

Randomized Comparison of Strategies for Type B Aortic Dissection

The INVESTIGATION of STent Grafts in Aortic Dissection (INSTEAD) Trial

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Background—Thoracic endovascular aortic repair (TEVAR) represents a novel concept for type B aortic dissection. Although life-saving in acute emergencies, outcomes and survival of TEVAR in stable dissection are unknown.

Methods and Results—One hundred forty patients in stable clinical condition at least 2 weeks after index dissection were randomly subjected to elective stent-graft placement in addition to optimal medical therapy (n=72) or to optimal medical therapy alone (n=68) with surveillance (arterial pressure according to World Health Organization guidelines $\leq 120/80$ mm Hg). The primary end point was all-cause death at 2 years, whereas aorta-related death, progression (with need for conversion or additional endovascular or open surgery), and aortic remodeling were secondary end points. There was no difference in all-cause deaths, with a 2-year cumulative survival rate of $95.6 \pm 2.5\%$ with optimal medical therapy versus $88.9 \pm 3.7\%$ with TEVAR ($P=0.15$); the trial, however, turned out to be underpowered. Moreover, the aorta-related death rate was not different ($P=0.44$), and the risk for the combined end point of aorta-related death (rupture) and progression (including conversion or additional endovascular or open surgery) was similar ($P=0.65$). Three neurological adverse events occurred in the TEVAR group (1 paraplegia, 1 stroke, and 1 transient paraparesis), versus 1 case of paraparesis with medical treatment. Finally, aortic remodeling (with true-lumen recovery and thoracic false-lumen thrombosis) occurred in 91.3% of patients with TEVAR versus 19.4% of those who received medical treatment ($P<0.001$), which suggests ongoing aortic remodeling.

Conclusions—In the first randomized study on elective stent-graft placement in survivors of uncomplicated type B aortic dissection, TEVAR failed to improve 2-year survival and adverse event rates despite favorable aortic remodeling.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00525356.

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Key Words: aneurysm ■ aorta ■ aortic dissection ■ stents ■ remodeling ■ prognosis

In 1999, thoracic endovascular aortic repair (TEVAR) was introduced as an alternative treatment option for patients with type B aortic dissection. TEVAR is considered life-saving in patients with acute type B aortic dissection complicated by contained rupture or organ malperfusion syndrome,¹⁻³ whereas its role in improving outcomes of uncomplicated type B aortic dissection is yet unknown. Traditionally, stable patients are managed with medical treatment (annual survival rate $\geq 80\%$); however, long-term outcomes remain sobering because of aneurysmal expansion of the false lumen and late complications.⁴⁻⁶ Consistently,

persistent false-lumen perfusion has been identified as a risk factor for adverse outcomes, whereas complete thrombosis has been associated with improved outcome.⁷⁻¹⁰ It was thus our hypothesis that nonsurgical reconstruction of the dissection with a membrane-coated stent might improve outcome prognosis in these patients.¹¹

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Although traditional management had focused on open surgery or medical interventions, the feasibility and efficacy

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All members of the Investigation of Stent Grafts in Aortic Dissection (INSTEAD) Study Group are listed in the Appendix in the online-only Data Supplement.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.109.886408/DC1>. Correspondence to Christoph A. Nienaber, MD, FESC, FACC, Department of Internal Medicine, Division of Cardiology, University of Rostock, Ernst-Heydemann-Straße 6, 18055 Rostock, Germany. E-mail christoph.nienaber@med.uni-rostock.de

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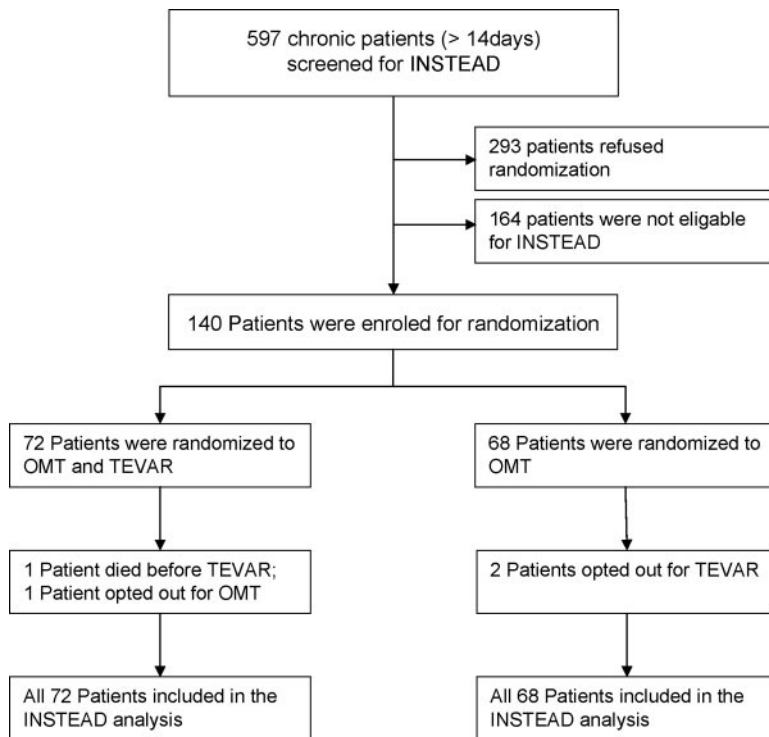


Figure 1. INSTEAD trial enrollment. OMT indicates optimal medical treatment.

of endovascular repair of aortic dissection are evident.^{1,2,12–14} Although endovascular strategies are therapeutic options for complicated aortic dissection as rescue maneuvers,^{5,6,15–18} there is ongoing controversy about clinically stable type B aortic dissection, with current consensus in support of surveillance and tight control of hypertension.^{19,20} Conversely, with a death rate up to 30% at 2 years¹¹ and a survival rate <50% in the long term,²¹ attention has shifted to TEVAR as a viable alternative. The INvestigation of STent grafts in Aortic Dissection (INSTEAD) trial was designed to clarify the impact of endovascular stent grafts as an adjunct to medical treatment and surveillance in patients with type B dissection considered uncomplicated at the time of trial inclusion.

