Tranexamic acid versus placebo to reduce perioperative blood transfusion in patients undergoing RP sarcoma resection

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Transfusion and RP sarcoma resection

- Incidence of transfusion for retroperitoneal sarcoma resection is up to 50%
- Associated with severe adverse events

Transfusion requirement, unit of packed red blood cells[c]			
Mean (range)	2.0 (0–67)		
No. of transfusions received			
0	320	59.7%	47.0
1–3	119		17.5
3+	97		14.2
Not available	145		21.3

TABLE 4. Results From the Univariate and Multivariate Logistic Models for Severe Complications (Clavien-Dindo ≥3 vs <3)

	Univariate Models			Multivariate Model		
	OR	95% CI	*P*	OR	95% CI	*P*
Age, yrs			0.003			0.012
67 vs 48*	1.52	1.20–1.93		1.42	1.11–1.83	
Tumor size, cm			0.354			0.653
30 vs 13*	1.24	0.93–1.67		0.91	0.65–1.28	
Resected organs score			0.042			0.007
4 vs 1*	1.51	1.10–2.07		1. 21	0.85–1.73	
8 vs 0†	4.33	1.96–9.57		3.00	1.24–7.29	
Transfusion requirement (blood units)			<0.001			<0.001
1–3 vs 0	2.74	1.68–4.46		2.56	1.53–4.26	
3+ vs 0	5.80	3.52–9.54		5.59	3.30–9.46	
Unknown vs 0	2.02	0.94–4.37		1.44	0.59–3.55	
Radiotherapy			0.997			0.622
Preintraoperative‡ vs no	1.16	0.74–1.82		1.19	0.73–1.94	
Only postoperative vs no	0.85	0.45–1.57		0.89	0.46–1.74	
Chemotherapy			0.201			0.209
Prepostoperative§ vs no	0.88	0.54–1.44		0.81	0.47–1.38	
Only postoperative vs no	0.16	0.02–1.18		0.19	0.02–1.45	

CI indicates confidence interval; DD LPS, dedifferentiated liposarcoma; FNCLCC, French National Federation of the Centers for the Fight Against Cancer; LMS, leiomyosarcoma; OR, odds ratio; WD LPS, well differentiated liposarcoma.

*Third versus first quartile.

†Maximum versus minimum value.

‡including patients with preoperative, intraoperative, pre- and intraoperative and intra- and postoperative radiotherapy.

§including patients with preoperative or pre- and postoperative CT.

TXA and surgery

- Systematic review and meta-analysis
  - 95 surgical randomized RCT (n=7838)
  - Majority cardiac (n=42) and ortho (n=36)

Outcomes	Events (tranexamic acid/control)	Pooled risk ratio (95% CI)	P value*	Heterogeneity I^2 (%)	Heterogeneity P value
Blood transfusion:					
All trials	1067/1520	0.62 (0.58 to 0.65)	<0.001	69	<0.001
Well concealed trials	459/ 609	0.68 (0.62 to 0.74)	<0.001	55	<0.001
Adequate blinding	847/1182	0.63 (0.59 to 0.68)	<0.001	54	<0.001
Myocardial infarction:					
All trials	23/35	0.68 (0.42 to 1.09)	0.11	0	0.90
Well concealed trials	16/25	0.70 (0.39 to 1.25)	0.22	0	0.82
Adequate blinding	18/33	0.59 (0.36 to 0.98)	0.04	0	0.81
Stroke:					
All trials	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Well concealed trials	5/4	1.18 (0.36 to 3.83)	0.78	0	0.92
Adequate blinding	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Deep vein thrombosis:					
All trials	25/29	0.86 (0.53 to 1.39)	0.54	0	0.96
Well concealed trials	13/14	0.92 (0.45 to 1.85)	0.81	0	0.81
Adequate blinding	18/22	0.82 (0.46 to 1.44)	0.49	0	0.98
Pulmonary embolism:					
All trials	4/8	0.61 (0.25 to 1.47)	0.27	0	0.96
Well concealed trials	1/3	0.52 (0.10 to 2.75)	0.44	0	0.80
Adequate blinding	4/6	0.70 (0.26 to 1.87)	0.48	0	0.91
Mortality:					
All trials	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97
Well concealed trials	9/15	0.67 (0.33 to 1.34)	0.25	0	0.85
Adequate blinding	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97

Ker et al, BMJ 2012

Clinicaltrials.gov

TXA And sarcoma

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Perioperative Use of **Tranexamic** (TXA) in Bone Tumor Surgery Will Change in Blood Loss and Transfusion Requirements.	• Ewing **Sarcoma** of Bone • Osteosarcoma	• Drug: **Tranexamic acid** injection • Other: Saline	• Children's Cancer Hospital Egypt 57357 Cairo, Egypt Cairo, Egypt
2	☐	Recruiting	**Tranexamic Acid** in Radical Resection and Endoprosthetic Reconstruction	• Musculoskeletal Cancer • **Sarcoma**,Soft Tissue	• Drug: **Tranexamic Acid** (TXA)	• University of Kansas Medical Center Kansas City, Kansas, United States
3	☐	Recruiting	Efficacy of **Tranexamic Acid** in Preventing Post Operative Blood Loss in Bone **Sarcoma** Patient	• Blood Loss, Surgical	• Drug: **Tranexamic acid** injection • Other: normal saline	• Shaukat Khanum Memorial Cancer Hospital & Research Center Lahore, Punjab, Pakistan

