Circulation

ORIGINAL RESEARCH ARTICLE

Nationwide Analysis of Persistent Type II Endoleak and Late Outcomes of Endovascular Abdominal Aortic Aneurysm Repair in Japan: A Propensity-Matched Analysis

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BACKGROUND: We reviewed the results of endovascular aneurysm repair in patients from the Japanese Committee for Stentgraft Management registry to determine the significance of persistent type II endoleak (p-T2EL) and the risk of late adverse events, including aneurysm sac enlargement.

METHODS: The prospectively captured medical records of 17 099 patients <75 years of age who underwent endovascular aneurysm repair for abdominal aortic aneurysm from 2006 to 2015 were reviewed. Patients were divided into 2 groups (with or without p-T2EL) and compared to examine the correlation between p-T2EL and the occurrence of aneurysm sac enlargement after endovascular aneurysm repair.

RESULTS: Of the patients, 4957 (29.0%) had p-T2EL and 12 142 (71.0%) had no p-T2EL (non-T2EL). Mean age was significantly higher ($P<0.001$), and there were fewer men ($P<0.001$) in the p-T2EL group. Among comorbidities, hypertension ($P=0.019$) and chronic kidney disease ($P=0.040$) were more prevalent and respiratory disorders were less prevalent ($P<0.001$) in the p-T2EL group. From each group, 4957 patients were matched according to propensity score to adjust for differences in patient characteristics. The cumulative incidence rates of abdominal aortic aneurysm–related mortality (p-T2EL: 52 of 4957 [1.0%] versus non-T2EL: 21 of 12 142 [0.2%]), rupture (p-T2EL: 38 of 4957 [0.8%] versus non-T2EL: 13 of 12 142 [0.1%]), sac enlargement (≥5 mm; p-T2EL: 1359 of 4957 [27.4%] versus non-T2EL: 332 of 12 142 [2.7%]), and reintervention (p-T2EL: 739 of 4957 [14.9%] versus non-T2EL: 91 of 12 142 [0.7%]) were significantly higher in the p-T2EL than the nonpT2EL group ($P<0.001$). Propensity score matching yielded higher estimated incremental risk, including abdominal aortic aneurysm–related mortality, rupture, sac enlargement (≥5 mm), and reintervention for p-T2EL ($P<0.001$). Cox regression analysis revealed older age ($P=0.010$), proximal neck diameter ($P=0.003$), and chronic kidney disease ($P<0.001$) as independent positive predictors and male sex as an independent negative predictor ($P=0.015$) of sac enlargement.

CONCLUSIONS: The Japanese Committee for Stentgraft Management registry data show a correlation between p-T2EL and late adverse events, including aneurysm sac enlargement, reintervention, rupture, and abdominal aortic aneurysm–related mortality after endovascular aneurysm repair. Besides p-T2EL, older age, female sex, chronic kidney disease, and dilated proximal neck were associated with sac enlargement.

Key Words: analysis ■ aortic aneurysm, abdominal ■ endoleak

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.121.056581.

For Sources of Funding and Disclosures, see page 1065

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Clinical Perspective

What Is New?

- The cumulative incidence rates of abdominal aortic aneurysm–related mortality, rupture, sac enlargement, and reintervention were higher in patients with persistent type II endoleak; specifically, the cumulative incidence rates of rupture and abdominal aortic aneurysm–related mortality increased to 2% at the 10-year follow-up, which is dissimilar to the previously reported frequency of ≈1%.
- Cox regression analysis revealed older age, female sex, proximal neck diameter, and chronic kidney disease as independent positive correlates of sac enlargement.

What Are the Clinical Implications?

- These results suggest that persistent type II endoleaks are not benign, considering their long-term implications.
- To reduce the incidence of persistent type II endoleak, preoperative or intraoperative embolization of the side branches of abdominal aortic aneurysm in specific patients might be beneficial; however, its role in reducing reinterventions or the incidence of rupture remains to be proven, and additional large-scale prospective cohort studies or randomized controlled trials are needed.
- Among risk factors for sac enlargement, older age, female sex, larger proximal neck diameter, and chronic kidney disease are not modifiable factors, and if a potential for long-term survival exists, open surgery might be recommendable for patients with those risk factors.

Nonstandard Abbreviations and Acronyms

AAA	abdominal aortic aneurysm
ACE	Anevrysme de l'aorte abdominale, Chirurgie Versus Endoprothese
CKD	chronic kidney disease
CT	computed tomography
DREAM	Dutch Randomized Endovascular Aneurysm Management
EVAR	endovascular aneurysm repair
HR	hazard ratio
JACSM	Japanese Committee for Stentgraft Management
non-T2EL	no persistent type II endoleak
p-T2EL	persistent type II endoleak
PS	propensity score

The current endovascular aneurysm repair (EVAR) technology appears well established, with lower operative mortality and morbidity rates than open repair. However, these advantages have not been sustained beyond 2 years; reintervention has been required for endoleak, so-called endoflow, which has not been reported after open repair.[1–3] Perigraft flow after EVAR is defined as endoleak: type I from attachment sites, type II from collateral branches to the aneurysm, and type III occurring from stent graft defects or junction sites.[4–6] Endoleaks of type Ia at proximal and Ib at distal landing zones of the stent graft are comparable to EVAR failure, with an incidence of 5% to 30%, and relate strongly to aneurysm sac growth and rupture.[4] Type IIIa at the junction of stent grafts and IIIb endoleaks with graft disruption, both attributable to device failure, should be treated because direct endoleaks are associated with a risk of aneurysm sac rupture[5,6] into the original aneurysmal wall covering the stent graft and perigraft cavity.

Unlike the ominous nature of type I and type III endoleaks, the clinical importance of type II endoleak remains unknown, although persistent type II endoleak (p-T2EL) is the most common complication of EVAR, with a widespread overall incidence (3.8%–45%), and relates to sac growth.[7,8] Most type II endoleaks are believed to be benign, and rupture has infrequently arisen from type II endoleaks.