Methods

Study Design

Methodological aspects of the INSTEAD trial have been described previously¹¹; the rationale of INSTEAD was to compare conservative with endovascular interventional treatment for improved outcomes.^{4,9,22,23} Sponsorship and external monitoring of the investigator-initiated INSTEAD trial were provided through an unrestricted research grant by Medtronic Bakken Research Institute, Maastricht, Belgium, and accompanied by research specialists uninvolved in the planning and execution of the trial. Supplemental support from the Institutional Research Unit at Rostock University included minor funding and in-kind (mostly statistical) support.

The study protocol was approved by the human rights and ethics committee at the coordinating center and by the local institutional review board at each participating center. An independent data and safety monitoring board oversaw conduct, safety, and efficacy of the trial in scheduled adjudication meetings and decided to continue the trial on the basis of an interim analysis after it enrolled half the required number of patients; data management and statistical analyses were performed by the coordinating center with oversight by members of the INSTEAD

executive committee (see Appendix in the online-only Data Supplement). No company providing financial support or products had any role in the design, analysis, or interpretation of the study.

Study Population

In brief, consecutive patients at 7 centers in Germany, Italy, and France who had uncomplicated type B aortic dissection between 2 and 52 weeks after onset were considered candidates for random assignment to TEVAR plus optimal medical therapy or to medical treatment alone between November 2003 and the end of 2005. Patients were considered unsuitable for randomization in the presence of traditional indications for endovascular or open surgery (diameter ≥ 6 cm), with recurrence of acute complications, and when anatomic conditions for TEVAR were not met, such as aortic kinking $>75^\circ$ or complete false-lumen thrombosis. After an interim period of ≥ 14 days to identify early complications and exclude spontaneous false-lumen thrombosis, all INSTEAD patients were considered uncomplicated chronic dissection cases. After 597 patients were evaluated and 140 were enrolled, randomization was performed centrally at a 1:1 ratio by means of a computer-generated permuted-block sequence with variable block size, with stratification according to study center (Figure 1); written informed consent was obtained.

Interventional Procedures

On the basis of diagnostic measurements obtained from multislice computed tomography or magnetic resonance imaging, individually selected TALENT stent grafts (Medtronic, Inc, Santa Rosa, Calif) were used both to scaffold ≤ 20 cm of dissected aorta and to seal major entries (Figure 2). The procedure was performed in a laboratory with imaging capabilities that included digital angiography for catheterization maneuvers and optional transesophageal ultrasound. The femoral artery could usually accommodate the 24F stent-graft system, which was advanced over a 260-cm stiff wire navigated in the true lumen under fluoroscopic or optional ultrasound guidance. The stent graft was deployed with systolic pressure lowered to ≈ 50 mm Hg by sodium nitroprusside or by rapid right ventricular pacing.^{24,25} After deployment, gentle inflation of a latex balloon was performed if proximal wall apposition was incomplete. Intentional coverage of the left subclavian artery was accepted to provide an appropriate

