Endovascular Repair of Type B Aortic Dissection

Long-term Results of the Randomized Investigation of Stent Grafts in Aortic Dissection Trial

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Background—Thoracic endovascular aortic repair (TEVAR) represents a therapeutic concept for type B aortic dissection. Long-term outcomes and morphology after TEVAR for uncomplicated dissection are unknown.

Methods and Results—A total of 140 patients with stable type B aortic dissection previously randomized to optimal medical treatment and TEVAR (n=72) versus optimal medical treatment alone (n=68) were analyzed retrospectively for aorta-specific, all-cause outcomes, and disease progression using landmark statistical analysis of years 2 to 5 after index procedure. Cox regression was used to compare outcomes between groups; all analyses are based on intention to treat. The risk of all-cause mortality (11.1% versus 19.3%; *P*=0.13), aorta-specific mortality (6.9% versus 19.3%; *P*=0.04), and progression (27.0% versus 46.1%; *P*=0.04) after 5 years was lower with TEVAR than with optimal medical treatment alone. Landmark analysis suggested a benefit of TEVAR for all end points between 2 and 5 years; for example, for all-cause mortality (0% versus 16.9%; *P*=0.0003), aorta-specific mortality (0% versus 16.9%; *P*=0.0005), and for progression (4.1% versus 28.1%; *P*=0.004); Landmarking at 1 year and 1 month revealed consistent findings. Both improved survival and less progression of disease at 5 years after elective TEVAR were associated with stent graft induced false lumen thrombosis in 90.6% of cases (*P*<0.0001).

Conclusions—In this study of survivors of type B aortic dissection, TEVAR in addition to optimal medical treatment is associated with improved 5-year aorta-specific survival and delayed disease progression. In stable type B dissection with suitable anatomy, preemptive TEVAR should be considered to improve late outcome.

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Key Words: aortic dissection ■ aortic remodeling ■ prognosis ■ stent graft

Thoracic endovascular aortic repair (TEVAR) as an option for patients with type B aortic dissection is considered life-saving in the setting of complications such as contained rupture or malperfusion syndrome,[1–4] although its role in uncomplicated dissection is unknown. Traditionally, stable patients are managed with medical treatment (annual survival ≥80%).[3,5–7] However, long-term outcomes are sobering because of aneurysmal expansion and a 30% cumulative mortality at 5 years.[3,8–10] Consistently, false lumen perfusion is considered a harbinger of adverse outcome, whereas complete thrombosis may invoke remodeling and improve outcomes.[11–14] Thus, we hypothesized that endovascular treatment of type B dissection may have long-term prognostic benefits.

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Although TEVAR is valuable for complicated aortic dissection both in the acute and chronic setting, controversy prevails in subacute uncomplicated type B aortic dissection with

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All members of the Investigation of Stent grafts in Aortic Dissection with extended length of follow-up (INSTEAD-XL) study group are listed in the Appendix in the online-only Data Supplement.

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.113.000463/-/DC1.

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WHAT IS KNOWN

- Short-term outcomes improve with endovascular management of complicated type B dissection.
- Long-term outcomes of uncomplicated (initially stable) type B dissection subjected to thoracic endovascular aortic repair are unknown.

WHAT THE STUDY ADDS

- In survivors of type B dissection, thoracic endovascular aortic repair is associated with improved 5-year aorta-specific survival and delayed disease progression.
- In stable type B dissection with suitable anatomy, thoracic endovascular aortic repair should be considered to avoid late complications.

consensus in support of surveillance and control of hypertension.[7,15–17] Conversely, with 30% death rate at 5 years[10] and <50% survival at long term,[18] attention has refocused on long-term outcomes because benefits of TEVAR in dissection may require prolonged follow-up to become apparent. The Investigation of Stent Grafts in Aortic Dissection with extended length of follow-up (INSTEAD-XL; extended for late follow-up) should clarify the late impact of TEVAR in type B dissection, which is considered uncomplicated at the time of trial inclusion.

Methods

Trial Design

The rationale of INSTEAD-XL was to compare medical management alone with additional TEVAR for long-term outcomes in uncomplicated type B dissection. INSTEAD was fully approved by an Institutional Review Committee and Human Rights and Ethics Committee at each participating center, including an amendment for 5 years follow-up (INSTEAD-XL); all subjects gave informed consent. An independent data and safety monitoring board overlooked the trial in scheduled adjudication meetings up to 5 years. Data management and statistical analysis were performed at the coordinating center with oversight by a Critical Event Committee (Appendix in the online-only Data Supplement). No manufacturer providing products or personal support had any role in design, analysis, or interpretation of data.

Trial Procedures

Consecutive patients with uncomplicated type B aortic dissection between 2 and 52 weeks after onset (clustering at 10–12 weeks)[19] in the early chronic phase of dissection were considered candidates for random assignment to TEVAR in addition to optimal medical treatment (OMT) or OMT alone at 7 European centers between November 2003 and December 2005; patients were unsuitable for randomization in presence of an aortic diameter >5.5 cm or with other emerging recurrent complications.[17,19] After evaluating 597 patients and enrolling 140 of them, randomization was performed at a 1:1 ratio according to a computer-generated permuted-block sequence with variable block size and stratified to each study center (sealed containers); written informed consent was obtained. Extended follow-up was amended by each Institutional Ethics Committee.

Interventional Procedures

Based on diagnostic measurements from multislice computed tomography or MRI individually selected, TALENT stent grafts (Medtronic, Inc; Santa Rosa, CA) were used to both scaffold up to 20 cm of dissected aorta (mean, 18.5 cm) and seal major entries (Figure 1) in an interventional suite equipped with digital angiography and optional transesophageal ultrasound. With thoracoabdominal dissection in 88.9% of cases, the extent of aortic coverage ranged from 15 to 35 cm covering the proximal half of the descending thoracic aorta in all cases, and the entire descending thoracic aorta in one third of cases. Femoral access could accommodate the 24 F stent graft system advanced on a 260-cm stiff wire within the true lumen under fluoroscopic or ultrasound guidance; procedural and technical details have been previously reported.[17,19] Surgical revascularization of left subclavian artery (LSA) was left to the discretion of the operator before intentional coverage of the LSA and was performed in 2 of 17 cases. Previous MR angiography was used to identify potential supra-aortic anomalies (lusorian artery, incomplete circle of Willis or dominant left vertebral artery) in case of intended occlusion of LSA.

Clinical Outcomes and End Points

Clinical outcomes including primary end point (all-cause mortality), and secondary end points (aorta-specific mortality and progression of disease) were adjudicated by an independent critical event committee; events were classified in approximation to reporting standards of the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery of The Society for Vascular Surgery/American Association for Vascular Surgery.[20] Classes of complications (systemic, local nonvascular, and local vascular) and grades of severity were assessed; mild complications were not considered for this analysis. The INSTEAD-XL study aimed for annual computed tomography and clinical visits for surveillance, with adjustment of antihypertensive medication if needed; with access to all images and charts, complete clinical follow-up was available in all patients.

Thus, end points were evaluated at 5 years, including all-cause mortality, aorta-specific mortality (defined as death from documented aortic rupture, malperfusion, or proximal dissection, or death within 1 hour of onset of signs, symptoms in absence of coronary, or valvular heart disease), and progression of aortic pathology defined as the combined end point of crossover (to stent graft)/conversion (to open repair), additional endovascular or open surgery for rupture, malperfusion or aortic expansion, or enlarging aortic diameter >5.5 cm. Aortic dimensions and morphological evidence of remodeling was assessed from the latest tomography imaging; aortic remodeling[21] required sealed entry, thrombosed thoracic false lumen with shrinkage along the stent graft, and absence of total diameter progression at levels A and B representing dissected proximal and distal thoracic aortic segments (Figure 1).