Some facilities are aggressively performing embolization, considering the reported cases of newly developed type I endoleak attributable to sac enlargement caused by type II endoleak.[9,10] However, to compensate for the insufficient evidence and to reveal the significance of p-T2ELs to the risk of late adverse events, larger population studies to clarify the effects of p-T2ELs and aneurysm sac enlargement after EVAR are warranted.

The Japanese Committee for Stentgraft Management[11] (JACSM) registry was established to prevent the inappropriate use of the commercial stent graft in 2006, and all EVAR procedures in Japan have been registered with the committee.[12,13] The aim of this study was to review the results of EVAR in >17 000 patients from the JACSM registry and to determine the significance of p-T2ELs to the risk of late adverse events. In addition, the risk factors of aneurysm sac enlargement after EVAR were investigated as a marker of clinical failure and indication for reintervention.

METHODS

Ethics Statement

Given the prospectively captured anonymized nature of the data, formal patient consent was neither necessary nor feasible. The JACSM registry was approved by the institutional review board of the University of Tokyo Hospital (approval 2019268NI). The study protocol was approved by the institutional review board

of the National Cerebral and Cardiovascular Center (approval N24-079-2).

Data Sharing and Availability

The data underlying this article cannot be shared publicly because of relevant data protection regulations. However, the anonymized participant data, the study protocol, and statistical analyses may be shared with other researchers on reasonable request to the corresponding author. Proposals will be reviewed and approved by investigators and collaborators on the basis of scientific merit. Data will be available at the time of publication and for a minimum of 5 years from the publication.

Study Design and Study Population in the JACSM Registry

This study is prospective, longitudinal, consecutive-patient multicenter cohort study. The participating institutions in the JACSM registry, which included >500 institutions in Japan, report data annually, including patients' preoperative condition; anatomic details of the aneurysm treated and endoleaks; postoperative features, including mortality, complications, and computed tomography (CT) findings, at 1 month, 6 months, and 1 year after EVAR and every year until the 10th follow-up; and occurrence of late death or graft replacement. Each clinician assessed the endoleaks, made these diagnoses for the database, and entered them online themselves.

The JACSM registry does not have data about implanted devices. As a reference, the following stent grafts were approved by the Ministry of Health, Labor and Welfare in Japan: Zenith (Cook Medical Inc, Bloomington, IN; year approved: 2006), Gore Excluder (W.L. Gore & Associates, In., Flagstaff, AZ; 2007), Powerlink and AFX (Endologix, Irvine, CA; 2008), Talent Abdominal and Endurant (Medtronic, Santa Rosa, CA; 2010 and 2014), and Aorfix (Lombard Medical, Oxfordshire, UK; 2014). All revised versions of the stent grafts were approved later.

The prospectively captured anonymized data of 21 283 patients <75 years of age who underwent EVAR and were discharged without type I or type III endoleaks until December 2015 and had at least 1 follow-up contrast-enhanced CT scan were reviewed.

To equalize the patients' characteristics, 4-step exclusions criteria were used. As the first step for survival and follow-up, we excluded 128 patients (0.6%) who died in hospital, 507 (2.4%) without a CT scan, and 718 (3.4%) without a follow-up contrast-enhanced CT scan. Second, we excluded 364 patients (1.7%) with dissecting abdominal aortic aneurysm (AAA), 166 (0.8%) with infective AAA, 1681 (7.9%) with solitary iliac aneurysm, 35 (0.2%) with prior graft replacement for AAA, 5 (0.02%) with prior EVAR, and 40 (0.2%) with other vascular pathologies. Third, we excluded 226 patients (1.1%) who underwent inferior mesenteric artery embolization to prevent type II endoleaks and 65 (0.3%) who were treated with fenestrated devices. Fourth, we excluded 249 patients (1.2%) with newly developed isolated type I (Ia/Ib, 96 of 117) and III endoleaks (IIIa/IIIb, 13 of 23) without type II endoleaks during follow-up (Figure 1).

After these exclusions, 17 099 patients (90.6% male; mean age, 68.1±5.3 years), ≈80% of all registered patients, with a mean follow-up of 4.1±2.6 years were further investigated.

CT Findings and Definition of p-T2EL

The CT findings consisted of aneurysm sac size, endoleak diagnosed by contrast-enhanced CT, and any adverse events, including rupture and graft infection described as additional comments. The aneurysm size registered was the minor axis of the largest axial cross section of the aneurysm. During EVAR surveillance, expansion of the aneurysm sac of ≥5 mm compared with that on preoperative CT within 6 months before EVAR was considered a significant enlargement.

Detected endoleaks by the CT were classified into type Ia or Ib, type II, type IIIa or IIIb, and type IV endoleaks.[1] When multiple endoleaks were diagnosed, all types were registered. Two kinds of type II endoleak were defined as persistent: (1) type II endoleak detected after the completion of EVAR on initial contrast-enhanced CT and during follow-up and (2) new type II endoleak not documented at the end of EVAR but reported at any point during follow-up.

Outcomes

The patients were divided into 2 groups according to the presence (p-T2EL group) or absence (non-T2EL group) of p-T2EL. These groups were compared to investigate the influence of p-T2EL on the occurrence of aneurysm sac enlargement after EVAR, which is an indicator of clinical success and an indication for reintervention for p-T2EL, by assessment of freedom from aneurysm sac enlargement as a primary outcome (Figure 1).[7–9]

Secondary outcome measures included reintervention-free survival, AAA-related mortality, and rupture-free survival after EVAR. Reintervention included conversion to graft replacement, transperitoneal sacotomy, inferior mesenteric artery ligation, and additional EVAR. AAA-related mortality was defined as death related to the aneurysm or endograft after EVAR, excluding hospital mortality.

