

Long-term outcomes of the frozen elephant trunk procedure: a systematic review

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Background: The frozen elephant trunk (FET) procedure remains an increasingly popular approach to address complex multi-segmental aortic pathologies, owing to their ability to promote false lumen thrombosis and reduce the need for second-stage operations. While the short-term outcomes of such procedures have been shown to be acceptable, much less is known regarding long-term outcomes. This systematic review evaluates long-term outcomes of the FET procedure.

Methods: Studies with at least 12 months follow-up data on FETs were identified in four electronic databases. All studies were reviewed by two independent researchers and relevant data extracted. Long-term outcomes, including overall survival, freedom from reintervention, and freedom from aortic events, were evaluated using patient data recreated from digitized Kaplan-Meier curves.

Results: Thirty-seven studies with 4,178 patients were identified. The majority of the studies focused solely on acute dissections. Average follow-up was 3.2 years. Overall survival at 1-, 3-, and 5-year was 89.6%, 85.2%, and 82.0%, respectively. Freedom from reintervention at the same timepoints were 93.9%, 89.3%, and 86.8%, respectively. Mortality, permanent neurological deficit and spinal cord injury were 10.2%, 7.7%, and 6.5%, respectively.

Conclusions: Survival after the FET procedure is favorable, though ongoing close serial monitoring is essential to assess for the need for further reintervention. Larger multi-institutional registries are required to provide more robust evidence to better elucidate the patient cohort that would most benefit from the FET.

Keywords: Frozen elephant trunk (FET); stent-graft; survival; freedom from reintervention; systematic review



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Introduction

Combining the advantages of the classical elephant trunk with modern stent technology, the frozen elephant trunk (FET) procedure has been instrumental in treating complex multi-segmental aortic pathologies in a single operation. The secured expansile stent-graft is able to facilitate downstream aortic remodelling by inducing false lumen thrombosis and depressurization of the false lumen, stabilize the dissecting membrane, and limit stent-graft migration and proximal type Ia endoleaks (1,2). While multiple meta-analyses have reaffirmed the relatively safe short-term

profiles of these devices, much less is known regarding long-term outcomes, particularly in terms of overall survival and freedom from reintervention (3-7). The present meta-analysis aimed to determine long-term outcomes following the FET procedure.

Methods

Literature search strategy

Electronic searches were performed using Ovid Medline, Embase, Scopus, and PubMed, from their date of inception

to October 2019. To achieve maximum sensitivity of the search strategy, the terms ‘elephant trunk’, ‘Thoraflex’, ‘E-vita’, ‘Gianturco Z’, ‘Chavan-Haverich’, or ‘Cronus’ were used as either keywords or MeSH terms. Determination of whether the descending endoprosthesis was stented (i.e., ‘frozen’) or not (i.e., conventional elephant trunk) was made upon full article review. The reference lists of all included studies were reviewed for further identification of other potentially relevant studies. All identified articles were systematically assessed using the inclusion and exclusion criteria.

Selection criteria

Eligible studies for the present systematic review included those which (I) examined the use of FETs, (II) had clinical follow-up data of at least 12 months, and (III) had at least 10 patients. The FET is required to be deployed via open surgery in an antegrade fashion into the proximal descending aorta, and secured at the proximal aspect by sutures. No distinction was made regarding the management of head and neck vessels. All publications were limited to those involving human subjects and in the English language. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded. Review articles were omitted because of potential publication bias and duplication of results. Primary endpoint was overall survival. Secondary outcomes included freedom from reintervention, freedom from aortic events, 30 day/in-hospital mortality, stroke/permanent neurological damage, spinal cord damage, temporary neurological deficit, acute kidney injury, and hospital and intensive care unit (ICU) length of stay.

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures. Two investigators (Y.J., H.H.) independently reviewed each retrieved article. Discrepancies between the two reviewers were resolved by the senior investigator (D.H.T.). Quality assessment was assessed using a modified schema used for assessing case series, developed by the Institute of Health Economics (Alberta, Canada) (8) (*Table S1*). This schema examines the suitability of study objective, design, population, intervention, outcome measure, statistical analysis, appropriateness of results and conclusions, and competing interests (*Table S1*). Each study was scored out of 15 points, with

13–15 representing high-quality, 10–12 as medium-quality, and less than 10 as low-quality.

Statistical analysis

Descriptive statistics were calculated for all collected variables. Categorical or continuous variables were aggregated using meta-analysis of proportions or means, as appropriate. Data is presented as N (%) or mean $\pm$ standard deviation (SD). Where continuous values are presented in median with range or interquartile ranges they were converted to mean and SD using methods published by Wan and colleagues (9). Guyot’s iterative algorithm was applied to digitized Kaplan-Meier curves to reconstruct individual patient data (10,11). This approach assumed a constant, non-informative censoring mechanism. The reconstructed patient data were then aggregated to form the combined survival curve. The estimated survival for a 57-year-old male in 2010, representing the median age, sex, and study period of all studies, is also plotted to represent general population survival curve. The American life tables were selected arbitrarily (Center for Disease Control, United States). All p-values were two-sided, and p-values less than 0.05 were considered statistically significant. All statistics were performed with R (version 3.3.5, R Core Team, Vienna, Austria).

Results

Literature search

Overall 2,084 records were identified from the literature search (*Figure S1*). Following review (1,2,12–29), 37 were included in the quantitative analysis with a total of 4,178 patients (*Table S2*) (30–46). No further studies were identified from review of references. Three studies were multi-center studies (12,14,42), including an international registry (14). The median size of included studies was 58 patients (interquartile range, 34–120). Most studies were published by Chinese centers (12 studies), followed by German (8 studies) and Japanese centers (7 studies). Median duration of study was 7 years, with average follow-up of 3.2 years.