Endovascular Stent-graft in type B-Dissection

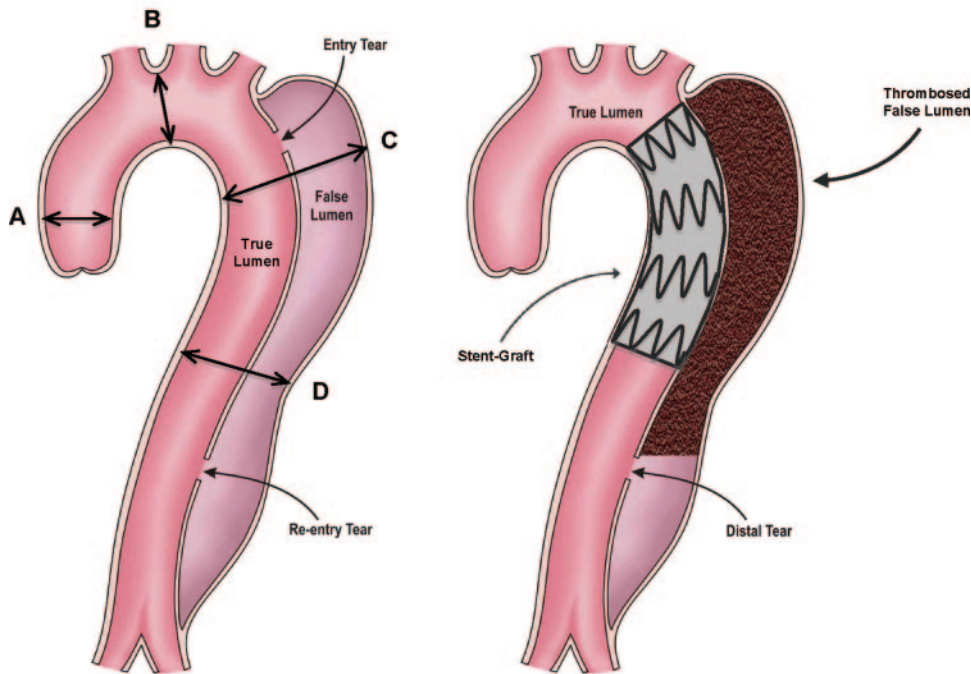


Figure 2. Endovascular stent graft in type B dissection. Cartoon demonstrating the typical features of type B dissection with flow in both the true and the expanded false lumen resulting from a major proximal entry tear (left); planes A to D were followed up longitudinally in every patient. A stent graft was placed to scaffold the dissected aorta and to seal the entry to the false lumen, resulting in reconstruction of the true lumen with subsequent false-lumen thrombosis (right). Levels were defined as (A) at the sinotubular junction, (B) at the center of the arch between truncus brachiocephalicus and left common carotid artery, (C) at the level of the maximum aortic diameter, and (D) at the hiatus.

landing zone and avoid endoleak; prophylactic surgical revascularization of the left subclavian artery was left to the discretion of the investigator. Magnetic resonance angiography was used to identify potential supra-aortic variants (eg, presence of a lusorian artery, incomplete circle of Willis, or dominant left vertebral artery) in case of intentional occlusion of the left subclavian artery.^{17,26}

Clinical Outcome and End Points

Clinical outcome was adjudicated by an independent committee with expert members; events were classified in approximation to the reporting standards of the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery/International Society for Cardiovascular Surgery.²⁷ Three classes of complications (systemic, local nonvascular, and local vascular) and 3 grades of severity (mild, moderate, and severe) were used; mild complications were not considered for the present analysis.

An outcomes adjudication committee that consisted of a cardiac surgeon, 2 vascular surgeons, and 2 cardiac interventionalists assessed each complication independently in blinded fashion; potential disagreements were to be resolved by consensus. The primary end point was all-cause death at 2 years; secondary end points were aorta-related death, a composite end point of progressive aortic pathology (including crossover/conversion or additional endovascular or open surgery for rupture, expansion, or malperfusion), and morphological evidence of aortic remodeling. With half the required number of patients enrolled at the interim analysis, the committee decided to continue the trial, although the incidence of death and (moderate and severe) complications was monitored continuously to safeguard against divergent outcomes.²⁸

Assessment of Aortic Remodeling

With serial tomographic imaging at 3 months and at 1 and 2 years by computed tomography or magnetic resonance, all patients underwent evaluation for false-lumen thrombosis and recording of true- and false-lumen diameter at defined transversal levels: Levels A and B reflect nondissected aorta, whereas levels C and D reflect dissected proximal and distal descending thoracic aortic segments (Figure 2). Furthermore, individual maximum diameter was documented.

Statistical Analysis

Considering the primary end point as a binary outcome rather than using a time-to-event calculation, we projected that 20% of patients in the medical group would have a primary end point event within 2 years, with an expected reduction from 20% to 3% to 5% in the stent-graft group. On the assumption of equal allocation in both groups, a sample size of 140 patients was required for 80% power to detect a difference with a 2-sided α -error of 0.05. Sample size was determined with the study planning software nQuery Advisor 7.0 (Statcon, Witzenhausen, Germany).

Patients were classified according to randomized allocation for all analyses; data were processed with the SPSS/PC software package version 15.0 (SPSS, Munich, Germany). Means (\pm SD) and medians and ranges were used to describe continuous variables; absolute numbers and percentage frequencies were used for categorical factors. For continuous variables, differences between groups were evaluated by use of a 2-sample *t* test or nonparametric Mann-Whitney *U* test depending on the distribution of variables. Categorical variables were compared by the Fisher exact test or χ^2 test. Longitudinal data within groups were compared by standard general linear model repeated-measures ANOVA. Time-to-event curves were calculated by the Kaplan-Meier method and compared by log-rank test on an intention-to-treat basis. Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals. All tests were 2 tailed, and $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics and Treatment Assignment

Between November 2003 and November 2005, of 597 screened patients, 140 who met the inclusion criteria were randomly assigned to elective TEVAR in addition to optimal medical therapy or to optimal medical treatment alone (Figure 1). Two patients failed to undergo stent-graft placement after randomization because of declined consent in 1 and sudden death in another; 2 patients eventually declined medical treatment and opted for early stent-graft placement