Statistical Analysis

All analyses were performed according to a predefined statistical plan. By using study planning software nQuery Advisor version 7.0 (Statsol, Boston, MA), a sample size of 140 patients was determined to detect a reduction of events reflecting the primary end point from 25 with medical management to ≈7.5% with additional TEVAR[10,17,18,22] within 5 years; with equal allocation in 2 groups, power was calculated at 80% at a 2-sided α error of 0.05. Patients and parameters were classified according to randomized allocation. Mean (±SD), medians, and ranges were used to describe continuous variables; intergroup differences were evaluated by use of 2-sample *t* test or nonparametric Mann–Whitney *U* test, depending on the distribution of variables. Categorical variables were presented as frequencies, and percentages were compared by Fisher exact or χ^2 test. Longitudinal data within groups were compared by standard generalized linear model repeated measures analysis of variance. The Mantel–Cox regression method was used to calculate hazard ratios and 95% confidence intervals (CI) for comparison of clinical outcomes. Survival curves were constructed for time-to-event variables using Kaplan–Meier estimates and compared using the log-rank test on an intention-to-treat basis. Landmark analysis was performed according to a prespecified breakpoint at 2

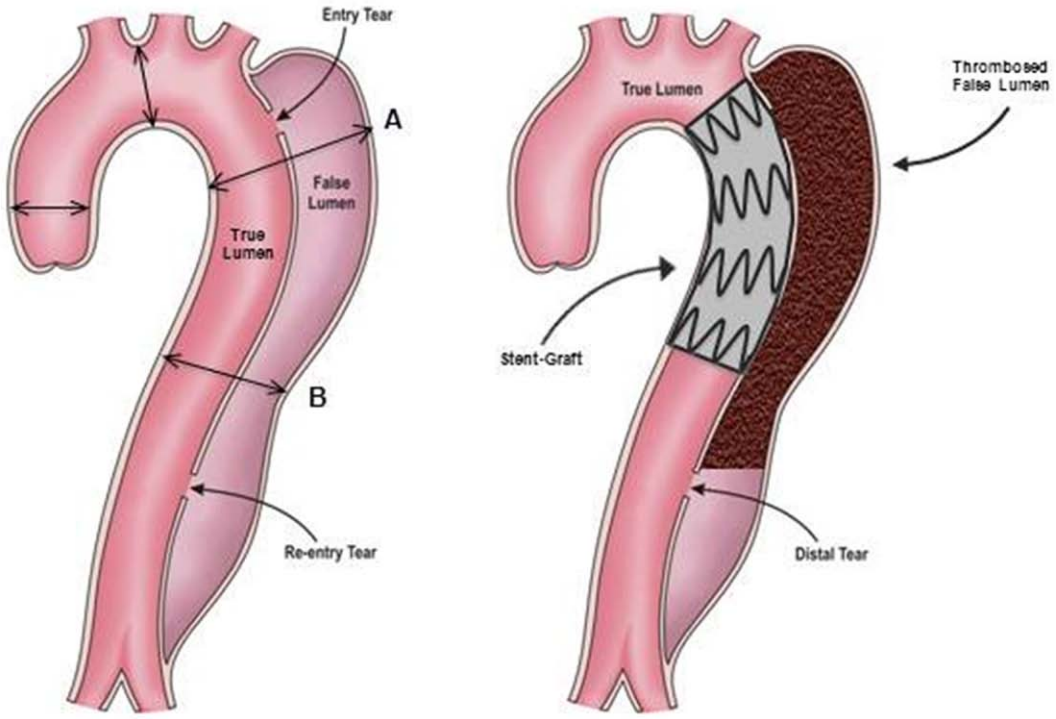

Figure 1. Illustration demonstrating typical features of type B dissection with flow in both the true and the expanded false lumen resulting from a major proximal entry tear (**left**). An endoprosthesis is placed to scaffold the dissected aorta and to seal the entry to the false lumen resulting in reconstruction of the true lumen with subsequent false lumen thrombosis (**right**). Aortic dimensions were defined at the level of the maximum aortic diameter (**A**), and at the hiatus (**B**), and followed over time.

years after randomization with hazard ratios calculated (if possible) for events from randomization up to 24 months and from 24 months to the end of the trial allowing to assess time-dependent response to treatment allocation; supplementary landmark analysis was performed at breakpoints 1 year and 1 month of follow-up. Interaction between treatment effect and follow-up intervals were assessed by χ^2 testing; tests were 2-tailed, and $P<0.05$ was considered statistically significant. Survival analyses were performed using Stata/IC 10.1 for Windows (StataCorp LP, College Station, TX) and IBM SPSS/PC software package version 20.0 (SPSS Inc, Chicago, IL).

Sponsorship for investigator initiated INSTEAD-XL was limited to minor support (Medtronic, Inc) for local study coordinators to collect long-term data; Supplemental (statistical) support was received from Institutional Research Funds (University of Rostock). Both funding sources had no role in trial design, data collection, and interpretation, or writing of the article.

Results

Patients

Between 2002 and 2005, a total of 597 patients were screened with 140 patients qualifying for random assignment to elective TEVAR in addition to OMT (n=72) or OMT alone (n=68); 2 patients failed to undergo TEVAR after randomization because of withdrawn consent in a case and sudden death in another case; 2 patients declined OMT only and opted for TEVAR despite randomization. Overall, 140 patients were followed up with 72 patients allocated to TEVAR and 68 to OMT alone on intention-to-treat basis (Figure 1; Appendix in the online-only Data Supplement). All patients underwent complete protocol-guided follow-up.

There were no significant differences between groups with respect to baseline characteristics, comorbidity profiles, risk factors, and dissection morphology; with a median of 45 and 39 days, respectively, time from dissection to randomization was identical between groups, reflecting the subacute phase of dissection (Table 1). In particular, the number of major abdominal side-branches emanating from the false lumen and perfused via natural fenestrations (reentries) was similar, underlining similarity of pathoanatomic features. The median interval between randomization to TEVAR was 12 days (range, 4–29).

TEVAR was successfully completed in 70 patients with no death or intraprocedural conversion; 1 endoprosthesis was used in 58 (82.9%) patients, 2 in 8 (11.4%), and 3 endoprostheses in 4 (5.7%) patients. Intentional LSA occlusion was documented in 17 cases (24.3%), 2 of which had previous revascularization with no sustained neurological sequelae. Periprocedural events included 3 ancillary endovascular procedures and 3 neurological events (1 paraplegia/hypotension, 1 stroke after LSA revascularization, and 1 transient paraparesis after LSA occlusion without previous revascularization; Table 1; Appendix in the online-only Data Supplement).

Patients were followed up until September 30, 2010 (minimum, 5 years; maximum, 8 years); the median interval until death or latest follow-up was 69 months (interquartile range, 62–83); and no patient was lost to follow-up. Clinical surveillance had documented adjusted antihypertensive medication and ≤130 mm Hg systolic pressure in 90% of cases in both groups (Table 2; Appendix in the online-only Data Supplement); active smoking was reduced to 12% in the OMT group and to 10% after TEVAR (P=0.788). Tomographic imaging at 5 years was available in 103 of 111 survivors with

Table 1. Baseline Characteristics of Patients

Characteristics	Medical Therapy (n=66)	Medical Therapy + Stent Graft (n=70)	*P* Value
Age, y	60.1±11.7	60.3±10.7	0.84*
Male sex, n (%)	56 (82.4)	62 (86.1)	0.64†
Atherosclerosis/ hypertension, n (%)	56 (82.4)	61 (84.7)	0.82†
Marfan Syndrom, n (%)	0 (0)	2 (2.8)	0.50†
Hypertension only, n (%)	11 (16.2)	7 (9.7)	0.44†
Unknown, n (%)	2 (2.9)	2 (2.8)	1.00†
Diabetes mellitus, n (%)	6 (8.8)	5 (6.9)	1.00†
Active smoking, n (%)	17 (25.0)	14 (19.4)	0.54†
Pulmonary disease, n (%)	9 (13.2)	7 (9.7)	0.60†
Body mass index	27.7±5.5	26.7±4.4	0.21*
NYHA classification, n (%)			0.33‡
I	51 (75.0)	55 (76.4)	
II	13 (19.1)	16 (22.2)	
III	4 (5.9)	1 (1.4)	
ASA class, n (%)			0.16‡
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 dissection aorta, mm	43.5±9.3	44.2±9.5	0.59§
Dissection morphology, n (%)			0.56†
Confined to descending thoracic aorta	5 (7.4)	8 (11.1)	
Thoracoabdominal extension	63 (92.6)	64 (88.9)	
Reentry, n (%)			0.23‡
No	23 (34.8)	20 (28.6)	
Thoracic	14 (21.2)	8 (11.4)	
Abdominal	24 (36.4)	33 (47.1)	
Thoracoabdominal	5 (7.6)	9 (12.9)	
False lumen, n (%)			0.86†
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)	0.79

Values are mean±SD. ASA denotes American Society of Anesthesiology class; and NYHA, and New York Heart Association functional class. Baseline characteristics reveal no significant differences between groups.