Patient characteristics

FETs were used exclusively for acute dissections in 23 studies involving 1,801 patients. In 10 studies the patient

Table 1 Demographic and intraoperative details

Variable	Overall (n=4,178)	Acute dissection (n=1,801)	Chronic dissection/ elective (n=698)	Mixed urgency (n=1,679)	Patients (studies)
Age (years)	57 [54–60]	45 [45–45]	55 [54–56]	52 [52–53]	3,876 (35)
Male (%)	72 [68–75]	73 [68–78]	76 [68–83]	68 [61–75]	3,415 (24)
Hypertension (%)	76 [72–80]	74 [68–80]	82 [74–88]	76 [69–82]	3,096 (30)
Diabetes (%)	8 [6–12]	7 [4–12]	9 [4–18]	9 [5–15]	3,186 (27)
Renal dysfunction (%)	8 [6–11]	7 [5–11]	11 [6–19]	9 [4–18]	3,249 (24)
Concomitant CABG (%)	11 [9–14]	10 [8–12]	14 [8–21]	13 [9–19]	3,324 (29)
CPB time (mins)	206 [191–220]	199 [177–221]	202 [179–225]	222 [200–243]	3,568 (32)
Cross-clamp time (mins)	118 [112–125]	117 [107–126]	120 [97–143]	123 [110–136]	3,276 (28)
HCA time (mins)	46 [41–51]	48 [43–53]	42 [16–67]	41 [31–51]	2,446 (23)
ACP time (mins)	63 [56–69]	65 [57–74]	58 [40–76]	59 [49–68]	2,093 (21)
Lowest temperature (°C)	23 [23–24]	24 [24–24]	23 [23–24]	26 [25–26]	3,224 (29)

Data is presented as value [95% confidence interval]. ACP, antegrade cerebral perfusion; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest.

cohorts were chronic dissections or elective surgeries (698 patients). In the remaining studies there was a mixture of emergent and elective indications. A variety of stent-grafts were used, including E-Vita Open/E-Vita Open Plus (13 studies), Cronus (10 studies), Thoraflex (6 studies), GORE TAG (3 studies), Valiant (2 studies), Medtronic TX2 (2 studies), JSOG (2 studies), as well as Frozenix (1 study), Gianturco stent/Hemashield Gold graft (1 study), and Chavan-Haverich (1 study).

Average age of included patients was 57 years old (IQR, 54–60 years), with 72% males (Tables 1, S3). The majority of patients were hypertensive (76%), with a small proportion having diabetes (8%), and renal dysfunction (8%). Other comorbidities, such as respiratory dysfunction, Marfan's syndrome, previous surgery, were insufficiently reported. Average cardiopulmonary bypass and cross-clamp times were 206 minutes and 118 minutes, respectively (Table S4). Average hypothermic circulatory arrest time was 46 minutes with antegrade cerebral perfusion time of 63 minutes (where reported). Circulatory arrest occurred at 23 °C on average.

Overall survival

Overall survival at 1-, 2-, 3-, 5-, and 10-year were 89.6%, 87.1%, 85.2%, 82.0%, and 68.0%, respectively (Figure 1). Survival at 1-, 2-, 3-, 5-, and 10-year for studies

that reported only acute dissections were 90.7%, 88.3%, 86.1%, 83.9%, and 73.5%, compared to 90.0%, 87.4%, 85.2%, 79.1%, and 56.0% for studies that only included chronic dissections/elective aneurysmal patients. Freedom from reintervention at 1-, 2-, 3-, and 5-year were 93.9%, 91.6%, 89.3%, and 86.8%, respectively (Figure 2). Freedom from aortic events at 1-, 2-, 3-, and 5-year were 98.3%, 96.2%, 91.3%, and 86.6%, respectively (Figure 3).

Secondary outcomes

Pooled in-hospital/30-day mortality was 10.2% (Tables 2, S5). Permanent neurological deficit and spinal cord injury were 7.7% and 6.5%, respectively. Acute kidney injury, with varying definitions, was 15.5%. There were insufficient data to evaluate temporary neurological deficit and hospital and ICU length of stay.

Quality assessment

The majority of studies were assessed to be medium-quality, with one high-quality and seven low-quality studies. Almost all of the studies were retrospective, single center trials, with no predetermined definitions of clinical outcomes. Loss to follow-up and the consecutive nature of patient enrolment were also inconsistently reported.