Table 1. Baseline Characteristics of Patients

Characteristics	OMT (n=68)	OMT+TEVAR (n=72)
Age, y, mean±SD	60.1±11.7	60.3±10.7
Male sex, n (%)	56 (82.3)	62 (86.1)
Atherosclerosis/hypertension, n (%)	56 (82.3)	61 (84.7)
Marfan syndrome, n (%)	0 (0)	2 (2.8)
Hypertension only, n (%)	11 (16.2)	7 (9.7)
Unknown, n (%)	2 (2.9)	2 (2.8)
Diabetes mellitus, n (%)	6 (8.8)	5 (6.9)
Active smoking, n (%)	17 (25.0)	14 (19.4)
Pulmonary disease, n (%)	9 (13.2)	7 (9.7)
Body mass index, kg/m ² , mean±SD	27.7±5.5	26.7±4.4
New York Heart Association classification, n (%)		
I	51 (75.0)	55 (76.4)
II	13 (19.1)	16 (22.2)
III	4 (5.9)	1 (1.4)
American Society of Anesthesiology class, n (%)		
I (healthy status)	20 (29.4)	23 (31.9)
II (mild systemic disease)	41 (60.3)	34 (47.2)
III (severe systemic disease)	7 (10.3)	15 (20.8)
Maximum diameter of dissected aorta, mm, mean±SD	43.5±9.3	44.2±9.5
Dissection morphology, n (%)		
Confined to descending thoracic aorta	5 (7.4)	8 (11.1)
Thoracoabdominal extension	63 (92.6)	64 (88.9)
False lumen, n (%)		
Perfused	45 (66.2)	46 (63.9)
Perfused with partial thrombosis	23 (33.8)	26 (36.1)
Days from dissection to randomization, median (range)	45 (20–252)	39 (18–252)

although randomized differently. Overall, 140 patients were followed up in both groups, with 72 patients in the endovascular treatment arm and 68 in the medical treatment arm on an intention-to-treat basis; all patients underwent complete protocol-guided follow-up.

Baseline and demographic characteristics, comorbidity profiles and risk factors, distribution of American Society of Anesthesiologists classification, and dissection morphology were evenly distributed. Moreover, the time interval between onset of dissection and randomization was identical between groups, with a median of 45 and 39 days, respectively, which reflects the early phase of chronic disease (Table 1). The median interval between randomization and stent-graft placement was 12 days (range 1 to 29 days); procedural details and hospital stay are listed in Table 2.

TEVAR was completed successfully in 70 patients with no intraprocedural conversion to open surgery; there were no complications related to general anesthesia or ventilation. One stent graft was inserted in 58 patients (82.9%), 2

Table 2. Procedural Characteristics in TEVAR Group

Days from randomization to stent-graft, median (range)	12 (1–29)
General anesthesia, n (%)	68 (97.1)
Duration of procedure, min, median (range)	108 (20–200)
Intraprocedural death, n (%)	0 (. . .)
Procedural success, n (%)	67 (95.7)
Stent grafts per patient, median (range)	1.34 (1–3)
Femoral access, n (%)	66 (94.3)
Occlusion of left subclavian artery, n (%)	17 (24.3)
Carotid-subclavian bypass, n (%)	2 (2.9)
Access-vessel patch repair, n (%)	1 (1.4)
Hospital stay, d, median (range)	8 (5–29)
Intensive care unit stay, h, median (range)	23 (12–128)

grafts in 8 (11.4%), and 3 grafts in 4 (5.7%). Intentional occlusion of the left subclavian artery without prior revascularization was documented in 17 cases (24.3%) with no neurological sequelae or need for revascularization. In 3 cases, calcification at the level of the femoral arteries required retroperitoneal access to the common iliac artery, with patch repair in 1 case. Although the majority of patients (74.3%) spent <24 hours under intensive care, median hospitalization in the TEVAR group was 8 days, which was required for imaging logistics and antihypertensive medication adjustment. Periprocedural outcomes (30 days) included 3 vascular injuries that required ancillary procedures and 3 cases of neurological complications, with 1 paraplegia, 1 transient paraparesis in the presence of extensive coverage (3 stent grafts) with left subclavian artery occlusion (without prior revascularization), and 1 stroke (Table 3); normalized arterial pressure according to World Health Organization criteria ($\leq 120/80$ mm Hg) was documented in all patients 1 month after randomization and at follow-up visits in both groups.

Primary Outcome

Figure 3A shows cumulative all-cause survival rate (estimated with the use of Kaplan-Meier curves) in both groups. Comparison between curves revealed no significant difference (log-rank test $P=0.15$). Survival probability at 2 years was $88.9\pm 3.7\%$ with TEVAR and $95.6\pm 2.5\%$ with medical

Table 3. Periprocedural Outcomes After TEVAR (30 Days)

Deaths, n (%)	2 (2.8)
Periprocedural events, n (%)	
Retrograde type A dissection	1 (1.5)
Rupture of iliac access vessel	1 (1.5)
Conversion to open surgery	0 (. . .)
Ancillary procedures/injuries	
Stenting of iliac artery	1 (1.5)
Aortic stent-graft extension	1 (1.5)
Aortic bare-stent extension	1 (1.5)
Periprocedural neurological events, n (%)	
Paraplegia/paraparesis	2 (2.9)
Major stroke	1 (1.5)