Statistical Analyses

Statistical analyses were conducted with the STATA version 16 software (StataCorp LLC, College Station, TX). Categorical data were compared by use of the Fisher exact test. Continuous variables were expressed as mean±SD and compared with the *t* test. Values of $P<0.05$ were considered statistically significant. The Fine-Gray model was used to evaluate freedom from aneurysm sac enlargement (≥5 mm), reintervention, AAA-related mortality, and AAA rupture after the initial EVAR between the 2 groups and to remove the effects of the observed confounding of death before these aortic events.[14] The difference between each group was compared with log-rank analysis. The patients lost to follow-up were treated as censored observations.

As a sensitivity analysis, freedom from aneurysm sac enlargement, reinterventions, AAA-related deaths, and AAA rupture was reassessed by propensity score (PS) matching to adjust for changes in the level of medical care over the decade. A patient in each group was matched with a patient in the non-T2EL group by use of the closest PS by caliper matching without replacement, and the maximum difference in PS was set at <0.01. Caliper matching was defined by the following equation:

$$\text{Caliper}=0.2\times\sqrt{\frac{1}{17099}\sum_{1}^{17099}(PSi-\overline{PS})^2}$$

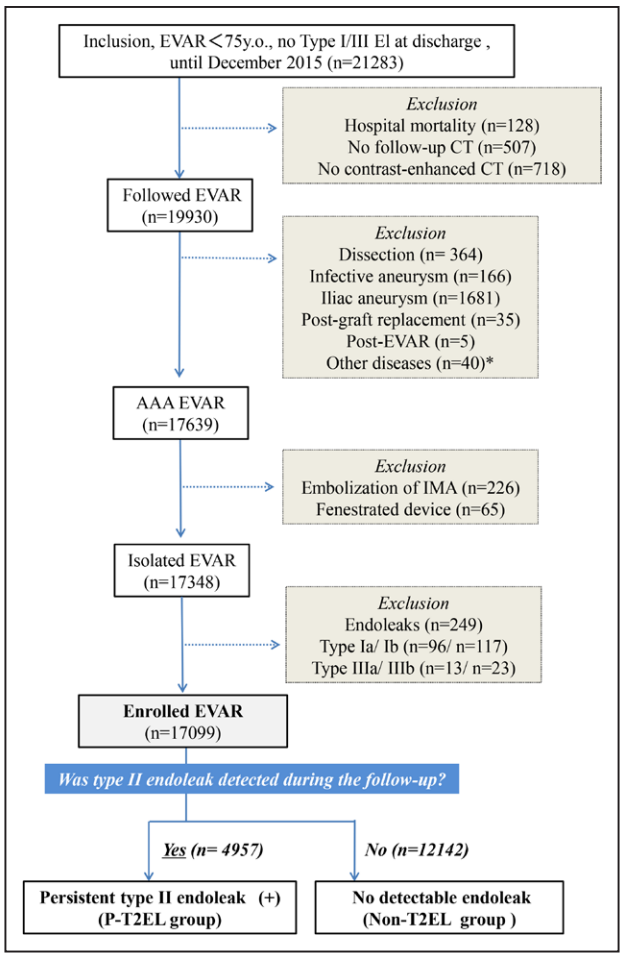

Figure 1. Study population and inclusion/exclusion criteria.
*Other diseases: 40 patients with other vascular pathologies—aortoiliac occlusive disease in 15, vascular injury in 11, renal artery aneurysm in 3, subclavian artery aneurysm in 2, aortoiliac fistula in 2, ureteroaortic fistula in 2, thrombosis in 2, femoral artery aneurysm in 1, superior mesenteric artery aneurysm in 1, and inferior mesenteric artery aneurysm in 1—were excluded. AAA indicates abdominal aortic aneurysm; EVAR, endovascular aortic repair; CT, computed tomography; IMA, inferior mesenteric artery; and p-T2EL, persistent type II endoleak.

A logistic regression analysis was performed to calculate PSs for the patients with p-T2EL using the patients' background characteristics. A 1-to-1 PS matching was performed by nearest-neighbor matching with replacement. The caliper width was set at 20% of the SD of the PSs. Baseline imbalance variables using standardized differences were also examined. Absolute values of <10% were considered balanced.[15] For adjusting factors that cause differences in the predisposition generating p-T2EL, multivariable analyses were performed in the PS-matched cohort with a Cox proportional hazard model accompanied by cluster-robust standard errors with the matched pairs as the clusters to evaluate the time-to-event effects of the covariables for the development of sac enlargement. Clinically significant variables, which were only those at a point in time that could be identified as before the onset of the event, based on previous research and experience were included in the multivariable regression analyses with the forced entry procedure.[9,16–21] Because of the exhaustive itemization, there are no excluded covariates to be evaluated by any sensitivity analyses. Proportional hazards assumption was visually checked with log-log plots (Figure S1).

RESULTS

Patient Characteristics (Entire Cohort)

Among the 17 099 patients investigated, 4757 (29.0%) had p-T2EL (p-T2EL group) and 12,142 (71.0%) did not have p-T2EL (non-T2EL group). Preoperative patients' characteristics, including the anatomic features of AAA in both the p-T2EL and non-T2EL groups, are listed in Table 1. None of participants had missing data for any variable. Because of the large number of patients investigated (>17 000), strict statistical differences were recognized as follows: Mean age was significantly higher ($P<0.001$) and men were fewer ($P<0.001$) in the p-T2EL group. The preoperative sac diameter was larger ($P<0.001$), proximal neck thrombosis was less prevalent ($P<0.001$), and suprarenal and proximal neck angulations (>60°) were greater ($P<0.001$) in the p-T2EL group. Among the comorbidities, hypertension was more prevalent ($P=0.019$) and respiratory disorders were less prevalent ($P<0.001$) in the p-T2EL group.

Preliminary Results (Entire Cohort)

One hundred twenty patients with hospital mortality were excluded, and no perioperative deaths in both study cohorts were observed. In-hospital complications are listed in Table S1. Access route injury was more prevalent in the p-T2EL group ($P=0.042$), but no significant difference was observed in the incidence of the other complications.