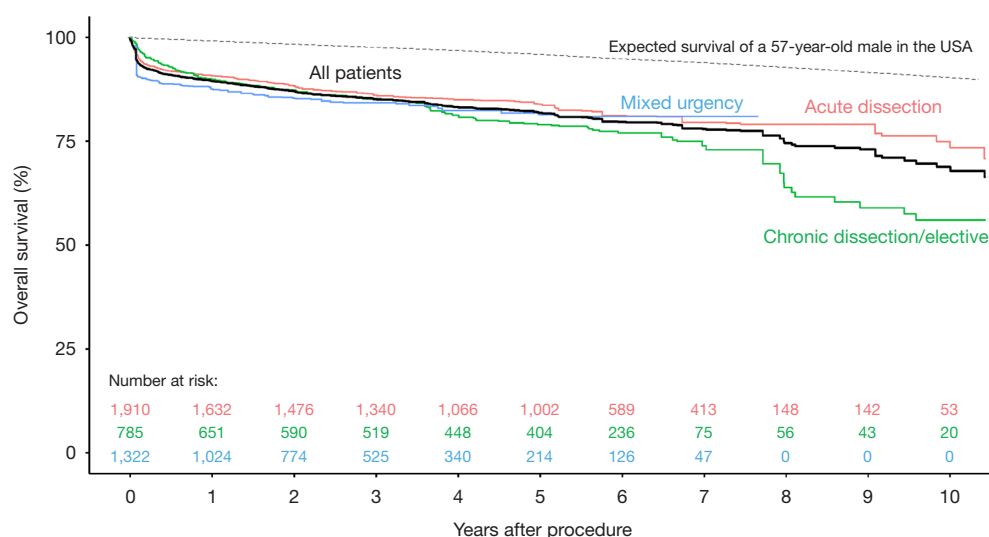


Figure 1 Overall survival. Dotted line represent expected survival of the general population, using the study mean age/gender as a reference.

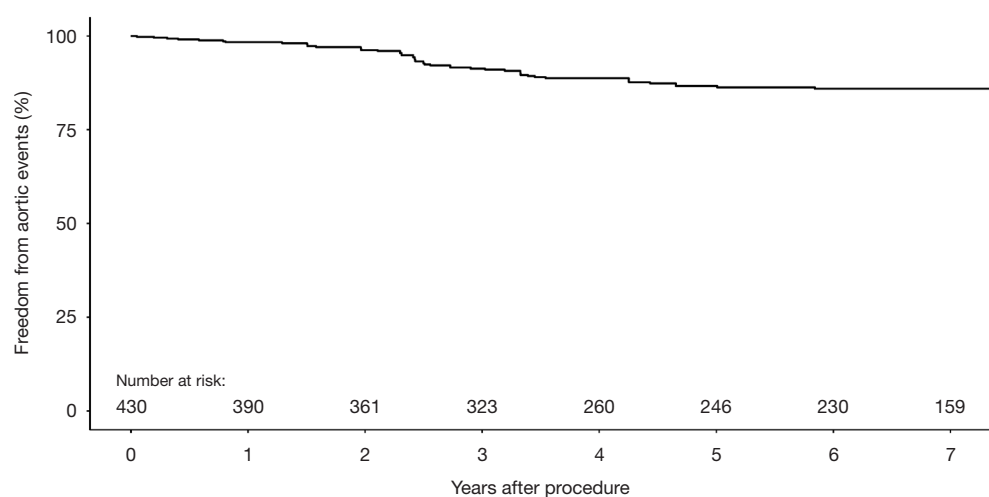


Figure 2 Freedom from aortic events.

Discussion

The present systematic review examined long-term outcomes of the FET technique. Aggregation of Kaplan-Meier curves found overall survival at 1-, 3-, and 5-year were 89.6%, 85.2%, and 82.0%, respectively. In comparison, patients who received planned second-stage procedures after a classic elephant trunk had a 3-year survival rate of 75% (47). Indeed, the interval mortality between the first-stage and second-stage completion procedures ranges between 2–11% (48), with the latter operation greatly precluded by the use of the FET.

Furthermore, it has been shown that a patent false lumen in the descending aorta is a predictor for late mortality and need for reintervention due to aortic expansion (49,50). In a meta-analysis of 11 cohort studies, residual patent false lumen was found to increase the risk of late mortality and aortic events in type A dissections by 71% and 179%, respectively (50). The FET's ability to promote downstream remodelling and induce false lumen thrombosis has been well validated (2,6), therefore providing an attractive option for management of such pathologies.

The need for reintervention after the FET procedure is not negligible. The ideal length of FET remains

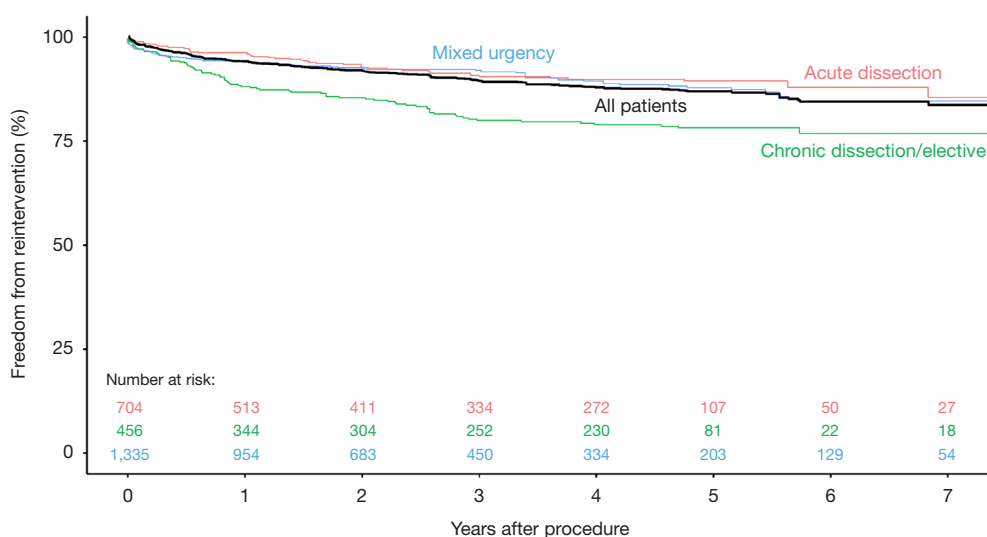


Figure 3 Freedom from reintervention.