*Two-sample *t* test.

†Fisher exact test.

‡χ^2 Test.

§Nonparametric Mann–Whitney *U* test.

a median interval of 63±4 months. During the entire study period, 93 TEVAR procedures were performed, including 21 TEVAR during 5 years follow-up beyond group assignment. In patients randomized to OMT alone, late TEVAR was necessary in 14 cases (including 5 emergencies) and conversions to open repair in 4 cases, both for enlarging false lumen diameter; conversely, in the TEVAR group, additional stent graft was required in 7 and conversion to open repair in 3 cases (Table 3; Appendix in the online-only Data Supplement). There was no periprocedural mortality with crossover to TEVAR or conversion to open repair; by the end of 2010, a total of 117 patients were alive, 27 of which had not undergone aortic repair.

Table 2. Aorta-Specific and Nonrelated Mortality Since Randomization

Outcome	OMT (n=68) n/Total n (Rate/100 Person-y)	OMT+TEVAR (n=72) n/Total n (Rate/100 Person-y)	*P* Value
Aorta-specific mortality			
All patients			
Time since randomization			
0–12 mo	2/68 (3.0)	5/72 (7.5)	0.44
12–24 mo	0/66 (0)	0/65 (0)	…
24–60 mo	11/66 (3.6)	0/64 (0)	0.001
>60 mo	1/50 (0.3)	0/55 (0)	0.48
Nonrelated mortality			
All patients			
Time since randomization			
0–12 mo	0/68 (0)	2/72 (3.0)	0.50
12–24 mo	0/66 (0)	1/65 (0.8)	0.50
24–60 mo	0/66 (0)	0/64 (0)	…
>60 mo	1/50 (0.3)	0/55 (0)	0.48

OMT indicates optimal medical treatment; and TEVAR, thoracic endovascular aortic repair.

All-Cause Mortality

Figure 2A shows the cumulative probability of all-cause death at 5 years with landmark analysis at 2 years breakpoint (top); >5 years all-cause mortality trended lower in patients randomized to TEVAR than with OMT alone (11.1±3.7% versus 19.3±4.8%; *P*=0.13; bottom). Kaplan–Meier curves demonstrate survival benefit with TEVAR seen between 2 and 5 years (100% versus 83.1±4.7%; *P*=0.0003), but not yet within 2 years of follow-up (88.9±3.7% versus 97.9±2.0%; hazard ratio, 3.96; 95% CI, 0.84–18.6; *P*=0.082). The test for interaction between treatment effect and time was significant ($P_{interaction}$=0.0002) suggesting a late survival benefit after TEVAR. Additional Landmark analysis at 1 year and at 1 month of follow-up revealed consistent findings (Figure IIA in the online-only Data Supplement).

Aorta-Specific Mortality

Figure 2B (top) depicts the estimated cumulative aorta-specific mortality at 5 years with landmark analysis at 2 years breakpoint. At 5 years, the aorta-specific mortality was 6.9±3.0% with TEVAR, and 19.3±4.8% with OMT alone (*P*=0.045; bottom). Again, Kaplan–Meier curves diverged during late follow-up with landmark analysis demonstrating survival benefit of TEVAR compared with OMT between 2 and 5 years (100% versus 83.1±4.7%; *P*=0.0005) rather than during the initial 2 years (93.1±3.0% versus 97.1±2.0%, hazard ratio, 2.46, 95% CI, 0.48–12.7; *P*=0.283). Test for interaction between treatment outcomes and time was significant ($P_{interaction}$=0.004),

Table 3. Causes of Death Since Randomization

	OMT	OMT+TEVAR
0–12 mo	#01 (AR-73) MPS	#01 (AR-6) type A
	#02 (AR-244) R	#02 (AR-15) R
		#03 (AR-30) MPS
		#04 (AR-53) R
		#05 (AR-71) R
		#06 (NR-112) AMI
		#07 (NR-293) PN
12–24 mo	#03 (AR-722) R	#08 (NR-429) cancer
24–36 mo	#04 (AR-745) R	
	#05 (AR-900) type A	
	#06 (AR-1000) SD	
36–48 mo	#07 (AR-1101) R	
	#08 (AR-1110) R	
	#09 (AR-1344) SD	
	#10 (AR-1349) R	
	#11 (AR-1401) R	
48–60 mo	#12 (AR-1629) SD	
	#13 (AR-1650) R	
60–72 mo	#14 (AR-2075) SD	
	#15 (NR-2421) cancer	

Numbers with AR or NR denote days from randomization to death. AMI indicates acute myocardial infarction; AR, aorta-related death; MPS, malperfusion syndrome; NR, not aorta-related death; OMT, optimal medical treatment; PN, pneumonia; R, aortic rupture; SD, sudden death (death within 1 hour in patients with known absence of coronary or structural heart disease); TEVAR, thoracic endovascular aortic repair; and Type A, type A aortic dissection.

suggestive of late benefit of TEVAR on aorta-related mortality; Landmark analysis at 1 year and at 1 month documented consistent findings of late benefit (Figure IIB in the online-only Data Supplement).

Progression of Disease and Aorta-Specific Events

Figure 2C illustrates the Kaplan–Meier analysis of the combined end point of disease progression (aorta-specific death, crossover/conversion, and secondary procedures) and aorta-specific events, including Landmark analysis at 2 years breakpoint. At 5 years of follow-up cumulative freedom from this cluster end point was 53.9±6.1% with OMT alone and 73.0±5.3% with TEVAR. Landmark analysis (top) revealed both for TEVAR and OMT similar pattern of freedom from progression until 2 years (76.1±5.1% versus 75.0±5.3%; hazard ratio, 0.997; 95% CI, 0.51–1.95; P=0.994), however, diverging survival estimates after 2 years with plateauing course after TEVAR versus ongoing events with OMT (95.9±2.8% versus 71.9±6.4%; hazard ratio, 0.112; 95% CI, 0.03–0.49; P=0.004) (attributed to crossover/conversion and aorta-specific death). Additional Landmark analysis with breakpoints at 1 year and at 1 month revealed nearly consistent results (Figure IIC in the online-only Data Supplement).

The observed deviation from the proportional-hazards assumption for total and aorta-specific mortality with slightly higher early death rate from peri- and postinterventional complications after TEVAR (hazard ratios, 3.96 and 2.46) was counterbalanced by decreasing late risk of all-cause and aorta-specific death between 24 and 60 months (Figure 2A and 2B; Table 2).

Individual causes of death stratified by temporal occurrence since randomization with 19 aorta-related fatalities are shown in Table 3. Events leading to crossover or open conversion occurred more frequently with OMT than after TEVAR (Table 3; Appendix in the online-only Data Supplement). There was no evidence of significant interactions between the TEVAR group and age, sex, or false lumen diameter for either total or aorta-specific mortality (P>0.10 for all comparisons). However, retrospective assessment revealed that the diameter of the proximal entry may identify an asymptomatic patient at risk. All patients in the medical arm that ruptured during follow-up had an entry tear >10 mm in diameter (14±4 mm), similar to patients who crossed over for critical expansion (13±4 mm).

