurysms in high-risk surgical candidates. After the feasibility and safety of stent-graft therapy for thoracic aneurysms were investigated, the technique has been applied to a variety of thoracic aortic diseases including acute and chronic dissection, intramural hematoma, penetrating ulcer, traumatic injury, mycotic aneurysms, and anastomotic aneurysms.[1-13]

In patients with aortic dissection, successful management with thoracic stent grafting requires sealing of the proximal entry tears by placing the endograft within the true lumen across the entry tear. Stent-graft coverage of the entry site interrupts both proximal communications and flow to the false lumen and causes depressurization of the false lumen and reconstruction of the true channel. Induced proximal thrombosis of the false lumen supports repositioning of the dissection *lamella*, progressive caudal thrombosis, and, finally, fibrosis of the false lumen, resulting in stent-induced aortic remodeling.[11]

In general, type B chronic aortic dissection is treated with antihypertensive drugs; surgery or emergency stent-graft placement is considered an option in complicated cases. With aggressive antihypertensive therapy, up to 85% of patients may survive their initial hospital stay.[14] Yet, long-term outcome is unsatisfactory even after successful initial stabilization, with an estimated 50% mortality at 5 years and late expansion of the false lumen in about 25% of patients at 4 years. Mortality

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Submitted October 10, 2003; accepted May 23, 2004.
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doi:10.1016/j.ahj.2004.05.060

Table I. Inclusion criteria

Age >18 years
No contraindication for an anesthetic procedure with intubation
Type B aortic dissection that occurred 2-52 weeks before randomization
Diameter of the targeted aortic segment ≤6 cm
Aortic kinking <75°
The subject or legal guardian understands the nature of the study and agrees to its provisions on a written informed consent form
Availability for the appropriate follow-up visits during the follow-up period
Capability to follow all study requirements

Table II. Exclusion criteria

Pregnant woman
Thrombocytopenia or ongoing anticoagulation therapy
Renal failure and/or creatinine >2.4 mg%
Complete thrombosis of the false lumen
Ongoing infection
Cancer is likely to cause death within 1 year
Enrolment in another clinical study
Unwillingness to cooperate with study procedures or follow-up visits

is related either to expansion of the false lumen and formation of a thoracic aneurysm with inherent risk of rupture or to retrograde progression of dissection with involvement of the proximal aorta with even higher mortality. Surgery for type B aortic dissection carries a 14% to 67% risk of irreversible spinal cord injury or postoperative mortality.[15-18]

Conversely, endovascular techniques may have potential for less complications and better outcomes of type B aortic dissection, considering preliminary promising results of both elective and emergency endoluminal treatments of type B dissection.[5,10,11,19]

Recent data from the International Registry of Aortic Dissection showed an increased use of stent grafts in type B aortic dissection and a 1-year mortality <5% after stent-graft placement (unpublished data).

Based on such observational evidence, the INSTEAD trial was designed as a multicenter, randomized trial that is ongoing in Europe. The purpose of the study is to compare the outcomes of type B aortic dissection subjected to interventional thoracic stent grafting combined as an adjunct with tailored antihypertensive treatment (stent graft group) to those of tailored antihypertensive treatment alone (medical treatment group).

Patients and methods

Patients

To be eligible for randomization, patients had to meet the inclusion and exclusion criteria listed in Tables I and II. The purpose of the INSTEAD trial is not the enrollment of patients at high risk in whom endovascular strategies have shown benefit but rather to address the issue of stent grafting in *uncomplicated* type B dissection. Moreover, spontaneous false lumen thrombosis usually occurring within the initial 14 days of index dissection is another criterion for exclusion because it infers a superior prognosis. Patients with type B aortic dissection and spontaneous false lumen thrombosis are excluded because of difficulty to evaluate the role of stent-graft treatment of reconstruction and healing of the dissection. Patency of the false lumen was documented at baseline by documenting false lumen flow with the use of one of the accepted imaging modality techniques (magnetic resonance imaging, computed tomography, or transesophageal echocardiography [TEE]).[20,21] Similarly, exclusion criteria are determined before randomization, based on clinical and tomographic information. Investigators from each participating center have agreed to offer randomization to all eligible patients.