Table 2 Short term outcomes

Variable	Overall (n=4,178)	Acute dissection (n=1,801)	Chronic dissection/ elective (n=698)	Mixed urgency (n=1,679)	Patients (studies)
Mortality (%)	10.2 (8.7–12)	9.4 (7.4–11.9)	8.3 (5.2–12.8)	13.1 (10.2–16.6)	4,127 (36)
Stroke (%)	6.2 (5–7.8)	4.7 (3.1–6.9)	7.2 (4.5–11.3)	7.7 (5.4–10.7)	4,127 (36)
Spinal cord injury (%)	4.1 (3.2–5.4)	2.6 (1.9–3.7)	5 (2.8–8.8)	6.5 (4.7–9)	4,111 (35)
Acute kidney injury (%)	15.5 (11.9–20.1)	10.5 (6.5–16.4)	14.5 (6.3–29.6)	28.6 (22.3–35.8)	3,415 (24)
Data is presented as value (95% confidence interval).					

controversial, requiring careful balance between sufficient length to achieve adequate distal false lumen occlusion and minimizing occlusion of vascular collaterals that supply the spinal cord. As such, it is often not possible to provide full distal coverage of the aortic pathology due to fear of spinal cord ischemia, thereby necessitating a second-stage procedure despite the use of FETs (43,51). However, it should be noted that the FET simplifies such reinterventions by providing a more appropriate landing zone for endovascular completion (52,53). In the present review, freedom from reintervention at 1-, 3-, and 5-year was 93.9%, 89.3%, and 86.8%, respectively, reaffirming the need for close serial follow-up after the FET procedure.

There are several limitations to the present review that must be considered when interpreting these results. First, in order to attain sufficient statistical power and increase overall representativeness of the findings, this analysis

included a heterogeneous cohort of patients, with varying comorbidities, pathologies, and surgical techniques. While subgroup classifications have been made based on clinical urgency, the assortment of surgical approaches, such as the extent of surgery, management of supra-aortic vessels (e.g., debranching procedures), neuroprotection strategies, and type and length of FETs is likely to have confounded results. Secondly, the volume of practice varied between hospitals, and particularly amongst geographic regions. Finally, the average length of follow-up is only 3.2 years, with limited data available beyond this period.

The present review demonstrates that survival after the FET procedure is favorable, though the need for reintervention still remains. Larger robust multi-institutional registries are required to elucidate the precise role of the FET in managing complex multisegmental aortic pathologies.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Study appraisal tool modified from Institute of Health Economics' Quality Appraisal Checklist for Case Series Studies (Canada). Each study was allocated a point for each criterion if it was deemed to have been met

Study appraisal schema

Was the hypothesis/aim/objective of the study clearly stated?

Was the study conducted prospectively?

Were the cases collected in more than one centre?

Were patients recruited consecutively?

Were the characteristics of the patients included in the study described?

Were the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?

Did patients enter the study at a similar point in the disease?

Was the intervention of interest clearly described?

Were additional interventions (co-interventions) clearly described?

Were relevant outcome measures established a priori?

Were losses to follow-up reported?

Did the study provided estimates of random variability in the data analysis of relevant outcomes?

Were the adverse events reported?

Were the conclusions of the study supported by results?

Were both competing interests and sources of support for the study reported?

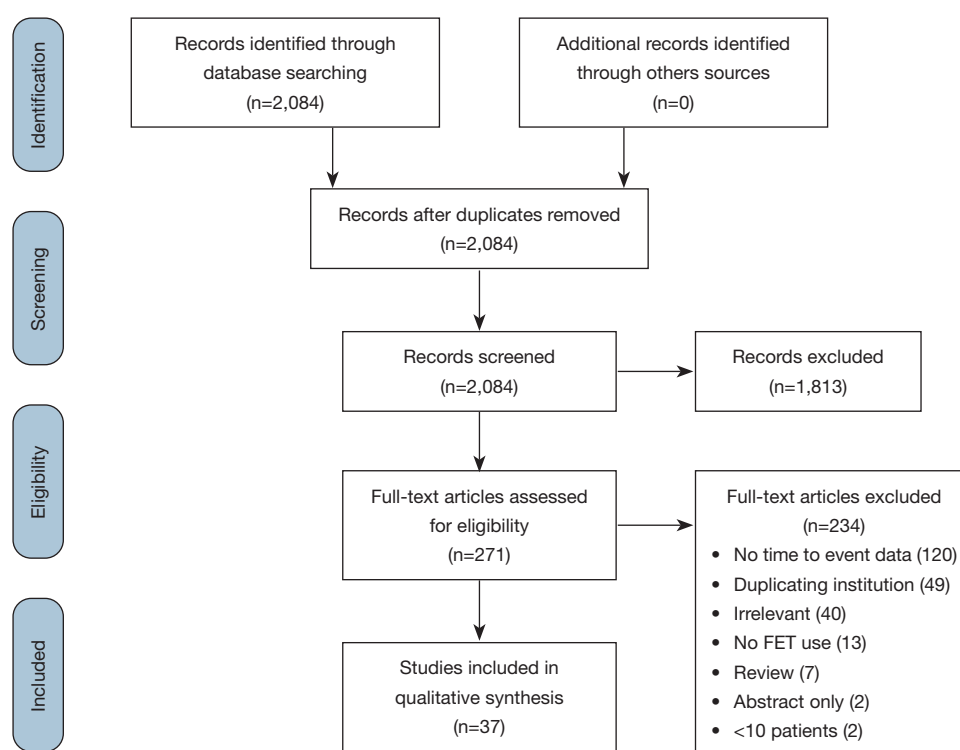


Figure S1 PRISMA flow chart of literature search.