Aortic Remodeling

Evolution of aortic remodeling is summarized in Table 4. Although baseline dimensions were similar in dissected segments A and B between groups, TEVAR led to expansion of the true lumen at level A from 19.4±8.4 to 32.4±5.5 mm at 2 years (P<0.0001), and to 32.6±5.5 mm at 5 years (P<0.0001); corresponding changes were documented at level B. Simultaneously, false lumen diameter at level A shrunk after TEVAR from 29.3±12.4 to 8.6±13.4 mm at 2 years (P<0.0001) and to 10.4±13.2 mm at 5 years (P<0.0001); similar evolution was seen at level B (Table 4).

Moreover, complete false lumen thrombosis was confirmed in 90.6% at thoracic level with morphological evidence of remodeling in 79.2% at 5 years after TEVAR (Figure 3). Conversely, OMT alone failed to demonstrate significant true lumen recovery or false lumen shrinkage, but was associated with expansion of maximum aortic diameter from 43.6±9.2 to 56.4±6.8 mm (P<0.0001); moreover, false lumen thrombosis and remodeling was rarely seen (Table 5). Subsequently, crossover/conversion continued to occur more often in the OMT group after 2 years (Table 3; Appendix in the online-only Data Supplement); conversely, with TEVAR, late reinterventions were only necessary in 2 cases (with the use of 1 stent graft for false lumen expansion and 1 bare stent for distal true lumen narrowing).

Discussion

Long-term results of INSTEAD-XL challenge the current consensus on treatment of uncomplicated type B aortic dissection, for example, default medical management with focus on blood pressure and surveillance. Because long-term prognosis of type B dissection is sobering with 20% to 42% mortality at 5 years[6,10,22] and an estimated rupture rate of 30% once aortic expansion reaches 60 mm,[23,24] medical management may at best delay progressive expansion. Conversely, TEVAR in the subacute (stable) phase of distal aortic dissection induces aortic remodeling and reduces aorta-related mortality >5 years as compared with controlled medical management with optional crossover to TEVAR or open repair when complications emerge. Early hazard with TEVAR is likely counterbalanced

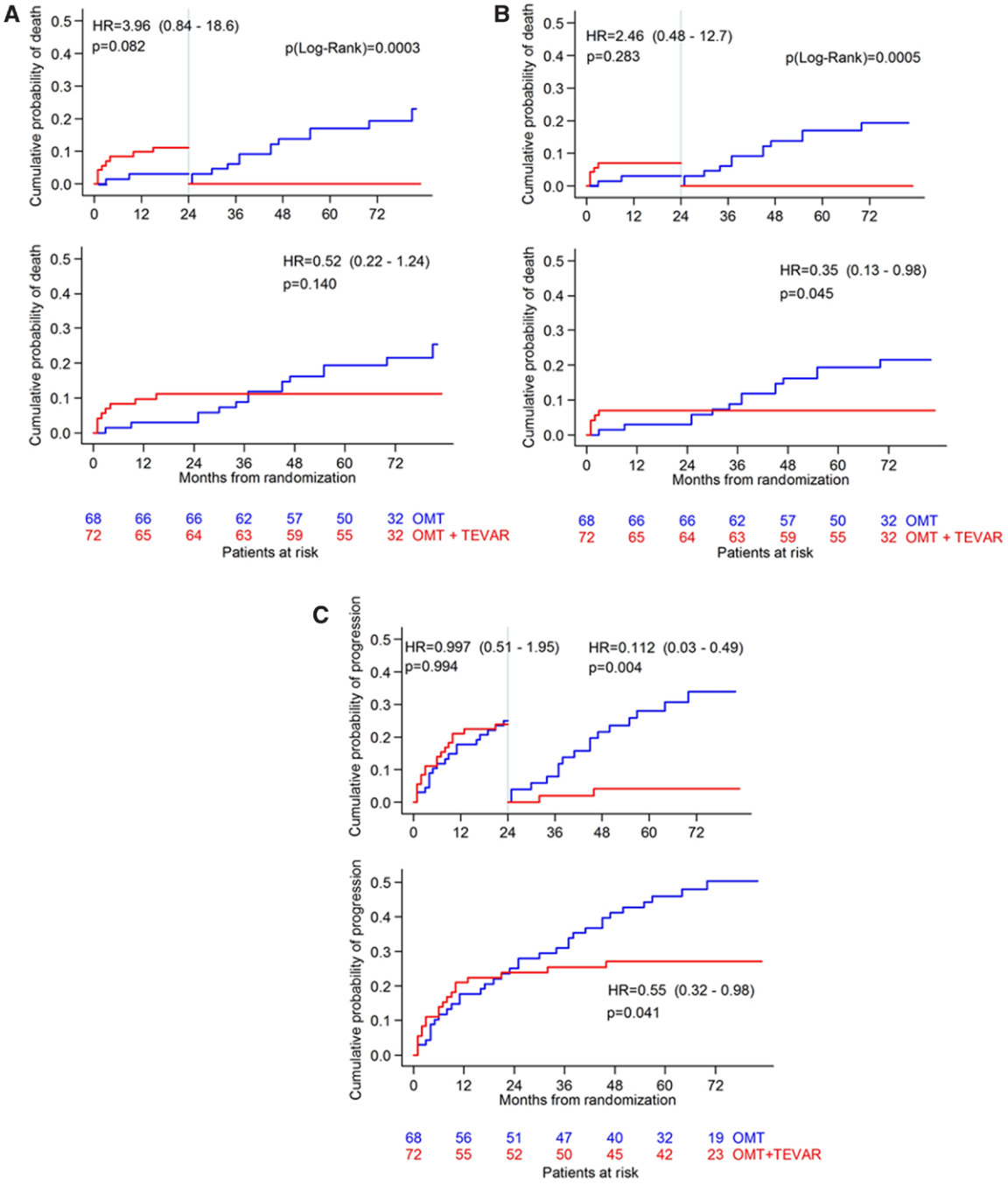

Figure 2. A, Kaplan–Meier estimates of all-cause mortality (death) and Landmark analysis with a breakpoint at 24 months after randomization to the end of the trial are shown for optimal medical treatment (OMT) and OMT + thoracic endovascular aortic repair (TEVAR) groups. After 2 years of follow-up, TEVAR revealed beneficial prognostic benefit. **B**, Kaplan–Meier estimates of aorta-specific mortality (death) and Landmark analysis with the breakpoint at 24 months after randomization to the end of the trial are shown for OMT and OMT+TEVAR groups. After 2 years of follow-up, the observed mortality was lower with TEVAR than with OMT alone. **C**, Kaplan–Meier estimates of a combined end point of progression and adverse events (aorta-related death, conversion, and ancillary interventions, including the second stent graft procedure, access revision, peripheral interventions) with a breakpoint at 24 months are shown for OMT and OMT+TEVAR. With TEVAR, less progression of disease was observed in the late phase of follow-up compared with OMT.

by prevention of late complications and (mostly emergent) crossover procedures; a reduction of aorta-specific mortality becomes evident after 24 months of follow-up (Table 2). Although preemptive TEVAR was associated with an excess early mortality (attributable to periprocedural hazards), the procedure turned beneficial at 5 years of follow-up with an number needed to treat of 13. Thus, INSTEAD-XL corroborates recent observational evidence, suggesting long-term beneficial results of TEVAR in subacute and chronic dissection.[4,12,25] With safer procedures attributable to improved operator skills and better technology, TEVAR may emerge as first-line therapy of type B dissection; the attempt to heal and remodel dissected aorta may replace the current complication-specific strategy.