Enrolment

Prerandomization procedures for eligibility of patients with type B aortic dissection consist of careful evaluation of inclusion and exclusion criteria and collection of an informed consent once the tests for serum creatinine and blood pressure and imaging of the entire aorta (computed tomography or magnetic resonance imaging) were completed. In addition, detailed medical history including demographic data, vital signs, risk factors, ongoing medication, clinical status at time of randomization, and dissection-related signs and symptoms was documented.

Randomization

Randomization follows a computer-generated list prepared for each site by the Medtronic Clinical Department, Peripheral Vascular Division. Patients are allocated to stent-graft or medical treatment by using sequentially numbered sealed envelopes with information disclosing the type of treatment to be applied. Randomization will be performed after at least 14 days of the index type B aortic dissection; tailored antihypertensive treatment is used at the discretion of attending physicians.

Type of treatment

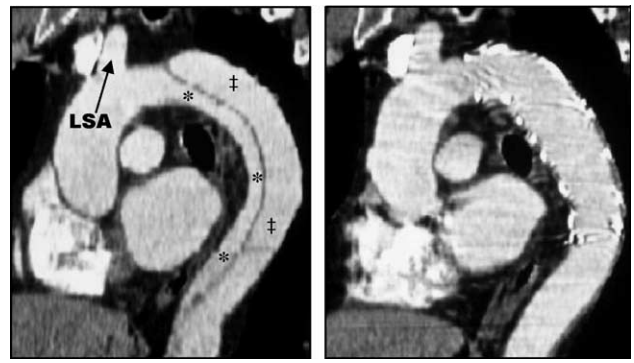
Patients are randomized to 1 of 2 treatment strategies: endovascular stent-graft placement in addition to tailored antihypertensive treatment vs tailored antihypertensive treatment alone. Patients randomized to endovascular treatment will receive a Medtronic Talent Stent-Graft-System (Medtronic, Maastricht, The Netherlands) customized to their individual anatomical requirements (Figure 1). Stent-graft implantation is performed either in the catheterization laboratory, angiographic suite (with digital angiographic equipment), or in an operating theater with appropriate imaging equipment to allow fluoroscopic guidance.

Arterial access is obtained by either needle puncture (Seldinger technique) or surgical arteriotomy. An angiographic catheter (pigtail) is advanced into the ascending aorta with a nontraumatic guide wire to navigate the true lumen. Intermittent angiograms or intravascular ultrasounds are performed to enable passage along the true lumen. Transesophageal echocardiography is helpful in the maneuver and guides to the exact location of the primary tear of the dissection.[19,22] After confirmation of correct catheter place-

Figure 1

The Medtronic Talent thoracic endograft.

Figure 2



On the left side, an angiographic display of type B aortic dissection with a proximal entry site close to the left subclavian artery (LSA) is shown; note the compressed true lumen (asterisk) and the perfused false lumen (double dagger). The right side shows the angiographic result after stent-graft placement. Note the completely reconstructed true lumen and the sealed proximal entry. The false lumen is no longer perfused and the left subclavian artery could be preserved.

ment, a stiff, extralong (280 cm) guide wire is exchanged for the pigtail catheter; the access artery is temporarily ligated by surgical banding or clamping before the stent-graft device is advanced coaxially over the guide wire under fluoroscopic and/or ultrasound guidance. The delivery system is tracked over the wire to the predetermined position aiming to seal the entry tear. Once the landing zone is identified after reaching the desired position, the patient's blood pressure is titrated by intravenous nitroprusside to approximately 60 mm Hg systolic pressure. The stent graft is subsequently launched by pulling the housing back and releasing the endovascular prosthesis. Transesophageal ultrasound and angiographic imaging will monitor successful closure of the entry tears and check for stent apposition and flow condition in the excluded false lumen (Figure 2). The procedure is completed when the targeted entry tear is sealed and proximal inflow into the false lumen is completely or nearly abolished. Supplemental procedures such as extension by use of a second stent graft or additional side branch stenting may be optionally used at the discretion of the operator. For long-term control of blood pressure, patients randomized to stent grafting and those randomized to medical therapy will be subjected to a tailored antihypertensive regimen. Combination pharmacotherapy should include a β-blocking agent and comply with international guidelines. All medications (including combination drug therapy) are logged, tracked, and followed throughout the follow-up period to allow statistical evaluation. Blood pressure will be monitored closely and adjusted during hospitalization.