Table S2 Study details

Author	Year of publication	Hospital	Country	Study period	Patients	Device name	Follow-up (months)	Study quality
Acute/emergent								
Sun	2011	Fuwai Hospital, Beijing Hospital, Beijing	China	2003–2008	148	Cronus	42±18	Medium
Zhao	2012	Beijing Anzhen Hospital, Beijing	China	2006–2011	24	Cronus	37±21	Medium
Jakob	2013	EVITA registry	International	2005–2012	138	E-Vita	NR	Low
Shi ^a	2014	First Affiliated Hospital Medical University, Shenyang	China	2006–2011	155	Cronus	43±18	Medium
Shi ^b	2014	First Affiliated Hospital Medical University, Shenyang	China	2010–2012	54	Cronus	24±9	Medium
Zhang	2014	Changhai Hospital, Second Military Medical College, Shanghai	China	2002–2010	88	Cronus	56±33	Medium
Katayama	2015	Hiroshima-City Asa General Hospital, Hiroshima	Japan	1997–2012	120	NR	105±52	Medium
Chen	2016	Tianjin Medical University, Tianjin	China	2009–2014	33	NR	NR	Low
Kobayashi	2016	Zurich University Hospital, Zurich	Switzerland	2001–2012	34	GoreTAG, Talent, E-Vita	74±45	Medium
Aalaei-Andabili	2017	The University of Florida College of Medicine, Florida, USA	USA	2010–2015	23	GoreTAG, Valiant, TX2	17±17*	High
Hu	2017	Renmin Hospital of Wuhan University, Hubei	China	2008–2015	106	Cronus	43±22	Medium
Shrestha	2017	Hannover Medical School, Hannover	Germany	2001–2016	100	Chavan-Haverich, E-Vita, Thoraflex	54±57*	Medium
Yamane	2017	Akane-Foundation Tsuchiya General Hospital, Hiroshima	Japan	2008–2015	24	JOSG	39±22*	Medium
Berger	2018	University Heart Center Freiburg University, Freiburg	Germany	2013–2017	31	Thoraflex	12±12	Medium
Goebel	2018	Robert-Bosch Hospital, Stuttgart	Germany	2009–2016	72	E-Vita	38±21	Medium
Lopez Almodovar	2018	Virgen de la Salud Hospital, Toledo	Spain	2011–2016	12	E-Vita	36±29	Medium
Ma	2018	Tongji Hospital, Wuhan	China	2013–2015	132	Cronus	22±8*	Medium
Roselli	2018	Cleveland Clinic, Ohio, USA	USA	2009–2016	72	GoreTAG	28±25	Low
Kremer	2019	Heidelberg University Hospital, Heidelberg	Germany	2006–2017	34	E-Vita, Thoraflex	NR	Medium
Lin	2019	Beijing Anzhen Hospital, Beijing	China	2013–2014	53	Cronus	52±19	Medium
Qian	2019	Beijing Anzhen Hospital, Beijing	China	2009–2012	218	NR	67±13	Medium
Tochii	2019	Fujita Health University, Toyoake	Japan	2005–2017	22	JOSG	9±8	Low
Yamamoto	2019	Akita University Hospital, Akita	Japan	2014–2018	108	Frozenix	NR	Medium
Chronic/emergent								
Flores	2006	Hokkaido University School of Medicine, Hokkaido	Japan	1996–2004	25	Gianturco stent/ Hemashield Gold graft	35±13	Low
Uchida	2010	Hiroshima-City Asa General Hospital, Hiroshima	Japan	1997–2008	58	NR	54±37	Medium
Sun	2011	FuWai Hospital, Beijing Hospital	China	2003–2008	143	Cronus	43±19	Medium
Jakob	2013	EVITA registry	International	2005–2012	142	E-Vita	NR	Low
Nakamura	2014	Miyazaki Prefectural Nobeoka Hospital, Nobeoka	Japan	1998–2010	51	NR	51	Medium
Aalaei-Andabili	2017	The University of Florida College of Medicine, Florida, USA	USA	2010–2015	25	GoreTAG, Valiant, TX2	17±17*	High
Shrestha	2017	Hannover Medical School, Hannover	Germany	2001–2016	151	Chavan-Haverich, E-Vita, Thoraflex	43±42*	Medium
Berger	2018	University Heart Center Freiburg University, Freiburg	Germany	2013–2017	34	Thoraflex	NR	Medium
Zhong	2018	Beijing Anzhen Hospital, Beijing	China	2010–2016	35	Cronus	49±22	Medium
Kremer	2019	Heidelberg University Hospital, Heidelberg	Germany	2006–2017	34	E-Vita, Thoraflex	NR	Medium
Mixed								
Leontyev	2013	Leipzig Heart Centre, Leipzig	Germany	2006–2013	51	E-Vita	41±5	Medium
Weiss	2016	Hospital Hietzing, Vienna, Austria	Austria	2005–2012	27	E-Vita	48±26	Medium
Mkalaluh	2018	European Medical School Oldenburg-Groningen, Oldenburg	Germany	2001–2017	25	E-Vita, Thoraflex	26	Low
Tsagakis	2018	West German Heart Center Essen, Essen	Germany	2005–2017	286	E-Vita	NR	Low
Alhussaini	2019	Assuit University, Assiut	Egypt	2003–2016	48	TX2, Valiant	31±32*	Medium
Chu	2019	9 Canadian hospitals	Multi-Canadian	2014–2017	40	Thoraflex	18±11	Medium
Dinato	2019	University of Sao Paulo Medical School, Sao Paulo	Brazil	2009–2018	79	E-Vita	17±20	Medium
Kozlov	2019	Tomsk National Research Medical Centre, Tomsk	Russia	2012–2018	26	E-Vita	NR	Medium
Leone	2019	Sant. Orsola-Malpighi Hospital, University of Bologna, Bologna	Italy	2007–2018	282	E-Vita, Thoraflex	NR	Medium
Zhang	2019	FuWai Hospital, Beijing Hospital	China	2010–2016	815	Cronus	NR	Medium