No significant difference was observed in the incidence of reintervention during hospitalization for complications (p-T2EL: 39 of 4957 [0.8%] versus non-T2EL: 110 of 12 142 [0.9%]; $P=0.469$). The findings of intraoperative aortography are listed in Table S1.

Survival and Late Follow-Up, Including Sac Enlargement (Entire Cohort)

The mean follow-up time was significantly longer in the p-T2EL group (4.6±2.6 years) than in the non-T2EL group (3.9±2.7 years; $P<0.001$). Late death occurred in 548 of 4957 patients (11.1%) in the p-T2EL group and 1255 of 12 142 (10.3%) in the non-T2EL group. The causes of late death (p-T2EL versus non-T2EL; Table S1) revealed no discriminating finding.

Freedom from all-cause mortality showed no significant difference between the groups (log-rank $P=0.086$). The cumulative incidence of AAA-related mortality (p-T2EL: 52 of 4957 [1.0%] versus non-T2EL: 21 of 12 142 [0.2%]), including 21 patients with AAA rupture, was significantly higher in the p-T2EL group than in the non-T2EL group ($P<0.001$; Figure 2A). AAA rupture, including mortality cases, was observed in 38 of 4957 patients (0.8%) with

Table 1. Comparison of Patient Characteristics (Entire and Matched Cohorts)

	Overall			Matched		
Variable	p-T2EL (4957)	Non-T2EL (12142)	ASD	p-T2EL (4957)	Non-T2EL (4957)	ASD
Mean age, y	68.4 (5.1)	68.0 (5.3)	0.079	68.4 (5.1)	68.4 (5.0)	0.002
<60, n (%)	304 (6.1)	888 (7.3)	…	304 (6.1)	286 (5.8)	0.015
60–64, n (%)	739 (14.9)	1886 (15.5)	…	739 (14.9)	716 (14.4)	0.013
65–69, n (%)	1316 (26.5)	3490 (28.7)	…	1316 (26.5)	1419 (28.6)	−0.047
70–74, n (%)	2598 (52.4)	5878 (48.4)	…	2598 (52.4)	2536 (51.2)	0.025
Male sex, n (%)	4358 (87.9%	11128 (91.6)	−0.123	4358 (87.9)	4349 (87.8)	0.006
Operative year, n (%)			…			
2006–2008	427 (8.6)	1088 (9.0)	−0.012	427 (8.60)	439 (8.9)	−0.009
2009	487 (9.8)	1064 (8.8)	0.037	487 (9.8)	492 (9.9)	−0.003
2010	687 (13.9)	1350 (11.1)	0.083	687 (13.9)	682 (13.8)	0.003
2011	715 (14.4)	1589 (13.1)	0.039	715 (14.4)	727 (14.7)	−0.007
2012	645 (13.0)	1660 (13.7)	−0.019	645 (13.0)	623 (12.6)	0.013
2013	694 (14.0)	1931 (15.9)	−0.053	694 (14.0)	725 (14.6)	−0.018
2014	741 (14.%)	2011 (16.6)	−0.044	741 (14.9)	733 (14.0)	0.005
2015	561 (11.3)	1449 (11.9)	−0.019	561 (11.3)	536 (10.8)	0.016
Etiology, n (%)						
True	4928 (99.4)	11838 (97.5)	0.156	4928 (99.4)	4929 (99.4)	0.005
Pseudo	19 (0.4)	250 (2.1)	−0.153	19 (0.4)	18 (0.4)	0.007
Other	9 (0.2)	43 (0.4)	−0.033	9 (0.2)	10 (0.2)	−0.021
Pathology, n (%)						
Atherosclerosis	4600 (92.8)	11076 (91.2)	0.058	4600 (92.8)	4603 (92.9)	0.015
Inflammatory	43 (0.9)	199 (1.6)	−0.069	43 (0.9)	36 (0.7)	0.021
Others	25 (0.5%)	131 (1.1%)	−0.065	25 (0.5)	30 (0.6)	0.003
Combined with IAA	343 (6.9)	647 (5.3)	0.066	343 (6.9)	342 (6.9)	−0.009
Anatomic features						
Mean sac diameter, mm	48.7±14.0	47.0±15.8	0.069	48.7±14.0	51.4±11	0.016
Proximal neck diameter, mm	21.5±3.0	21.5±3.8	−0.005	21.5±3.0	21.5±3.3	−0.004
Proximal neck length, mm	32.6±15.1	32.5±15.8	0.009	32.6±15.1	32.3±15.2	−0.027
Proximal neck calcification, n (%)	356 (7.2)	860 (7.1)	0.004	356 (7.2)	369 (7.4)	−0.009
Proximal neck thrombosis, n (%)	439 (8.9)	1497 (12.3%)	−0.113	439 (8.9%)	437 (8.8%)	0.016
Suprarenal angulation (>45°) , n (%)	522 (10.5)	825 (6.8)	0.133	522 (10.5)	508 (10.2)	−0.019
Proximal neck angulation (>60°), n (%)	723 (14.6)	1194 (9.8)	0.146	723 (14.6)	744 (15.0)	0.007
Short distal landing zone, n (%)	479 (10.0)	1464 (12.1)	−0.077	479 (10.0)	484 (9.8)	−0.005
Comorbidities, n (%)						
Hypertension	3333 (67.2)	7936 (65.4)	0.04	3333 (67.2)	3311 66.8)	−0.012
Diabetes	744 (15.0)	1782 (14.8)	0.009	744 (15.0)	738 (14.9)	0.003
Coronary artery disease	1471 (29.8)	3591 (29.6)	0.002	1471 (29.8)	1455 (29.4)	0.007
Cerebrovascular disease	674 (13.6)	1579 (13.0)	0.017	674 (13.6)	692 (14.0)	0.001
Respiratory disorder	726 (14.6)	2056 (16.9)	−0.063	726 (14.6)	762 (15.4)	−0.031
House oxygen therapy	39 (0.8)	95 (0.8)	<0.001	39 (0.8)	36 (0.7)	−0.009
CKD (Cr >1.5)	314 (6.3)	876 (7.2)	−0.035	314 (6.3)	309 (6.2)	−0.008
Hostile abdomen	907 (18.3)	2001 (16.5)	0.048	907 (18.3)	889 (17.9)	−0.002

ASD indicates absolute standardized difference; CKD, chronic kidney disease; Cr, creatinine; IAA, iliac artery aneurysm; non-T2EL, no persistent type II endoleak; and p-T2EL, persistent type II endoleak.