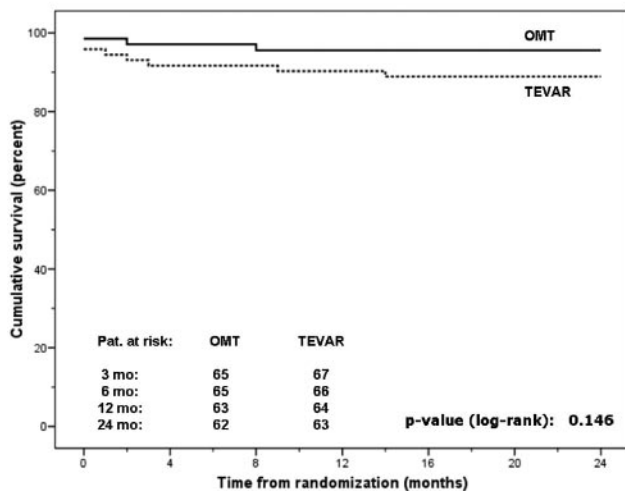
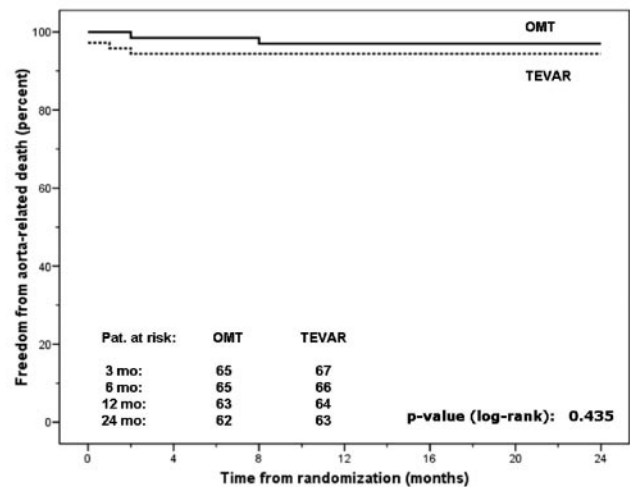
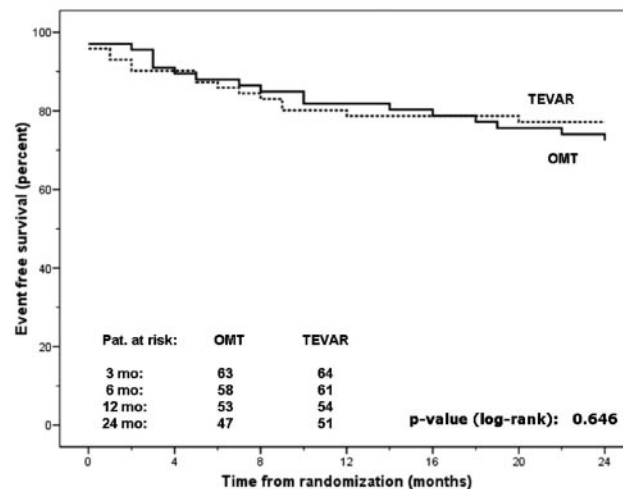
A Cumulative survival within 24 months after randomization**B** Freedom from aorta-related mortality within 24 months after randomization**C** INSTEAD: Freedom from progressive aortic disease

Figure 3. A, Kaplan-Meier estimates of 2-year overall cumulative survival rate in both groups; $P=0.15$ by log-rank test. B, Kaplan-Meier estimates of 2-year aorta-related survival rate in both groups; $P=0.44$ by log-rank test. C, Kaplan-Meier estimates of 2-year cumulative freedom from combined end point of progression and adverse events. The combined end point consisted of related death, conversion, and ancillary interventions (including a second stent-graft procedure, access revision, and peripheral interventions). Endovascular interventions (conversion to TEVAR in the control group or additional TEVAR in the stent-graft group) are an integral part of the combined end point of progressive aortic pathology. There was no difference between groups (log-rank test $P=0.65$). Pat. at risk indicates patients at risk; OMT, optimal medical therapy.

treatment. Unadjusted Cox regression analysis for all-cause survival revealed a hazard ratio of 0.34 with a 95% confidence interval from 0.068 to 1.670 ($P=0.183$); with 11 fatalities, the 2-year death rates did not achieve the assumption of 28 events to achieve the desired statistical power.

Secondary End Points and Adverse Events

Figure 3B depicts the estimated cumulative freedom from aorta-related death (log-rank test $P=0.44$). At 2 years, the survival probabilities were $94.4\pm 2.7\%$ with TEVAR and $97.0\pm 2.0\%$ with medical treatment alone. Analysis of individual fatalities revealed that 4 patients had been included despite protocol violation; with acute malperfusion in 1 case after dissection-related renal dysfunction on dialysis, 2 cases with acute leg ischemia, and 1 case with ongoing pain and extra-aortic blood collection since onset

of dissection, none of these 4 patients should have entered the study. A detailed list of case fatalities is summarized in Table 4.

Figure 3C illustrates the Kaplan-Meier analysis of a combined end point of aorta-related death, crossover/conversion for expansion, and ancillary procedures, with no differences between groups (log-rank test $P=0.65$). At 2 years, cumulative freedom from the combined end point was $72.5\pm 5.5\%$ with optimal medical treatment and $77.2\pm 5.0\%$ with additional stent grafting.

Table 5 summarizes all events including overall and aorta-related deaths within 2 years of randomization. Aortic expansion >60 mm occurred more frequently with medical treatment and was followed by crossover to TEVAR in 16.2% and by conversion to open surgery in 4.4% of patients; 1 patient crossed over because of additional late malperfusion