Table 4. Morphological Characteristics Over Time

Characteristics	OMT (n=68)	OMT+TEVAR (n=72)	*P* Value
Baseline type B dissection			
Maximum aortic diameter	43.6±9.2*	44.1±9.6	0.65
True lumen diameter at level A	20.3±9.3*	19.4±8.0*	0.55
False lumen diameter at level A	27.7±11.6*	29.3±12.4*	0.65
True lumen diameter at level B	17.3±8.7	17.4±10.7*	0.91
False lumen diameter at level B	24.0±10.4*	26.9±10.9*	0.13
2-y follow-up			
Maximum aortic diameter	46.3±9.9	43.9±11.4	0.24
True lumen diameter at level A	22.7±10.9	32.4±5.5	<0.0001
False lumen diameter at level A	25.4±14.8	8.6±13.4	<0.0001
True lumen diameter at level B	19.1±8.6	29.7±7.0	<0.0001
False lumen diameter at level B	24.3±12.2	11.5±13.7	<0.0001
False lumen thrombosis at 2 y†			
Complete, n (%)	13/67 (19.4)	63/69 (91.3)	<0.0001
Partial‡, n (%)	6/66 (9.1)	6/69 (8.7)	1.00
5-y follow-up			
Maximum aortic diameter	56.4±6.8	44.5±11.5	<0.0001
True lumen diameter at level A	18.7±6.7	32.6±5.5	<0.0001
False lumen diameter at level A	37.1±9.1	10.4±13.2	<0.0001
True lumen diameter at level B	16.9±7.2	28.6±6.4	<0.0001
False lumen diameter at level B	31.2±11.9	13.4±13.1	<0.0001
False lumen thrombosis at 5 y†			
Complete, number (%)	11/50 (22.0)	48/53 (90.6)	<0.0001
Partial‡, number (%)	6/50 (12.0)	5/53 (9.4)	0.76

Values are mean±SD, numbers in parenthesis reflect percentage; OMT indicates optimal medical treatment; and TEVAR, thoracic endovascular aortic repair.

*P<0.001 vs 2 y and 5 y (repeated measures analysis).

†Throughout the level of the descending thoracic aorta.

‡Partial false lumen thrombosis used as defined in Tsai et al[40] with residual (retrograde) perfusion of the false lumen despite evidence of layered thrombosis.

Moreover, INSTEAD-XL suggests medical management and surveillance were associated with failure to prevent late complications, such as expansion, rupture, and late crossover/conversion to emergent TEVAR, conveying a higher aorta-specific mortality. The notion of uncomplicated type B dissection may in fact be a misnomer and should be reconsidered because the need for late repair of critical expansion and progression of dissection is common.[6,10,26,27] Thus, initial clinical stability does not preclude emergent silent expansion and even rupture; both events are preventable by endovascular management in the early phase.

Despite encouraging early and mid-term survival of uncomplicated type B dissection with medical management,[5,6,17] chronic expansion and late rupture even without critical expansion were not heralded; although TEVAR in an early complicated scenario reveals immediate therapeutic resolution of the complication, elective TEVAR embodies a preemptive element requiring long-term observation to prove benefit. Finally, the association between TEVAR and aortic remodeling suggests concordance of healing with clinical outcomes.

INSTEAD-XL reveals, with elective TEVAR of aortic dissection, an association with favorable aortic remodeling and long-term survival despite early hazard, although medical management was associated with failure to prevent progressive expansion or late complications triggering steady crossover to TEVAR at 5 years. Conversely, reinterventions after primary TEVAR were few and clustered in the first year. Such long-term stability in patients with stented aorta may be dissection specific and explained by healing, and thereby different from less encouraging experience in aneurysmatic disease.[28] Although elective crossover and endovascular reintervention were generally safe, corroborating observations in chronic type B dissection,[14] emergency TEVAR portends considerable mortality[29,30]; emergencies may in fact be avoided by both imaging surveillance and elective TEVAR.

The concept of TEVAR already embraced to replace open surgery for managing complications of type B dissection (even without any randomized data)[2,4,31–33] may now be extended to manage stable (initially uncomplicated) type B dissection because the potential to remodel dissected aorta and prevent late expansion and malperfusion has been confirmed.[21,34] With completed 5-year surveillance in all survivors, any discordance

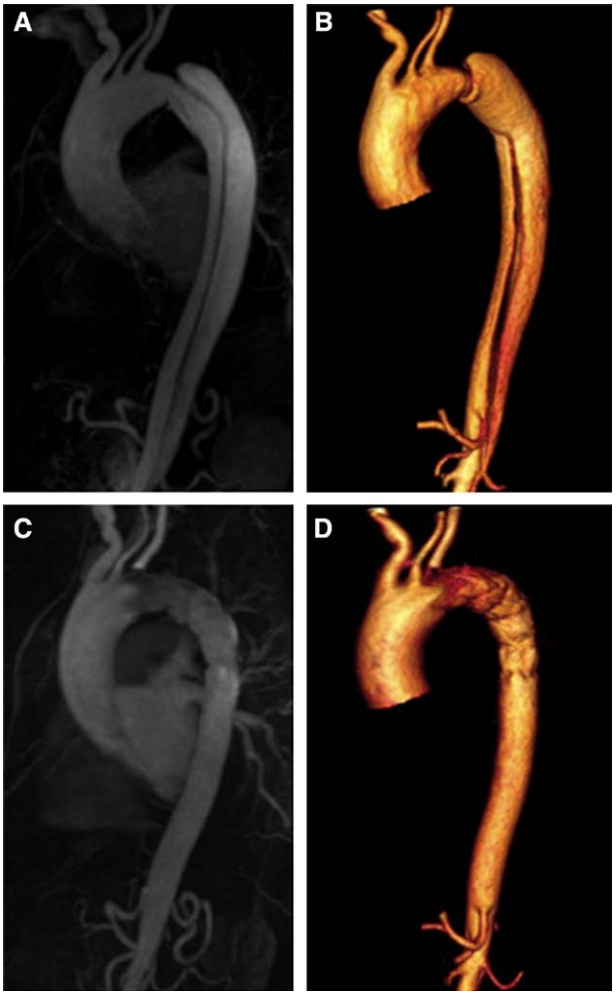

Figure 3. Gadolinium-enhanced sagittal MR angiogram of type B dissection before randomization (**top**) and 5 years after endovascular repair (**bottom**). Sagittal maximum intensity projection (**A** and **C**) and 3-dimensional reconstructed scans (**B** and **D**) show complete aortic remodeling with time; the left subclavian artery is filled by collaterals after intentional coverage with the endograft.

Table 5. Aortic Morphology at 5 Years

	OMT	OMT+TEVAR	*P* Value
FL thrombosis	11/50 (22.0%)	48/53 (90.6%)	<0.0001
Partial FL/no FL thrombosis	39/50 (78.0%)	5/53 (9.4%)	<0.0001
Remodeling of thoracic aorta*	5/50 (10.0%)	42/53 (79.2%)	<0.0001
Critical expansion of thoracic aorta†	33/50 (66.0%)	11/53 (20.8%)	<0.0001

FL indicates false lumen; OMT, optimal medical treatment; and TEVAR, thoracic endovascular aortic repair.

*Based on aortic morphology as assessed vs baseline.

†Occurring within long-term follow-up.

of aortic remodeling with clinical outcomes after TEVAR was refuted. These initial findings are promising and may prelude a paradigm shift in managing type B aortic dissection.

Nonetheless, with 3 conversions to open surgery in both groups within 2 years, and 2 cases of spinal injury, TEVAR is not always safe[35,36]; however, procedural risk may be lowered by referral to high-volume centers, preemptive carotido-subclavian bypass and dissection-specific endoprosthetic technology. Moreover, elective TEVAR within 90 days of dissection benefits from ongoing aortic plasticity with better remodeling.[37]

Thus, different from early outcomes, INSTEAD-XL suggests survival benefit from preemptive TEVAR in patients surviving type B dissection in addition to OMT and surveillance. Considering the few cases of progression after 2 years of elective TEVAR, surveillance may be tapered once remodeling was documented. Finally, remodeling of dissected aorta seems in concordance with long-term vascular survival.