Device details: E-vita: Evita Open/Open Plus (Jotec Inc., Hechingen, Germany), Thoraflex: Vascutek Thoraflex hybrid graft (Vascutek, Scotland), Chavan-Haverich: Chavan-Haverich endograft (Curative GmbH, Dresden, Germany), Cronus: Cronus stented elephant trunk (MicroPort Medical Co. Ltd., Shanghai, China), GoreTAG: Gore TAG thoracic endoprosthesis (W. L. Gore and Associates, Flagstaff, USA), Talent: Talent thoracic stent graft (Medtronic/AVE, Santa Rosa, USA), Valiant: Valiant thoracic stent graft (Medtronic, Santa Rosa, USA), TX2: Zenith TX2 Dissection Endovascular Graft (Cook Medical Inc., Bloomington, USA), JSOG: J Graft open stent graft (Japan Lifeline Co., Tokyo, Japan), Frozenix: J Graft FROZENIX (Japan Lifeline Co Ltd., Tokyo, Japan), Gianturco: Gianturco stent (Cook Medical Inc., Bloomington, USA) with Hemashield Gold graft (Boston Scientific, Natick, USA). *, mean and standard deviation recalculated using methods of Wan *et al.*^a, DOI: 10.1016/j.jtcvs.2013.10.058; ^b, DOI: 10.1016/j.jtcvs.2014.02.077.

Table S3 Patient demographics						
Study	Age	Male	Hypertension	Diabetes	Renal dysfunction	Concomitant CABG
Acute/emergent						
Sun	45±11	126 [85]	107 [72]	6 [4]	9 [6]	17 [11]
Zhao	41±1	19 [79]	15 [63]	2 [8]	NR	NR
Jakob	61 ^M	NR	NR	NR	NR	NR
Shi ^a	56±10	53 [75]	55 [77]	12 [17]	5 [7]	7 [10]
Shi ^a	54±12	57 [68]	67 [80]	19 [23]	4 [5]	6 [7]
Shi ^b	60±13	37 [69]	40 [74]	13 [24]	3 [6]	2 [4]
Zhang	46±14	74 [84]	64 [73]	4 [5]	3 [3]	8 [9]
Katayama	64±11	64 [53]	NR	NR	8 [7]	NR
Chen	46±11	18 [82]	17 [77]	1 [5]	NR	NR
Chen	54±11	9 [82]	10 [91]	0 [0]	NR	NR
Kobayashi	60±11	21 [62]	21 [62]	2 [6]	NR	NR
Aalaei-Andabili	62±12	14 [61]	20 [87]	2 [9]	2 [9]	8 [35]
Hu	51±12	69 [65]	77 [73]	NR	4 [4]	10 [9]
Shrestha	NR	NR	NR	NR	NR	13 [13]
Yamane	59±14	14 [58]	14 [58]	0 [0]	3 [13]	3 [13]
Berger	64±12	24 [77]	25 [81]	0 [0]	2 [6]	4 [13]
Goebel	59±12	55 [76]	68 [94]	3 [4]	9 [13]	7 [10]
Lopez Almodovar	57	10 [83]	10 [83]	NR	NR	0 [0]
Ma	47±8	108 [82]	97 [73]	31 [23]	12 [9]	12 [9]
Roselli	59±15	51 [71]	NR	NR	NR	3 [4]
Kremer	59±15	28 [82]	28 [82]	1 [3]	2 [6]	2 [6]
Lin	46±9	41 [77]	44 [83]	NR	4 [8]	5 [9]
Qian	48±11	170 [78]	153 [70]	5 [2]	48 [22]	20 [9]
Tochii	60±36*	18 [82]	NR	NR	NR	1 [5]
Yamamoto	67±12	50 [46]	32 [30]	4 [4]	4 [4]	5 [5]
Subtotal	45 [45–45]	73 [68–78]	74 [68–80]	7 [4–12]	7 [5–11]	10 [8–12]
Chronic/elective						
Flores	73±7	19 [76]	21 [84]	2 [8]	3 [12]	3 [12]
Uchida	74	52 [90]	53 [91]	15 [26]	13 [22]	15 [26]
Sun	45±10	112 [78]	100 [70]	5 [3]	3 [2]	8 [6]
Jakob	60M	NR	NR	NR	NR	NR
Nakamura	NR	NR	NR	NR	NR	NR
Aalaei-Andabili	66±10	17 [68]	19 [76]	4 [16]	3 [12]	4 [16]
Shrestha	NR	NR	NR	NR	NR	23 [28]
Shrestha	NR	NR	NR	NR	NR	8 [12]
Berger	58±12	24 [71]	31 [91]	1 [3]	7 [21]	1 [3]
Zhong	49±10	29 [83]	27 [77]	4 [11]	3 [9]	2 [6]
Kremer	65±11	20 [59]	29 [85]	2 [6]	3 [9]	7 [21]
Subtotal	55 [54–56]	76 [68–83]	82 [74–88]	9 [4–18]	11 [6–19]	14 [8–21]
Mixed						
Leontyev	69±10	27 [53]	27 [53]	9 [18]	NR	10 [20]
Weiss	56±12	21 [78]	17 [63]	6 [22]	3 [11]	0 [0]
Mkalaluh	67±9*	14 [56]	18 [72]	NR	NR	5 [20]
Tsagakis	59±11	199 [70]	NR	22 [8]	59 [21]	NR
Alhussaini	64±11	31 [65]	39 [81]	6 [13]	NR	13 [27]
Chu	66±14	22 [55]	32 [80]	5 [13]	1 [3]	6 [15]
Dinato	58±13	50 [63]	70 [89]	12 [15]	14 [18]	6 [8]
Kozlov	54±11	10 [67]	12 [80]	1 [7]	NR	NR
Kozlov	52±4	7 [64]	9 [82]	1 [9]	NR	NR
Leone	54±48*	233 [83]	237 [84]	11 [4]	13 [5]	26 [9]
Zhang	47±10	637 [78]	594 [73]	19 [2]	40 [5]	82 [10]
Subtotal	52 [52–53]	68 [61–75]	76 [69–82]	9 [5–15]	9 [4–18]	13 [9–19]
Overall	57 [54–60]	72 [68–75]	76 [72–80]	8 [6–12]	8 [6–11]	11 [9–14]
Data is presented as number of patients [%], or mean ± standard deviation. Aggregated subtotal and overall values are presented with 95% confidence intervals, using random-effects meta-analysis of proportions or means. *, mean and standard deviation recalculated using methods of Wan <i>et al.</i> ^a , DOI: 10.1016/j.jtcvs.2013.10.058; ^b , DOI: 10.1016/j.jtcvs.2014.02.077. M, median.						