Table 4. Case Fatalities After Randomization

Patient	Age, y	Sex	Group	Interval, d		Thoracic False-Lumen Status	Related Death	Detailed Information
				Dissection to Randomization	Randomization to Stent Graft			
1	65	M	OMT	244	N/A	Minimal partial thrombosis	Yes	Delayed rupture of enlarging false lumen
2	73	M	TEVAR	71	1	Complete thoracic thrombosis	Yes*	Postprocedural rupture of access vessel
3	53	M	TEVAR	30	29	Complete thoracic thrombosis	Yes*	Abdominal redissection with intestinal malperfusion
4	66	F	TEVAR	15	1	Complete thoracic thrombosis	Yes*	Postprocedural type A dissection with tamponade
5	68	M	OMT	73	N/A	Minimal partial thrombosis	Yes	Rupture of thoracic aorta
6	56	M	TEVAR	53	40	Entry closed, partial thrombosis	Yes*	Rupture of thoracic aorta
7	61	M	TEVAR	293	22	Type I endoleak, partial thrombosis	No	Fatal hemorrhagic stroke in severe hypertension
8	74	M	TEVAR	112	12	Complete thoracic thrombosis	No	Sudden cardiac death from ventricular fibrillation
9	63	M	OMT	15	N/A	Complete thoracic thrombosis	No	Metastasized renal cancer
10	70	M	TEVAR	17	Died 2 days after randomization but before TEVAR	No false-lumen thrombosis	No	Pulmonary embolism
11	77	M	OMT	90	Died 10 days after randomization; opted out for stent graft and died before TEVAR	No false-lumen thrombosis	No	Myocardial infarction

M indicates male; F, female; OMT, optimal medical treatment; and N/A, not available.

*Patients with violation of inclusion protocol.

syndrome. There were 2 cases of ischemic spinal injury after stent grafting and 1 with medical therapy ($P=0.90$); the latter case developed true-lumen collapse with malperfusion to various pairs of intercostal arteries 11 months after dissection followed by conversion to late stent-graft placement. In the stent-graft group, all aorta-related deaths had occurred within 2 months; an additional stent graft for false-lumen flow and diameter expansion was implanted in 6 cases, whereas 3 patients were converted to open surgery for expansion, retrograde type A dissection, or malperfusion. Interestingly,

all crossover cases from medical treatment to TEVAR had uneventful outcomes, no deaths, and documented aortic remodeling.

Clinical Follow-Up and Aortic Remodeling

Table 6 summarizes morphological evolution over time in both groups and evidence of aortic remodeling. Although baseline dimensional variables were similar in nondissected (A and B) and dissected (C and D) segments of the aorta, placement of a stent graft was followed by expansion of the thoracic true lumen from 17.4 ± 10.7 to 25.7 ± 6.7 mm at 3 months, with further expansion to 27.0 ± 7.3 mm at 2 years ($P<0.001$) at level D; similar changes were documented at level C. Simultaneously, maximal false-lumen diameter shrank from 26.9 ± 10.9 to 17.2 ± 13.7 mm at 3 months after stent grafting ($P<0.001$) and to 13.8 ± 14.9 mm at 2 years ($P<0.001$) at level D, with similar changes at level C. Moreover, the process of false-lumen thrombosis in the thoracic aorta was enhanced after stent-graft placement, with 91.3% complete false-lumen thrombosis and morphological evidence of aortic remodeling ($P<0.001$), as demonstrated in Figure 4. Conversely, medical treatment alone failed to demonstrate significant true-lumen recovery or false-lumen shrinkage and revealed false-lumen thrombus formation only in a minority of patients.

Discussion

The INSTEAD trial, as the first randomized comparison between elective endovascular surgery and best medical

Table 5. Events Within 2 Years of Randomization

	OMT	OMT+TEVAR	<i>P</i>
Overall deaths, n (%)	3 (4.4)	8 (11.1)	0.20
Aorta-related deaths, n (%)	2 (2.9)	4 (5.6)	0.68
Secondary interventions, n (%)	15 (22.1)	13 (18.1)	0.74
Crossover	11 (16.2)	N/A	N/A
Conversion to surgery	3 (4.4)	3 (4.2)	1.00
Stent-graft extension	N/A	6 (8.3)	N/A
Aortic bare-stent extension	N/A	1 (1.4)	N/A
PTA/access-vessel repair	1 (1.5)	3 (4.2)	0.62
Adverse events, n (%)			
Persistent paraplegia/paraparesis	1 (1.4)	2 (2.8)	0.90
Major stroke	0 (. .)	2 (2.8)	0.53

OMT indicates optimal medical treatment; N/A, not applicable; and PTA, percutaneous transluminal angioplasty.

Table 6. Morphological Characteristics Over Time (Remodeling)

Characteristics	OMT (n=68)	OMT+TEVAR (n=72)	P
Baseline type B dissection			
Maximum aortic diameter	43.6±9.2*	44.1±9.6	0.65
True-lumen diameter at level C	20.3±9.3	19.4±8.0*	0.55
False-lumen diameter at level C	27.7±11.6	29.3±12.4*	0.65
True-lumen diameter at level D	17.3±8.7	17.4±10.7*	0.91
False-lumen diameter at level D	24.0±10.4	26.9±10.9*	0.13
3-Month follow-up			
Maximum aortic diameter	46.2±11.1	44.7±8.3	0.75
True-lumen diameter at level C	21.9±8.8	30.6±6.0	<0.001
False-lumen diameter at level C	29.4±15.0	14.0±14.2†	<0.001
True-lumen diameter at level D	17.1±8.8	25.7±6.7	<0.001
False-lumen diameter at level D	27.4±12.9	17.2±13.7†	<0.001
1-Year follow-up			
Maximum aortic diameter	45.5±7.9	44.7±11.9	0.37
True-lumen diameter at level C	23.9±9.9	31.8±5.9	<0.001
False-lumen diameter at level C	24.7±15.5	13.1±18.9	<0.001
True-lumen diameter at level D	19.3±9.0	27.1±7.0	<0.001
False-lumen diameter at level D	24.8±11.5	14.6±14.7	<0.001
2-Year follow-up			
Maximum aortic diameter	48.3±13.1	43.8±12.5	0.31
True-lumen diameter at level C	22.7±10.9	32.3±6.4	<0.001
False-lumen diameter at level C	26.8±9.4	12.5±16.7	<0.001
True-lumen diameter at level D	18.3±7.8	27.0±7.3	<0.001
False-lumen diameter at level D	26.9±10.3	13.8±14.9	<0.001
False-lumen thrombosis at 2 y, n (%)‡			
Complete	13 (19.4)	63 (91.3)	<0.001
Incomplete	6 (9.1)	6 (8.7)	0.79

Values are mean±SD.