Follow-up

All study patients are scheduled for follow-up visits at 3, 12, and 24 months post-randomization. The visits consist of clinical and imaging evaluation and completion of the short form (SF) 12 questionnaire; adverse events, patient discontinuation, assessment of thrombosis of the false lumen, changes in aortic diameter, and complications or crossovers will be documented. Unplanned follow-up visits are also recorded. A list of potential morbidities is summarized in Table III.

Outcome measures

The primary end point is all-cause mortality; ancillary end points include thrombosis of the false lumen, cardiovascular morbidity, degree of aortic expansion, quality of life from the SF12 questionnaire, length of intensive care and hospital stay, and quantitative assessment of single or combination antihypertensive drug therapy.

Quality of life

At baseline and at each follow-up assessment, study patients will undergo quality of life evaluation with the SF12 questionnaire. License was obtained to allow administration of this questionnaire. Use of the 12-item validated questionnaire was preferred to the longer and more complex SF36 health survey.[23,24] In fact, although the 36-item health survey is established for a variety of purposes, it is perceived as too long for use in large-scale health measurements and monitoring efforts. Moreover, it has been reported that older patients would feel more comfortable completing the shorter form; the SF12 was previously compared with SF36 and validated.[25] For the INSTEAD trial, validated translations of SF12 were used in the language of each participating country.[26]

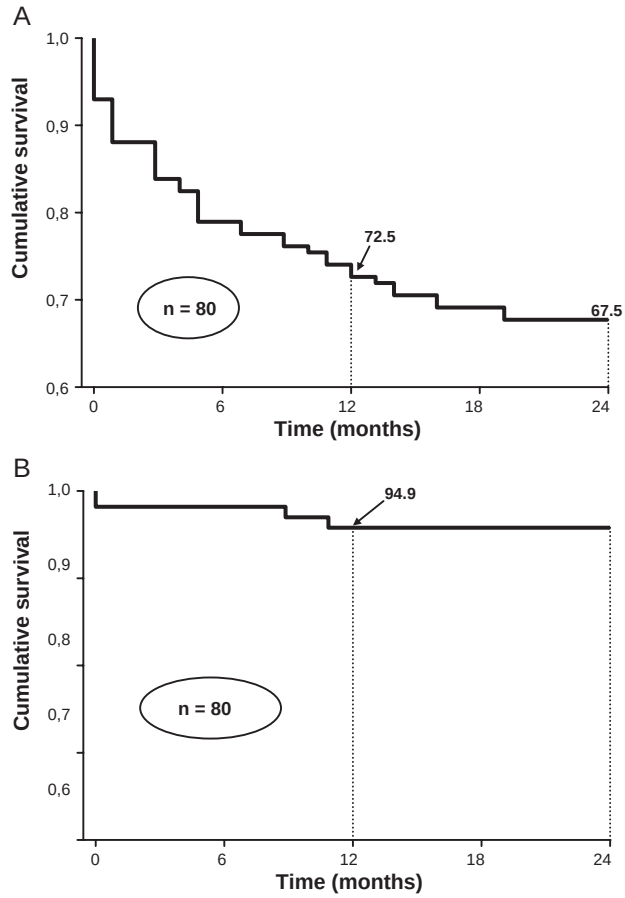
Sample size calculation

The INSTEAD study began in February 2002 and is planned to include 136 consecutive patients to be followed over a 2-year period. The study is designed to find an 18% difference in mortality over 1 year between the 2 types of treatment (Figure 3*A* and *B*). The null hypothesis would mean no