Table S4 Intraoperative characteristics					
Study	CPB time (mins)	Cross-clamp time (mins)	HCA time (mins)	ACP time (mins)	Lowest temp (°C)
Acute/emergent					
Sun	197±47	107±27	NR	24±9	18–22
Zhao	168±41	87±24	NR	21±5	20
Jakob	241±75	NR	140±54	68±30	NR
Shi ^a	104±21	76±16	31±5	31±5	23±2
Shi ^a	165±20	109±18	29±4	55±6	24±1
Shi ^b	96±18	76±16	29±3	27±2	23±2
Zhang	182±34	113±26	35±12	NR	20–28
Katayama	173±42	109±23	NR	72±20	28
Chen	142±36	103±28	41±17	NR	18–22
Chen	135±33	103±29	38±9	NR	18–22
Kobayashi	NR	NR	NR	NR	NR
Aalaei-Andabili	253±114	NR	33±32	NR	19±4
Hu	163±68	93±22	23±6	NR	20
Shrestha	254±64*	119±67*	NR	84±30*	20–25
Yamane	255±57	126±39	49±145	120±46	27±1
Berger	228±52	135±52	NR	95±44	24±1
Goebel	226±46*	157±35*	71±17*	NR	28
Lopez Almodovar	235±43	171±33	75±20	96±23	25
Ma	243±66	122±26	27±9	NR	22±2
Roselli	NR	NR	33±22	NR	20
Kremer	252±74	148±35	62±37	NR	23±4
Lin	199±62	108±39	NR	27±9	25
Qian	199±59	111±36	NR	29±14	NR
Tochii	296±80	183±49	88±24	206±57	NR
Yamamoto	214±65*	133±47*	53±14*	108±37	23±2
Subtotal	199 [177–221]	117 [107–126]	48 [43–53]	65 [57–74]	24 [24–24]
Chronic/elective					
Flores	NR	NR	NR	NR	22
Uchida	148±34	NR	NR	72±12	28
Sun	182±38	102±28	NR	24±6	18–22
Jakob	NR	NR	NR	NR	NR
Nakamura	NR	NR	NR	NR	20–25
Aalaei-Andabili	270±59	NR	29±25	NR	19±3
Shrestha	203±63*	97±47*	NR	68±29*	20–25
Shrestha	237±68*	202±68*	NR	81±31*	20–25
Berger	219±58	116±51	NR	76±37	25±3
Zhong	176±47	89±30	NR	29±6	25
Kremer	189±48	116±35	55±37	NR	24±2
Subtotal	202 [179–225]	120 [97–143]	42 [16–67]	58 [40–76]	23 [23–24]
Mixed					
Leontyev	213±66	98±38	50±14	47±14	26±2
Weiss	204±46	95±34	4±2	54±12	26
Mkalaluh	229±53	100±58	42±33	NR	25±2*
Tsagakis	NR	NR	NR	NR	NR
Alhussaini	268±81	NR	31±28	NR	NR
Chu	246±78	155±72	47±21	NR	NR
Dinato	155±31	119±33	NR	60±13	25
Kozlov	237±82*	161±40*	63±28*	47±22*	NR
Kozlov	186±27*	148±61*	55±10*	39±22*	NR
Leone	329±400*	157±191*	60±65*	138±197*	25
Zhang	196±64	101±29	23±8	NR	20–25
Subtotal	222 [200–243]	123 [110–136]	41 [31–51]	59 [49–68]	26 [25–26]
Overall	206 [191–220]	118 [112–125]	46 [41–51]	63 [56–69]	23 [23–24]
Data is presented as number of patients [%] or mean ± standard deviation. Aggregated subtotal and overall values are presented with 95% confidence intervals, using random-effects meta-analysis of proportions or means. Temperatures also presented as ranges as per individual studies. *, mean and standard deviation recalculated using methods of Wan <i>et al.</i> ^a , DOI: 10.1016/j.jtcvs.2013.10.058; ^b , DOI: 10.1016/j.jtcvs.2014.02.077.					