* $P<0.001$ vs 3 months, 1 year, and 2 years.

† $P<0.001$ vs 1 and 2 years (repeated-measures analysis).

‡At the level of descending thoracic aorta.

treatment, justifies medical management for uncomplicated type B aortic dissection and corroborates excellent survival rate with tight blood pressure control and close surveillance.^{20,29,30} Moreover, for patients who fail to respond to medical management and with progressive expansion or late malperfusion, deferred endovascular therapy is feasible and safe.

Although the concept of endovascular stent grafting has been embraced to replace open surgery for managing complications of type B dissection (even without any randomized data),^{18,31,32} the revelations of INSTEAD do not challenge the perception of an endovascular alternative to open surgery. Instead, the potential of endografting to remodel a dissected aorta³³ and to successfully deal with late expansion and distal malperfusion has been confirmed.³² Although there were 3 late conversions to open surgery in both groups, there was no case of induced distal

malperfusion after placement of a stent graft. Spinal injury occurred in 2 cases after stent grafting and in 1 case spontaneously. Nevertheless, endovascular therapy in clinically stable, low-risk patients failed to improve 2-year survival rate and was associated with spinal injury in 2.8%, as expected from previous observations.^{14,34–36} Thus, the perception of prophylactic scaffolding as a better alternative to tailored medical management was diminished given ongoing complications such as distal expansion and late rupture regardless of therapy. In light of documented successful medical management with monitored pharmacotherapy, TEVAR appeared appropriate in cases of emerging complications. Interestingly, all crossover patients survived elective TEVAR for expansion and had an uneventful follow-up with remodeling despite rather late intervention.³⁷

Thus, INSTEAD supports the notion of a complication-specific approach instead of endovascular surgery for all type B dissections; patients who survive type B dissection and who are subjected to best medical management with surveillance show an excellent 2-year survival rate and accelerated progression in only a few cases.^{28,30} Moreover, with surveillance, progression was identified by follow-up imaging and was used to qualify patients for timely crossover to TEVAR or to ancillary procedures in the primary endovascular group. Finally, anatomic remodeling of the dissected aorta was not only feasible in the initial phase of dissections but also in crossover patients after false-lumen expansion.

INSTEAD was initiated with an assumption of a late death rate of up to 30% in type B dissections,^{4,19,30} which, however, was not confirmed with current modern medical management and surveillance. Although the concept of prophylactic scaffolding to initiate remodeling is intriguing and intuitively promising, a follow-up period longer than 2 years in larger cohorts is probably warranted to reveal differences. INSTEAD was designed to exert a level of power that it eventually failed to reach because the projected absolute difference in mortality rate of 15% from an estimated 20% first-year mortality rate was not seen. Nevertheless, the observed mortality rate in both the medical and endovascular groups was considerably lower than expected.

Thus, INSTEAD calls for a reappraisal of standardized care with blood pressure control and surveillance for patients with distal dissection regardless of treatment. Tailored medical management (in uncomplicated type B dissection) avoids procedure-related adverse events, but patients should be followed up for late complications. In essence, given the outcome of modern medical management, INSTEAD was underpowered, a characteristic, however, that is germane to controlled randomized trials based on historical mortality data. Finally, corroborating previous findings, INSTEAD confirmed that stent grafts enhance false-lumen thrombosis and aortic remodeling in 90% of cases.^{10,33}

Study Limitations

INSTEAD focused on uncomplicated dissections likely to develop late complications; thus, potential benefits of TEVAR may emerge in some patients beyond the 2-year