INSTEAD-XL was initiated assuming 35% late mortality in type B dissection[6,10,22] with medical management; however, with surveillance, adjusted medication, and an option to crossover, OMT outcomes were better than in previous registries, further explaining the need for long-term follow-up to demonstrate the impact of preemptive TEVAR. Although real world 5-year cumulative mortality of type B dissection is 28% with β-blockers, and 25% with calcium antagonists compared with 33% and 36% without those drugs,[10] 21.6% mortality with OMT was even lower in INSTEAD-XL, reflecting the nature of a controlled trial. INSTEAD-XL confirms standardized care with blood pressure control for patients with distal dissection regardless of symptoms but eventually encourages elective TEVAR in suitable patients for long-term benefit.

Limitations

For stable survivors of type B dissection, benefits of TEVAR begin to show after 2 years of follow-up. Landmarking at 2 years of follow-up was selected a priori in anticipation of events both before and after 2 years.[17] Nevertheless, with Landmark analysis, findings become observational because some confounders may not be accounted for, and early events may be omitted, thus rendering the analysis susceptible to time point–specific results and loss of power.[38] The risk of dependence on any lack of proportionality of hazards, however, was partly defused by additional Landmarking at 12 months and at 1 month of follow-up with consistent results with late benefit of TEVAR (Figure IIA–IIC in the online-only Data Supplement).

Nevertheless, for some very old patients, the benefit may not emerge during expected lifetime; yet, preemptive TEVAR seems useful for younger patients, although advanced age and severe comorbidities may still favor medical management. Similarly, patients with hereditary connective tissue disease will probably require open surgery. Conversely, advancing TEVAR technology and growing operator skills may avoid procedure-related risks and lower the threshold for early TEVAR to avoid late complications.[39] Before preemptive scaffolding is widely accepted, asymptomatic patients at risk, for example, with partial false lumen thrombosis ideally addressed by cine-MRI,[40] critical false lumen diameter,[41] or a large entry tear should be considered for TEVAR.

Outlook

Our current picture of best medical care for aortic dissection may be supplanted by growing insight into disease progression regardless of symptoms or complications. Uncomplicated aortic dissection seems a misnomer, and any distal dissection may be considered a vascular complication requiring repair by an effective strategy.

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Endovascular Repair of Type B Aortic Dissection: Long-term Results of the Randomized Investigation of Stent Grafts in Aortic Dissection Trial

Christoph A. Nienaber, Stephan Kische, Hervé Rousseau, Holger Eggebrecht, Tim C. Rehders, Guenther Kundt, Aenne Glass, Dierk Scheinert, Martin Czerny, Tilo Kleinfeldt, Burkhart Zipfel, Louis Labrousse, Rossella Fattori and Hüseyin Ince
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Supplemental material:

Supplemental Table 1
Procedural and periprocedural characteristics with TEVAR

Days from randomization to stent-graft– median (range)	12 (4 – 29)
General anesthesia - number (%)	68/70 (97.1)
Duration of procedure – median minutes (range)	108 (20 – 200)
Intraprocedural death - number (%)	0 (-)
Procedural success - number (%)	67 (95.7)
Stent-graft per patient - number (range)	1.34 (1 – 3)
Femoral access - number (%)	66 (94.3)
Occlusion of LSA - number (%)	17 (24.3)
Carotido-subclavian bypass - number (%)	2 (2.9)
Hospital stay – median days (range)	8 (5 – 29)
ICU stay - median hours (range)	23 (12 – 128)
Mortality, n (%)	2 (2.8)
Periprocedural events	
Retrograde type A dissection - number (%)	1 (1.4)†
Rupture of iliac access vessel - number (%)	1 (1.4)†
Conversion to open surgery - number (%)	0 (-)
Ancillary procedures/injuries - number (%)	3 (4.3)
Stenting of iliac artery - number (%)	1 (1.4)
Aortic stent-graft extension - number (%)	1 (1.4)
Aortic bare stent extension - number (%)	1 (1.4)
Periprocedural neurologic events - number (%)	
Paraplegia - number (%)	1 (1.4)
Major stroke - number (%)	1 (1.4)
Transient paraparesis – number (%)	1 (1.4)

ICU, intensive care unit; LSA, left subclavian artery.

†, death at day 24 and 30

Supplemental Table 2

Blood pressure and medication (in both groups over time)

	OMT	OMT + TEVAR
Baseline		
Mean blood pressure (mmHg)	118	117
≤ 130 mmHg systolic (%)	35	37
Antihypertensive medication (%)	64	65
- ßeta-receptor blockers	52	51
- diuretics	30	30
- ACEI/ARB	18	19
- Calcium blockers	6	5
- Direct renin antagonists	-	-
- α-receptor blockers	-	-
1 year F/U		
Mean blood pressure (mmHg)	95	96
≤ 130 mmHg systolic (%)	90	90
Antihypertensive medication (%)	100	100
- ßeta-receptor blockers	96	97
- diuretics	66	66
- ACEI/ARB	58	60
- Calcium blockers	40	41
- Direct renin antagonists	10	10
- α-receptor blockers	10	10
2 years F/U		
Mean blood pressure (mmHg)	97	96
≤ 130 mmHg systolic (%)	90	91
Antihypertensive medication (%)	100	100
- ßeta-receptor blockers	92	93
- diuretics	64	62
- ACEI/ARB	62	63
- Calcium blockers	42	44
- Direct renin antagonists	9	8
- α-receptor blockers	5	6

5 years F/U		
Mean blood pressure (mmHg)	97	95
≤ 130 mmHg systolic (%)	91	91
Antihypertensive medication (%)	100	100
- ßeta-receptor blockers	90	89
- diuretics	62	60
- ACEI/ARB	62	63
- Calcium blockers	40	43
- Direct renin antagonists	8	10
- α-receptor blockers	3	4

Supplemental Table 3

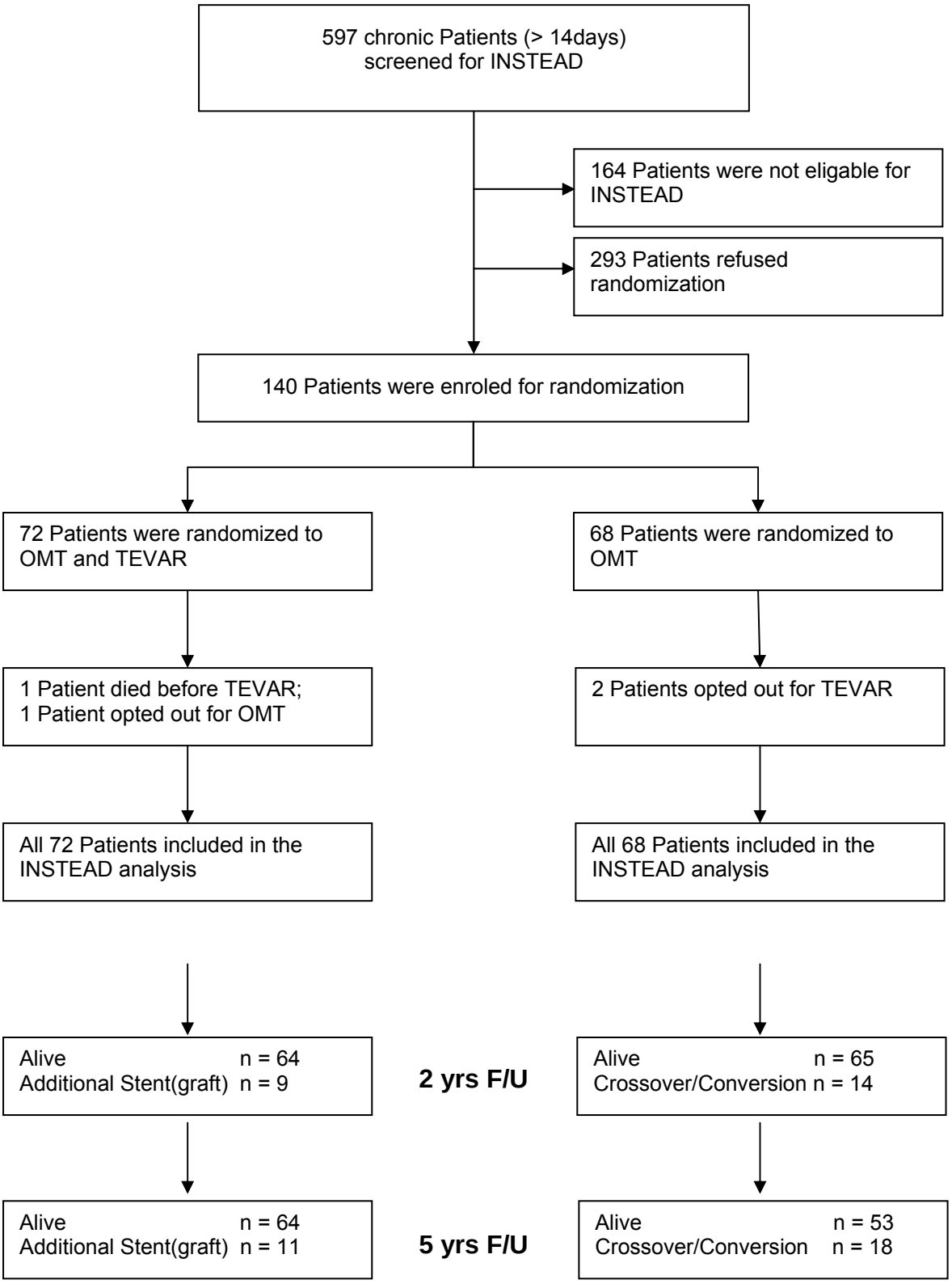
Crossover, TEVAR extension and conversion to surgery during 5 years F/U