Table S5 Clinical outcomes					
Study	Mortality	Stroke	Spinal cord injury	Acute kidney injury	ICU stay [days]
Acute/emergent					
Sun	7 [5]	4 [3]	3 [2]	1 [1]	NR
Zhao	1 [4]	0 [0]	0 [0]	NR	NR
Jakob	22 [16]	10 [7]	6 [4]	NR	NR
Shi ^a	3 [4]	0 [0]	0 [0]	4 [6]	NR
Shi ^a	5 [6]	0 [0]	0 [0]	7 [8]	NR
Shi ^b	2 [4]	0 [0]	0 [0]	4 [7]	NR
Zhang	5 [6]	2 [2]	0 [0]	2 [2]	NR
Katayama	7 [6]	4 [3]	2 [2]	4 [3]	NR
Chen	6 [27]	0 [0]	NR	NR	10±11
Chen	3 [27]	1 [9]	NR	NR	12±12
Kobayashi	5 [15]	2 [6]	NR	NR	NR
Aalaei-Andabili	4 [17]	2 [9]	1 [4]	6 [26]	11±6*
Hu	8 [8]	0 [0]	0 [0]	NR	3±2
Shrestha	11 [11]	18 [18]	1 [1]	21 [21]	6±5*
Yamane	2 [8]	1 [4]	0 [0]	NR	NR
Berger	2 [6]	4 [13]	0 [0]	NR	NR
Goebel	11 [15]	2 [3]	3 [4]	18 [25]	6±5*
Lopez Almodovar	2 [17]	1 [8]	0 [0]	NR	NR
Ma	19 [14]	7 [5]	0 [0]	20 [15]	8±4
Roselli	3 [4]	3 [4]	3 [4]	2 [3]	NR
Kremer	5 [15]	3 [9]	3 [9]	23 [68]	9±9
Lin	3 [6]	1 [2]	0 [0]	5 [9]	4±4
Qian	25 [11]	2 [1]	5 [2]	35 [16]	3±3
Tochii	0 [0]	4 [18]	0 [0]	2 [9]	11±12
Yamamoto	3 [3]	4 [4]	0 [0]	6 [6]	NR
Subtotal	9.4 [7.4–11.9]	4.7 [3.1–6.9]	2.6 [1.9–3.7]	10.5 [6.5–16.4]	7 [5–8]
Chronic/elective					
Flores	3 [12]	4 [16]	6 [24]	NR	NR
Uchida	1 [2]	2 [3]	2 [3]	1 [2]	NR
Sun	2 [1]	3 [2]	4 [3]	2 [1]	NR
Jakob	20 [14]	7 [5]	13 [9]	NR	NR
Nakamura	NR	NR	2 [4]	NR	NR
Aalaei-Andabili	4 [16]	1 [4]	1 [4]	6 [24]	13±9*
Shrestha	9 [11]	11 [13]	3 [4]	16 [20]	5±5*
Shrestha	3 [4]	8 [12]	0 [0]	15 [22]	7±8*
Berger	2 [6]	2 [6]	0 [0]	NR	NR
Zhong	2 [6]	0 [0]	0 [0]	NR	NR
Kremer	5 [15]	4 [12]	2 [6]	16 [47]	9±9
Subtotal	8.3 [5.2–12.8]	7.2 [4.5–11.3]	5 [2.8–8.8]	14.5 [6.3–29.6]	8 [5–11]
Mixed					
Leontyev	4 [8]	6 [12]	10 [20]	13 [25]	NR
Weiss	2 [7]	3 [11]	2 [7]	8 [30]	4±11*
Mkalaluh	5 [20]	6 [24]	1 [4]	6 [24]	11±11*
Tsagakis	32 [11]	16 [6]	14 [5]	91 [32]	NR
Alhussaini	9 [19]	3 [6]	2 [4]	NR	NR
Chu	2 [5]	3 [8]	2 [5]	1 [3]	2±2*
Dinato	16 [20]	4 [5]	2 [3]	38 [48]	NR
Kozlov	0 [0]	1 [7]	0 [0]	NR	NR
Kozlov	0 [0]	0 [0]	0 [0]	NR	NR
Leone	48 [17]	25 [9]	17 [6]	55 [20]	1±3*
Zhang	87 [11]	36 [4]	56 [7]	263 [32]	3±3
Subtotal	13.1 [10.2–16.6]	7.7 [5.4–10.7]	6.5 [4.7–9]	28.6 [22.3–35.8]	3 [1–4]
Overall	10.2 [8.7–12]	6.2 [5–7.8]	4.1 [3.2–5.4]	15.5 [11.9–20.1]	6 [5–7]
Data is presented as number of patients [%] or mean ± standard deviation. Aggregated subtotal and overall values are presented with 95% confidence intervals, using random-effects meta-analysis of proportions or means. *, mean and standard deviation recalculated using methods of Wan <i>et al.</i> ^a , DOI: 10.1016/j.jtcvs.2013.10.058; ^b , DOI: 10.1016/j.jtcvs.2014.02.077.					