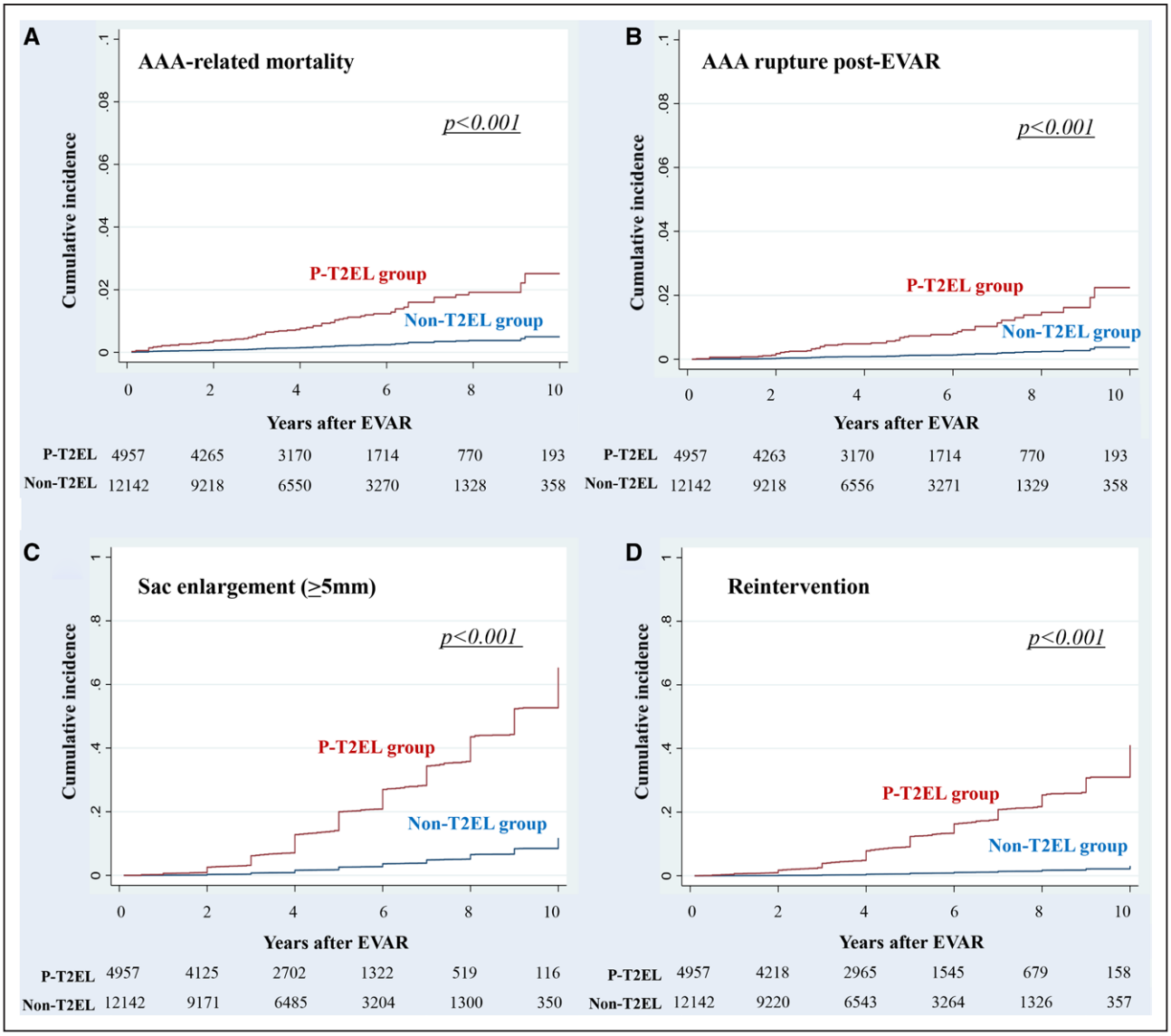

Figure 2. Cumulative incidence curves (entire cohort).
A, Cumulative incidence of abdominal aortic aneurysm (AAA)–related mortality was significantly higher in the persistent type II endoleak (p-T2EL) group than in the non-T2EL group (*P*<0.001). **B**, Cumulative incidence of AAA rupture after endovascular aortic repair (EVAR) was significantly higher in the p-T2EL group than in the non-T2EL group (*P*<0.001). **C**, Cumulative incidence of aneurysm sac enlargement (≥5 mm) was significantly higher in the p-T2EL group than in the non-T2EL group (*P*<0.001). (**D**) Cumulative incidence of reintervention was significantly higher in the p-T2EL than in the non-T2EL group (*P*<0.001). AAA,; EVAR,; p-T2EL,.

p-T2EL and 13 of 12 142 (0.1%) without p-T2EL. The cumulative incidence of AAA rupture after EVAR was significantly higher in the p-T2EL group than in the non-T2EL group (*P*<0.001; Figure 2B). Details of p-T2EL and univariable predictors of sac enlargement (≥5 mm) related to the side branches of AAA in p-T2EL are given in Table S2.

Sac Enlargement and Reintervention (Entire Cohort)

During follow-up, sac enlargement (≥5 mm) was observed in 1359 of 4957 (27.4%) in the p-T2EL and 332 of 12 142 patients (2.7%) in the non-T2EL groups. The cumulative incidence of sac enlargement (≥5 mm) was significantly higher in the p-T2EL group (*P*<0.001; Figure 2C).