Table III. Morbidities monitored in the INSTEAD trial

Perforation of aorta
Perforation of pelvic artery
Occlusion of aortic branches
Left common carotid artery
Left subclavian
Visceral arteries
Right renal artery
Left renal artery
Right iliac artery
Left iliac artery
Peripheral embolization
Infection
Bronchopulmonary infection
Urinary tract infection
Wound infection
Sepsis
Limb ischemia
Gastric ulcer
Pneumothorax
Respiratory insufficiency
Neurological complications
Paraplegia
Paraparesis
TIA
Stroke
Gastrointestinal bleeding
Bleeding of access site
Acute renal failure
Malperfusion syndrome
Myocardial infarction
Cardiac arrest
Stent occlusion
Others

Figure 3



(**A**) Kaplan-Meier format of survival in 80 patients with type B aortic dissection followed under medical therapy; actuarial survival was 72.5% after 12 months. (**B**) Similar display in Kaplan-Meier format of survival in 80 patients subjected to elective stent-graft placement after type B dissection; actuarial survival was 94.9%.

difference in mortality between the 2 treatment groups. The null hypothesis will be rejected in favor of one alternative if a difference in mortality between the 2 treatment arms reveals a P value <.05 and/or if the 95% CI of the difference will not include zero. Allowing for a type I error of 5% ($\alpha = .05$), a sample of 136 patients (68 per arm) will give an 80% power to reject the null hypothesis, calculated under the assumption that the group undergoing stent-graft treatment plus antihypertensive medications has an expected 1-year mortality of 5%. Conversely, with antihypertensive treatment alone, 1-year mortality is expected around 23% or even higher. This estimate is based on the observed difference in outcomes of 2 sets of 80 patients each with stable type B aortic dissection who underwent either elective stent-graft placement or tailored medical (antihypertensive) treatment in the pre–stent-graft era and were followed for 2 years (Figure 3*A* and *B*). Although both groups of patients are historic and retrospectively analyzed and compared, their baseline characteristics and comorbidities were not significantly different (Table IV); with this comparable set of patients, power estimates for the prospective INSTEAD trial appeared legitimate, considering the lack of other supportive data in the literature.

Data analysis

The primary outcome analysis will be the comparison of survival curves for all-cause mortality between the 2 study groups on an intent-to-treat basis. Survival curves will be plotted, and the statistical difference between the curves will be assessed by nonparametric log rank test statistics. An *on-treatment analysis* will also be performed. Data will be analyzed and compared by χ^2 test (Yates' corrected), Fisher's exact test, and Student's t test when appropriate. Corresponding ORs and 95% CIs will be calculated; stepwise multivariate logistic regression analysis will be performed to identify independent predictors of end points.

Secondary end points of the INSTEAD study do not form the basis for sample size determination. As a result, there may or may not be sufficient power to demonstrate statistical difference or equivalence between the 2 study groups. For the SF12 health status questionnaire, changes from baseline will be compared between groups using analysis of covariance. No interim analyses are planned; the study data will be analyzed when sample size requirements are met. The external safety

Table IV. Demographics and comorbidities

Variable	Medical therapy	Stent-graft placement	*P*
Age (y)	63 ± 9	62 ± 10	ns
Percent male	80	78	ns
Follow-up (y)	5.3 ± 2.9	4.9 ± 3.0	ns
Hypertension (%)	84	80	ns
CAD	12	14	ns
Diabetes (%)	18	18	ns
Dyslipidemia (%)	50	50	ns
Current smoker (%)*	36	40	ns
Marfan	–	–	ns

CAD, Coronary artery disease.
*At the time of the index aortic dissection.

and monitoring committee assesses progress of the study, safety issues, and critical efficacy and will eventually recommend continuation, modification, or suspension of the trial for safety or ethical reasons. Data analysis will be performed by professional biostatisticians.

Participating centers and investigators

The primary concerns in operator selection for the INSTEAD trial were adequate experience, commitment to safety, and consistency in adherence to the study protocol. Participating physicians had performed at least 10 endoluminal repair procedures for aortic type B dissection as primary operators. Fourteen European centers were chosen for the trial; participating centers and investigators are listed in Appendix A.

Study organization and monitoring

The INSTEAD study is a clinical trial conducted in 11 European centers. The conduct of the study is supervised by a steering committee and monitored by an external safety and monitoring committee. Members of the committees are listed in Appendices B and C. The steering committee is responsible for the design and conduct of the study. Medtronic provides methodological and administrative support to centers and is responsible for monitoring conduct and compliance with both European guidelines and study protocol.