	OMT (n=68)	**OMT + TEVAR (n=72)**
Since randomization	2 received TEVAR	2 did not receive TEVAR
2 years F/U	14 events 3 conversions 3 emergent TEVAR 8 elective TEVAR	10 events 3 conversions 6 elective TEVAR 1 bare stent
5 years F/U	4 events 1 conversion 2 emergent TEVAR 1 elective TEVAR	2 events 1 elective TEVAR 1 bare stent extension
Overall ITT Σ	18/68 (26.5%)	12/72 (16.7%)
per protocol	18/66 (27.3%)	12/72 (16.7%)

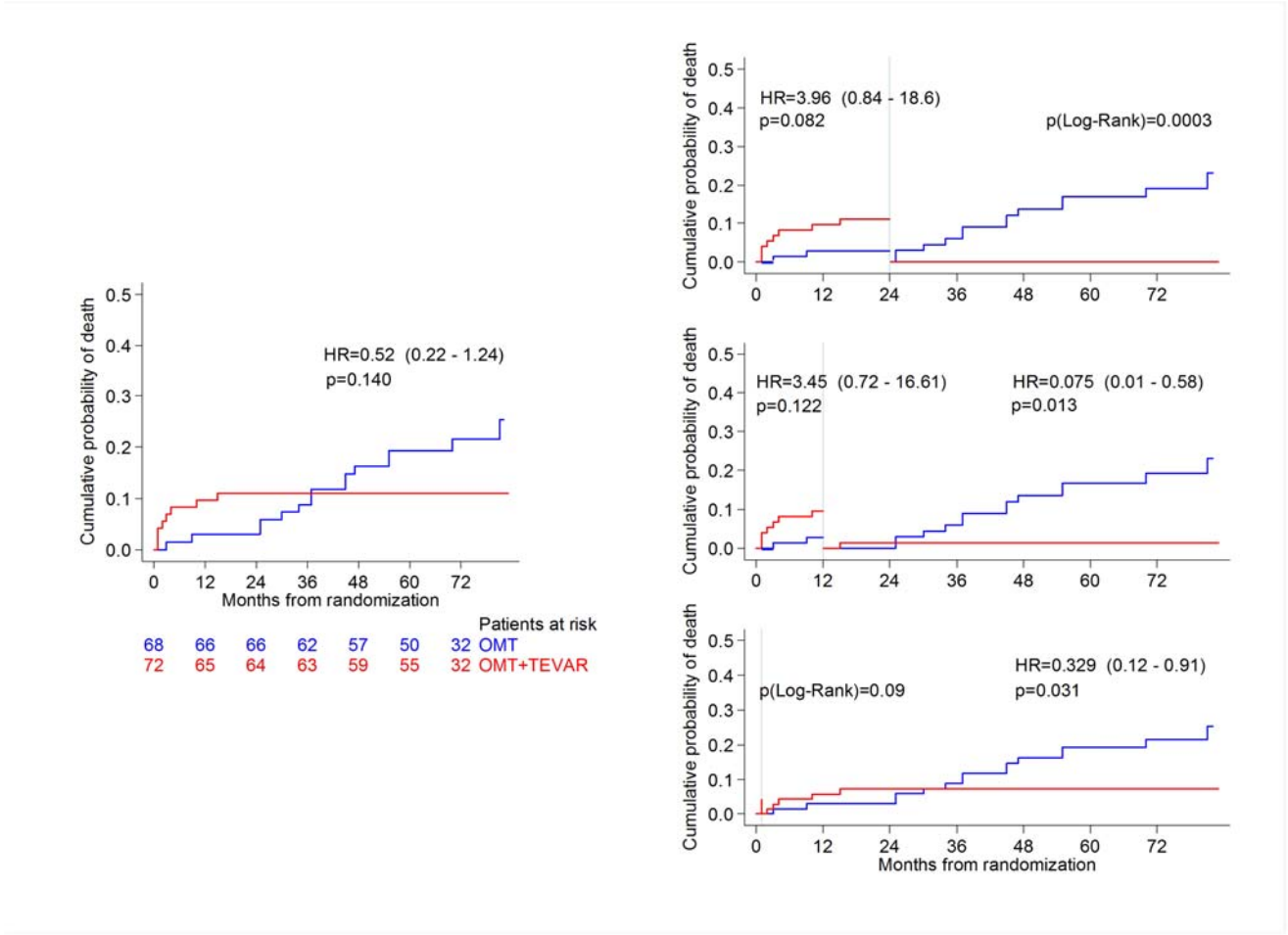
ITT, intention to treat;