Reintervention for sac enlargement was required in 739 of 12 142 patients (14.9%) in the p-T2EL group and 91 of 4957 (0.7%) in the non-T2EL group. Conversion to graft replacement was performed in 158 of 4957 (3.2%) in the p-T2EL group and 71 of 12 142 patients (0.6%) in the non-T2EL group. The frequency of open conversions among reinterventions was higher in the non-T2EL group (78.0% [71 of 91] versus 21.4% [158 of 739]). The cumulative incidence of reintervention was significantly higher in the p-T2EL group (*P*<0.001; Figure 2D).

De Novo Endoleaks Other Than Type II Endoleaks During Follow-Up (Entire Cohort)

During follow-up, 103 endoleaks other than type II endoleaks not detected immediately after EVAR were finally detected, including type I in 74 patients (Ia, 44; Ib, 30), type III in 12 (IIIa, 6; IIIb, 6), and type IV in 3. The incidence of any type of endoleaks excluding type II endoleaks was significantly higher in the p-T2EL group (1.9% [95 of 4957] versus 0.07% [8 of 12 142]; $P<0.001$).

Analysis of the PS-Matched Cohorts

No significant differences were observed in the baseline patient characteristics of the 4957 PS-matched pairs (Table 1). A balance check was performed after matching; the 2 groups were comparable for all confounders (absolute standardized difference <0.10).

All PS-matching analyses enhanced the results from the entire cohort. Freedom from all-cause mortality showed no significant difference between the groups (log-rank $P=0.053$). The cumulative incidence of AAA-related mortality was significantly higher in the p-T2EL group than in the non-T2EL group ($P<0.001$; Figure 3A). The cumulative incidence of AAA rupture after EVAR was significantly higher in the p-T2EL group ($P<0.001$; Figure 3B). The cumulative incidence rates of sac enlargement (≥5 mm; $P<0.001$) and reintervention ($P<0.001$) were significantly higher in the p-T2EL group (Figure 3C and 3D).

Risk Factor of Sac Enlargement (Matched Cohort)

p-T2EL was identified as an independent positive predictor of aneurysm sac enlargement after EVAR (hazard ratio [HR], 9.40 [95% CI, 8.33–10.6]; $P<0.001$) in a Cox regression analysis. Age (HR, 1.02 [95% CI, 1.01–1.03]; $P=0.002$) was also an independent predictor. Male sex was identified as an independent negative predictor (HR, 0.85 [95% CI, 0.73–0.98]; $P=0.015$). As an anatomic feature, proximal neck diameter was identified only as an independent positive predictor (HR, 1.02 [95% CI, 1.00–1.03]; $P=0.003$). Among the comorbidities, chronic kidney disease (CKD) was identified as an independent positive predictor (HR, 1.69 [95% CI, 1.42–2.00]; $P<0.001$). No other factors of AAA diameter (HR, 1.00; $P=0.27$), proximal neck length (HR, 0.99; $P=0.19$), and hypertension (HR, 1.06; $P=0.27$) were identified as predictors of sac enlargement after EVAR (Table 2).

DISCUSSION

Guidelines on the management of abdominal aortoiliac artery aneurysms by the European Society for Vascular Surgery disclosed that although EVAR should be the preferred treatment modality in most patients, an open surgical repair should be recommended as first-line therapy in younger patients with a long life expectancy of >10 to 15 years.[22] The long-term durability of EVAR has been brought into question by some randomized controlled trials, including EVAR-1, DREAM (Dutch Randomized Endovascular Aneurysm Management), and Anevrysme de l'aorte abdominale, Chirurgie Versus Endoprothese (ACE), which revealed higher reintervention rates after EVAR.[23,24]

In terms of the necessity of reinterventions, type I and III endoleaks should be treated in cases of enlarged AAA.[5,6] However, the treatment strategy for the most common type II endoleaks remains unclear because most type II endoleaks are believed to be benign owing to their low rates (<1%) of rupture in a systematic review in 2013.[25] However, several recent studies have demonstrated that p-T2ELs are associated with adverse events.[20,21] Eden et al[16] reported that type II endoleak with sac enlargement had a higher association with type Ia endoleak, a well-known risk factor of late rupture. They highlighted that the median change in sac size at the time of type Ia endoleak identification in patients with type II endoleak was 13 mm. Deery et al[26] revealed that an aneurysm sac growth of at least 5 mm at 1 year contributed to late mortality and was significantly associated with type II endoleak (odds ratio, 2.9; 95% CI, 2.0–4.3; $P<0.001$).

In the present study, the cumulative incidence rates of rupture and AAA-related mortality were significantly higher in the p-T2EL group, and the PS-matching analysis enhanced these results. Moreover, the cumulative incidence rates of rupture and AAA-related mortality had increased by 2% at the 10-year follow-up, which is dissimilar to the reported frequency of ≈1%.[22] These results suggest that p-T2ELs are not benign. To achieve the same durability as open repair, the outcomes after EVAR should be improved; the EVAR-1 trial pointed out that rupture is attributable mostly to higher aneurysm-related mortality rate 8 years after EVAR.[23]

In the largest study about the impact of type II endoleak, Lo et al[17] performed a Kaplan-Meier analysis for >2000 patients and found that about half of p-T2EL/new type II endoleaks were related with sac enlargement and an increased reintervention rate at 2 years. Moreover, they reported that age ≥80 years (odds ratio, 2.7 [95% CI, 1.4–5.3]; $P=0.004$) was a significant predictor of p-T2EL/new type II endoleaks. In the present study, p-T2ELs were also associated with aneurysm sac enlargement and reintervention. This study included 17 099 patients from the JACSM registry who were ≤75 years of age to minimize the impact of aging and to evaluate the long-term prognosis by limiting the study to a younger patient population. Moreover, to exclude the impact of non–aorta-related mortality before these aortic events, the Fine-Gray model was applied for the evaluation of the cumulative incidence