Prior to patient enrolment, a study initiation visit was performed at each investigational site to ensure that an ethics committee approval has been obtained and documented, that investigators and study personnel are appropriately trained and clearly understand the study, and that investigators and study personnel accept the obligations of undertaking this clinical investigation.

Periodic monitoring visits are made at all investigational sites throughout the study to ensure that all obligations are fulfilled and that applicable regulations and guidelines are being followed. These visits ensure that facilities operate adequately, the protocol is being adhered to, the ethics committee has been notified of approved amendments, record keeping is complete, and appropriate reports are sent in time to the ethics committee. Moreover, device inventory is checked periodically. The frequency of visits is based on the rate of patient enrolment, time elapsed since the last visit, problems observed during monitoring visits, and occurrence of interim problems. Source document verification is being performed to confirm that all patients meet the enrolment criteria. Finally, reported adverse events are compared with source documentation. Upon completion of the clinical study, a termination visit will conclude activity at each investigational site.

Current status

Recruitment began on February 22, 2002, and by the end of December 2004, a total of 125 patients was randomized, representing 92% of the target. Final results of the INSTEAD trial should be available in 2006.

Discussion

Dissection of the aorta is a life-threatening condition, with separation of the aortic media layer and creation of true and false lumina.[22,27] Both the extent of dissection and the number of communication sites may vary as much as anatomical and clinical *sequelae*. Patients with complicated type B aortic dissection have been shown to benefit from early endovascular interventions likely to avoid imminent rupture and malperfusion syndrome, scenarios associated with high early mortality.[10,28-30] Thus, based on observational evidence, emergency cases are shown to benefit from early stent-graft therapy. Conversely, outcome analysis of stable type B aortic dissection after stent-graft placement has not been assessed in a prospective trial yet.

Although standard treatment of uncomplicated type B dissection and patients is based on tailored medical therapy with antihypertensive drugs including β-blockers,[31] cases complicated by progression, impending rupture, refractory hypertension, localized large false aneurysm, continued pain, or malperfusion syndrome have been reported to benefit from surgical therapy[32] or endovascular interventions.[28-30]

The INSTEAD trial is the first randomized trial using endoluminal treatment of type B aortic dissection between 2 and 52 weeks after an index dissection and investigating the 24-month outcomes of endoluminal treatment vs conservative therapy. The *historic* distinction in acute and chronic dissection was deliberately not made. The study design excluded emergency cases of impending rupture and malperfusion (already known to benefit from endovascular treatment) and allowed enough time for custom-made devices. Subsequently, characterization as "complicated" or "uncomplicated" dissection appeared more useful than "acute" or "chronic" dissection. Thus, patients considered to benefit from and subjected to emergency interventions were not eligible for the INSTEAD trial. The 52-week upper limit from onset of dissection was considered the maximum window of opportunity with respect to aortic plasticity because the lamella may become too rigid late in chronic dissection to allow for safe stent-induced

aortic remodeling. Sample size figures were drawn from 12-month outcome data collected from the principal investigator's series of 80 previous patients in local databases at the Hamburg and Rostock University hospitals (Figure 3*A* and *B*); Kaplan-Meier life-table analysis shows at 12 months a risk of death in the stent-graft–treated patient group of 5.1% vs a historic mortality of 27.5% with conventional therapy. Besides mortality, secondary end points such as conversion to open or endovascular repair or significant expansion of aortic diameter overtime are being investigated. Moreover, successful aortic remodeling, length of hospitalization, and quality of life will be documented to allow cost-efficacy calculations.

Although a superiority of endovascular therapy in comparison with surgery for type B aortic dissection has been suggested in small series and the concept of stent-induced aortic remodeling may be intuitively convincing even for uncomplicated type B aortic dissection, this strategy needs to be subjected to the scrutiny of a larger, randomized trial. The multicenter randomized INSTEAD trial is currently recruiting patients to answer the missing link.

We are indebted to Gitta Knoop, Sylvia Lehr, and Jeanett Heine for secretarial assistance and art work.

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