Type B aortic dissection before and after TEVAR

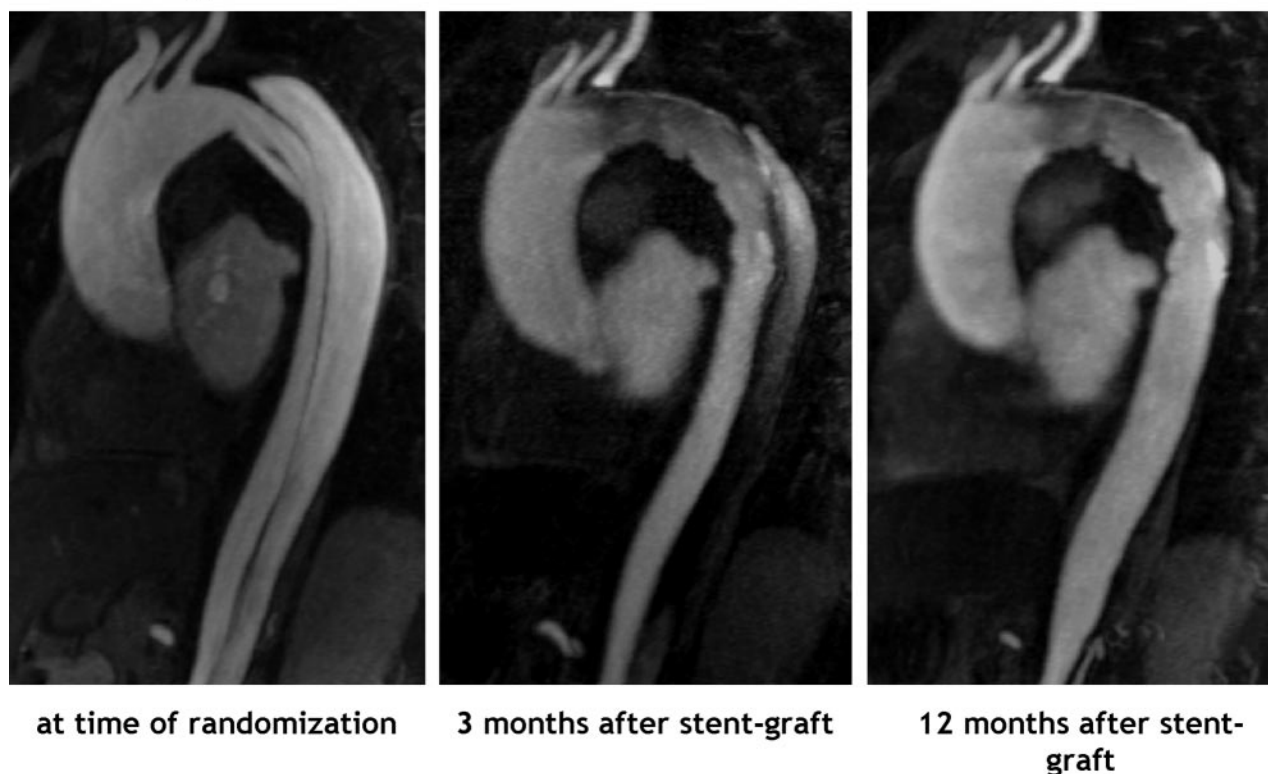


Figure 4. Gadolinium-enhanced sagittal magnetic resonance images of type B dissection before and after endovascular repair. The image at baseline shows a patient at the time of randomization to stent-graft placement; the center image demonstrates the aorta 3 months after TEVAR; and the 12-month scan shows remodeling with complete resolution of false lumen.

window of INSTEAD, whereas all patients were exposed to the risk of TEVAR. Given that high-risk patients with early complications did not qualify for INSTEAD (but were readily treated with TEVAR), stent grafting in INSTEAD was of a prophylactic nature. Chronic dissection ranging from 2 to 52 weeks of onset may include patients with a heterogeneous risk; nevertheless, the trial turned out to be underpowered on the basis of previous outcome assumptions. Both advancing TEVAR technology and growing operator skills are likely to lead to an avoidance of procedure-related adverse events, thus lowering the threshold to use TEVAR in asymptomatic patients at risk despite best medical management.³⁸ Given the current lack of reliable prognostic tools, new risk conditions such as partial false-lumen thrombosis³⁹ or critical false-lumen diameter⁴⁰ may become important for identification of patients for prophylactic TEVAR.

Outlook

The current picture of clinical care is transient, and our current views of best management will soon be outdated; both may be supplanted by growing insight into disease progression in patients with “asymptomatic” or “uncomplicated” dissection. New interventional platforms and improved devices will emerge to address current stent-graft inadequacies.⁴¹ Future trials should focus on defined subgroups to test the prophylactic use of refined and dedicated endografts.

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Disclosures

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CLINICAL PERSPECTIVE

INSTEAD, the first randomized comparison between elective endovascular stent grafting and best medical treatment, justifies medical management for uncomplicated type B aortic dissection and corroborates excellent survival rate with tight blood pressure control and close surveillance. For patients with complications such as progressive expansion or late malperfusion who fail to respond to medical management, deferred endovascular therapy is feasible and safe. The results of INSTEAD do not challenge the endovascular treatment alternative to open surgery and confirm the potential of endovascular therapy to successfully deal with late expansion and distal malperfusion. Nevertheless, primary endovascular therapy in stable type B dissection failed to improve the 2-year survival rate and was associated with spinal injury in 2.9% of cases. Although low death and complication rates in both groups suggest a need for a reappraisal of standardized medical management with monitored blood pressure control, TEVAR is an appropriate crossover strategy in cases of emerging complications. Interestingly, all crossover patients survived elective TEVAR with uneventful follow-up and remodeling despite rather late intervention. INSTEAD supports the notion of a complication-specific approach instead of TEVAR for all type B dissections; patients who survive type B dissection and are given best medical management with surveillance show an excellent 2-year survival rate, with progression to crossover/conversion in only 21%. Surveillance can be used to identify patients with evidence of progression who qualify for safe crossover or conversion. Finally, INSTEAD confirmed that stent-graft scaffolding enhances false-lumen thrombosis and aortic remodeling in type B dissection not only in the early phase of dissections but also in the chronic phase after false-lumen expansion, a notion that may translate to prognostic benefits that could potentially be seen at longer (5-year) follow-up.

Randomized Comparison of Strategies for Type B Aortic Dissection: The INvestigation of STent Grafts in Aortic Dissection (INSTEAD) Trial

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Appendix

The members of the INSTEAD trial consortiums were as follows:

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