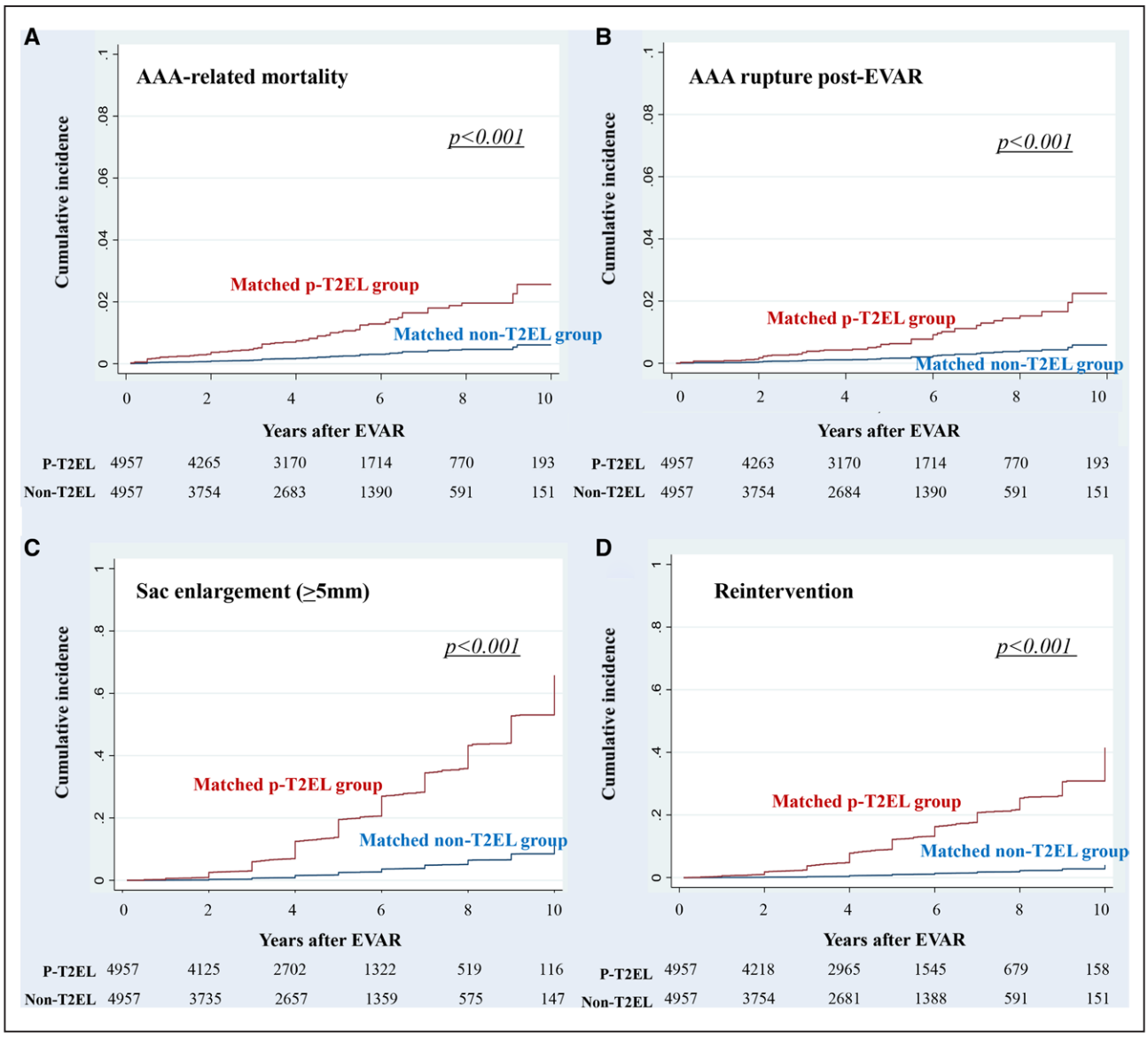

Figure 3. Cumulative incidence curves (propensity score–matched cohort).
A, Cumulative incidence of abdominal aortic aneurysm (AAA)–related mortality was significantly higher in the persistent type II endoleak (p-T2EL) group than in the non-T2EL group ($P<0.001$). **B**, Cumulative incidence of AAA rupture after endovascular aortic repair (EVAR) was significantly higher in the p-T2EL group than in the non-T2EL group ($P<0.001$). **C** and **D**, Cumulative incidence of aneurysm sac enlargement (≥5 mm; $P<0.001$) and reintervention ($P<0.001$) was significantly higher in the p-T2EL group than in the non-T2EL group.

of sac enlargement and reintervention. For further compensation for the bias, PS matching was applied to equalize the patients' characteristics, which revealed similar results of worse cumulative incidence of sac enlargement and reintervention for p-T2EL.

In the actual clinical settings of this large series of patients, the indication and method of reintervention for sac enlargement might not be unified. Therefore, this study focused on recognizing a predictor of sac enlargement. Several recent studies have demonstrated older age, chronic obstructive pulmonary disease, smoking history, inferior mesenteric artery patency/diameter, lumbar artery patency/diameter, and aneurysm thrombus volume as risk factors of sac enlargement due to p-T2ELs.[25,26] In the multiple regression analysis in the present study, age, proximal neck diameter, and CKD were identified as independent positive predictors of sac enlargement. On the contrary, male sex was identified as an independent negative predictor. As shown in Table 2, the HR increased with age. Age was identified as a risk factor of sac enlargement, similarly in the study of Lo and colleagues.[17] Proximal neck diameter has never been reported as a risk factor of sac enlargement; nevertheless, it was reported to be related to poor aortic remodeling attributable to extended history of aneurysmal change.[27] Regardless of aortic disease, CKD is generally associated with high morbidity and mortality, and reduced estimated glomerular filtration rate is a well-accepted risk factor of all-cause mortality.[28] The

Table 2. Predictors of Sac Enlargement (>5 mm; Matched Cohort)