Supplemental Figure 1

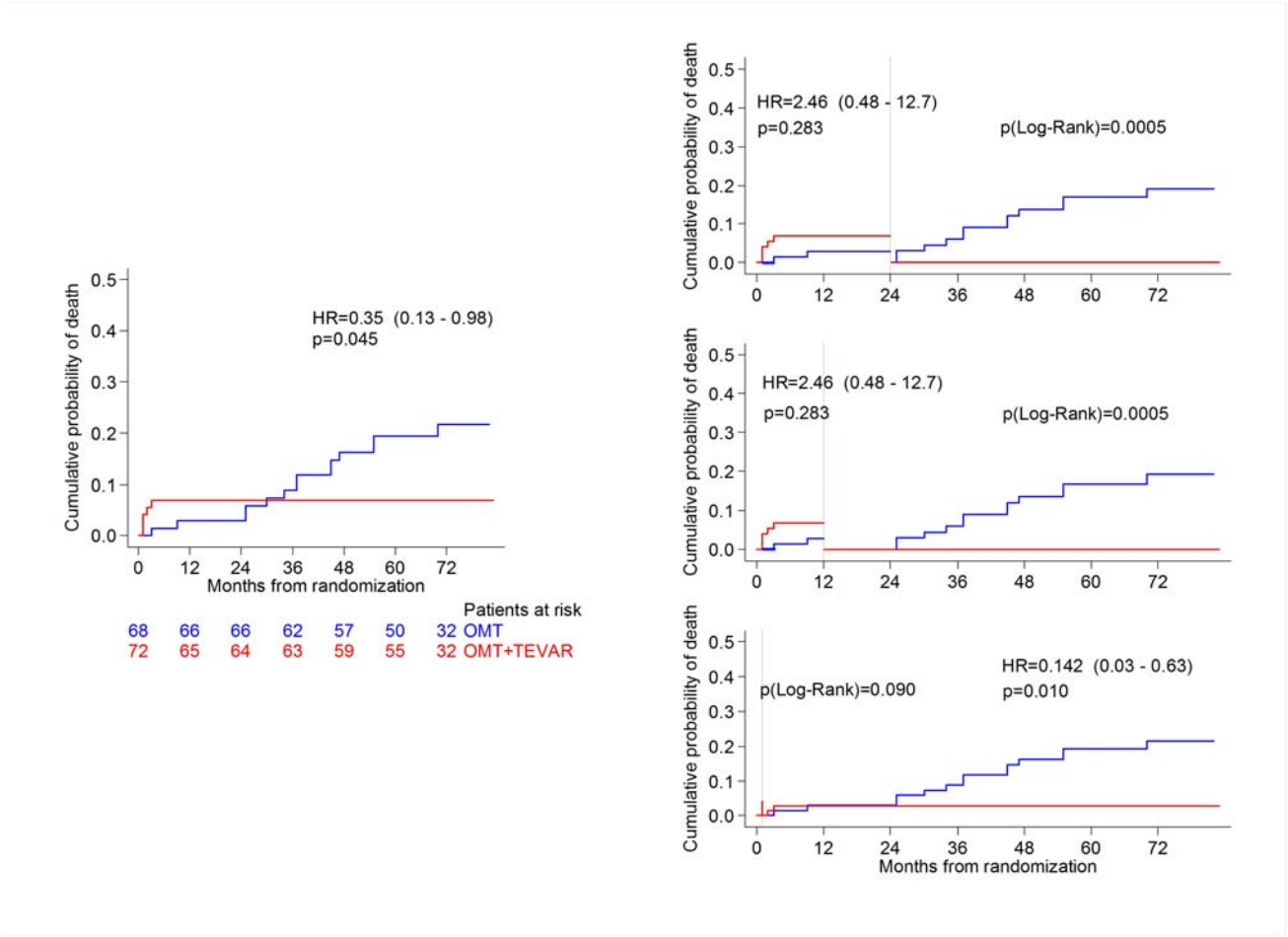
INSTEAD Trial Enrolment and long-term Follow-Up



Supplemental Figure 2a



Supplemental Figure 2b



Supplemental Figure 2c

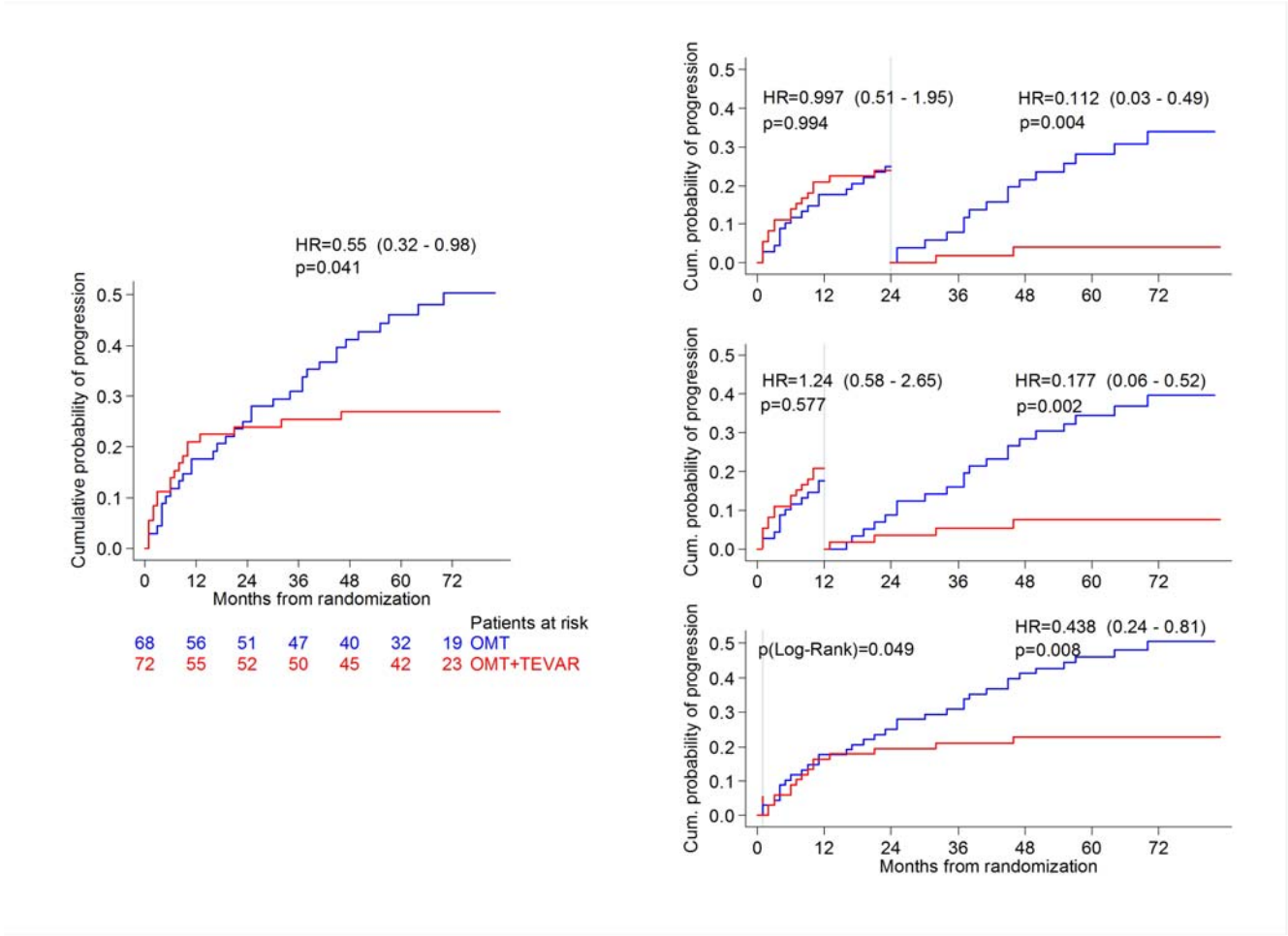


Figure legends

Figure 1

INSTEAD trial enrolment and long-term follow-up; OMT, optimal medical treatment; TEVAR, thoracic endovascular aortic repair.

Figure 2a:

Composite graphical display of standard Kaplan-Meier estimates of all-cause mortality over ≥ 5 years of follow-up in INSTEAD-XL (left), and in the format of Landmark analysis with breakpoints at 24 months, 12 months and 1 month. The consistency of the findings with various breakpoints defuses the risk of stage migration with Landmark analyses.

Figure 2b:

Composite display of standard Kaplan-Meier estimates of aorta-specific mortality over ≥ 5 years of follow-up in INSTEAD-XL (left), and formatted as Landmark analysis with breakpoints at 24 months, 12 months and 1 month. Consistent results with various breakpoints minimizing the risk of stage migration.

Figure 2c:

Composite display of standard Kaplan-Meier estimates of progression and adverse events over ≥ 5 years of follow-up in INSTEAD-XL (left), and in the format of Landmark analysis with breakpoints at 24, 12 and 1 month. Findings trend towards consistency with various breakpoints.

Appendix

The members of the INSTEAD trial consortiums were as follows:

Steering committee

Thomas Meinertz, MD, University Hospital Hamburg-Eppendorf, Germany;
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Rossella Fattori, MD, University Hospital St. Orsola Malpighi, Bologna, Italy;
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Clinical Centers (number of patients randomized in paranthesis)

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