	Univariable			Multivariable		
Covariate	HR	95% CI	*P* value	HR	95% CI	*P* value
p-T2EL	10.24	8.513–10.82	<0.001	10.11	8.453–12.10	<0.001
Age, y						
<60	1	…	…	1	…	…
60–64	1.117	0.862–1.447	0.43	1.151	0.888–1.491	0.288
65–69	1.186	0.932–1.509	0.166	1.299	1.020–1.655	0.034
70–74	1.287	1.201–1.622	0.033	1.36	1.078–1.716	0.01
Male sex	0.824	0.709–0.957	0.011	0.825	0.707–0.964	0.015
Etiology						
True	1.132	0.565–2.267	0.727	1.666	0.412–6.734	0.474
Pseudo	1.183	0.531–2.638	0.681	2.011	0.402–10.06	0.395
Pathology						
Atherosclerosis	1.001	0.845–1.205	0.917	0.941	0.780–1.135	0.527
Inflammatory	0.542	0.243–1.209	0.135	0.542	0.238–1.232	0.144
Combined with IAA	1.149	0.962–1.371	0.123	1.077	0.902–1. 287	0.414
Anatomic features						
Mean AAA diameter, mm	1.001	0.996–1.006	0.643	0.999	0.993–1.000	0.625
Proximal neck diameter, mm	1.017	1.002–1.033	0.026	1.024	1.001–1.042	0.005
Proximal neck length, mm	0.997	0.994–1.000	0.081	0.998	0.994–1.001	0.21
Proximal neck calcification	1.108	0.912–1.347	0.301	1.072	0.878–1.301	0.494
Proximal neck thrombosis	0.941	0.778–1.139	0.534	0.836	0.688–1.016	0.072
Suprarenal angulation (>45)	1.128	0.958–1.329	0.149	1.044	0.863–1.262	0.659
Proximal neck angulation (>60)	1.244	1.083–1.428	0.002	1.138	0.978–1.339	0.118
Short distal landing zone	0.902	0.771–1.055	0.197	1.006	0.848–1.192	0.949
Comorbidities						
Hypertension	0.981	0.879–1.094	0.726	0.958	0.873–1.091	0.665
Diabetes	1.037	0.902–1.192	0.612	1.044	0.906–1.203	0.55
Coronary artery disease	0.954	0.909–1.117	0.884	0.959	0.857–1.074	0.472
Cerebrovascular disease	1.121	0.967–1.299	0.131	1.054	0.906–1.223	0.486
Respiratory disorder	1.001	0.868–1.165	0.943	1.016	0.875–1.181	0.833
House oxygen therapy	1.375	0.738–2.562	0.315	1.323	0.707–2.498	0.377
CKD (Cr >1.5)	1.556	1.284–1.884	<0.001	1.57	1.292–1.907	<0.001
Hostile abdomen	0.934	0.817–1.067	0.312	0.905	0.791–1.036	0.146

AAA indicates abdominal aortic aneurysm; CKD, chronic kidney disease; Cr, creatinine; HR, hazard ratio; IAA, iliac artery aneurysm; and p-T2EL, persistent type II endoleak.

impact of CKD as a cause of sac enlargement remains unclear, but the significance of CKD in worse outcomes could be emphasized in a large cohort study. Female sex was a risk factor of sac enlargement. Thus, surgical strategies, considering the longer life expectancy of women, should be planned with caution, especially in younger patients.

Limitations

This study limitations are as follows: First, this nationwide, prospective, longitudinal study on a specific cohort of patients was limited by the insufficient data on the devices used and differing institutional methods of device selection. Second, some patients who underwent EVAR were excluded from the study because of hospital mortality, dissection, infection, iliac aneurysm, redo cases, fenestrated devices, inferior mesenteric artery embolization, type I/III endoleaks, and incomplete data from the last follow-up. Third, the influence of minor type IV endoleak or endoleak of undefined origin could not be assessed owing to the inaccurate diagnosis of such endoleaks in this large-scale registry. Fourth, matched comparisons were not possible over the follow-up period of the results. Fifth, the differences in facilities as clusters were not analyzed because no data were available. Last, the

high significance levels (*P* values) caused by this large cohort could indicate unmeasured confounding in the propensity model, and other potential causes of residual confounding, including the impact of medical treatments of anticoagulant, antiplatelet, and antihypertension therapies, were not evaluated, although they were identified as risk factors of type II endoleaks in several studies.[21]

Conclusions

The JACSM registry data showed the significance of p-T2ELs to the risk of late adverse events, including aneurysm sac enlargement, reintervention, rupture, and AAA-related mortality after EVAR. Evaluation using PS matching of 4957 pairs enhanced these observations. Other than p-T2EL, older age, female sex, CKD, and dilated proximal neck were associated with sac enlargement.

ARTICLE INFORMATION

Received July 13, 2021; accepted January 14, 2022.

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Acknowledgments

This work was supported by the Japan Cardiovascular Research Foundation, which was not involved in the conduct of this study. The authors thank all collaborators (listed in the Appendix) of the JASCM who registered the patients and outcome data in the JASCM registry.

Sources of Funding

This study was funded by the Japan Cardiovascular Research Foundation.

Disclosures

None.

Supplemental Material

Tables S1 and S2

Figure S1

APPENDIX

Collaborators and affiliated academic societies involved in the JACSM are as follows: Takao Ohki, Japanese Society for Cardiovascular Surgery; Kimihiro Komori, Japan Society for Vascular Surgery; Kunihiro Shigematsu, Japanese College of Angiology; Yuji Ikari, Japanese Circulation Society and Japanese Association of Cardiovascular Intervention and Therapeutics; Koji Sugimoto, Japanese Society of Interventional Radiology; Yutaka Hosoi, Japanese Society for Phlebology; Hiroshi Nishimaki, Japanese Society of Endovascular Intervention; Hirotsugu Fukuda, Japanese Society for Artificial Organs; Norihiko Shiiya, auditor of the JACSM; Hiroyuki Ishibashi, auditor of the JACSM; Shin Ishimaru, advisor of the JACSM; and Masaaki Kato, executive director of the JACSM.

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