NEJM 2022

ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Noncardiac Surgery

P.J. Devereaux, M. Marcucci, T.W. Painter, D. Conen, V. Lomivorotov, D.I. Sessler, M.T.V. Chan, F.K. Borges, M.J. Martínez-Zapata, C.Y. Wang, D. Xavier, S.N. Ofori, M.K. Wang, S. Efremov, G. Landoni, Y.V. Kleinlugtenbelt, W. Szczeklik, D. Schmartz, A.X. Garg, T.G. Short, M. Wittmann, C.S. Meyhoff, M. Amir, D. Torres, A. Patel, E. Duceppe, K. Ruetzler, J.L. Parlow, V. Tandon, E. Fleischmann, C.A. Polanczyk, A. Lamy, S.V. Astrakov, M. Rao, W.K.K. Wu, K. Bhatt, M. de Nadal, V.V. Likhvantsev, P. Paniagua, H.J. Aguado, R.P. Whitlock, M.H. McGillion, M. Prystajecky, J. Vincent, J. Eikelboom, I. Copland, K. Balasubramanian, A. Turan, S.I. Bangdiwala, D. Stillo, P.L. Gross, T. Cafaro, P. Alfonsi, P.S. Roshanov, E.P. Belley-Côté, J. Spence, T. Richards, T. VanHelder, W. McIntyre, G. Guyatt, S. Yusuf, and K. Leslie, for the POISE-3 Investigators*

Marcucci M, al. Rationale ISchemic Ev randomized tranexamic a hypotension

- In patients undergoing noncardiac surgery who are at risk for bleeding and cardiovascular events, does tranexamic acid result in a lower incidence of life-threatening bleeding, major bleeding, or bleeding into a critical organ than placebo,
- AND
- is it noninferior to placebo with respect to the incidence of major cardiovascular complications within 30 days?

- 6/2018-6/2021
- 114 countries in 22 countries
- >45 yo
- risk for bleeding and cardiovascular complications according to criteria previously associated with perioperative bleeding and cardiovascular complications
  - (e.g., known atherosclerotic disease, undergoing major surgery, an age of ≥70 years, and a serum creatinine level of >175 µmol per liter [2.0 mg per deciliter])

- 1:1 TXA 1g at start and end of case
- Blinded
- Primary outcome: composite of life-threatening bleeding, major bleeding, and bleeding into a critical organ at 30 days after randomization.
- The primary safety outcome was a composite of myocardial injury after noncardiac surgery (i.e., myocardial infarction or isolated ischemic troponin elevation), nonhemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days after randomization.
- Stopped enrollment at 9500 due to COVID
  - incidences of the aggregate composite bleeding and composite cardiovascular outcome events were higher than originally estimated

Table 1. Baseline Characteristics of the Patients, Type of Surgery, and Medications.*

Characteristics	Tranexamic Acid (N=4757)	Placebo (N=4778)
Age — yr	69.5±9.5	69.3±9.4
Male sex — no./total no. (%)	2669/4755 (56.1)	2681/4778 (56.1)
Eligibility criteria met — no. (%)	4742 (99.7)	4766 (99.7)
NT-proBNP ≥200 ng/liter	574 (12.1)	552 (11.6)
History of coronary artery disease	1410 (29.6)	1466 (30.7)
History of peripheral artery disease	714 (15.0)	722 (15.1)
History of stroke	400 (8.4)	388 (8.1)
Undergoing major vascular surgery	541 (11.4)	544 (11.4)
Risk criteria		
Met ≥3 of 9 criteria	3988 (83.8)	4003 (83.8)
Undergoing major surgery†	3741 (78.6)	3798 (79.5)
Undergoing urgent or emergency surgery	555 (11.7)	540 (11.3)
Age ≥70 yr	2611 (54.9)	2588 (54.2)
Current diabetes for which medication is taken	1749 (36.8)	1812 (37.9)
Preoperative serum creatinine level >175 μmol/liter	57 (1.2)	73 (1.5)
History of congestive heart failure	674 (14.2)	671 (14.0)
History of transient ischemic attack	282 (5.9)	247 (5.2)
History of hypertension	4293 (90.2)	4321 (90.4)
History of smoking within 2 yr before surgery	1131 (23.8)	1128 (23.6)
Other medical history — no. (%)		
Atrial fibrillation	478 (10.0)	445 (9.3)
Active cancer	1311 (27.6)	1360 (28.5)
Surgery — no./total no. (%)		
Any procedure	4729/4757 (99.4)	4740/4778 (99.2)
General‡	1769/4729 (37.4)	1773/4740 (37.4)
Orthopedic	1083/4729 (22.9)	1063/4740 (22.4)
Vascular	699/4729 (14.8)	700/4740 (14.8)
Urologic	598/4729 (12.6)	624/4740 (13.2)
Spinal	237/4729 (5.0)	206/4740 (4.3)
Gynecologic	162/4729 (3.4)	171/4740 (3.6)
Thoracic	127/4729 (2.7)	146/4740 (3.1)
Low-risk	39/4729 (0.8)	34/4740 (0.7)
Plastic	14/4729 (0.3)	23/4740 (0.5)
Data missing on type of procedure performed	1/4729 (<0.1)	0/4740
No procedure performed	27/4757 (0.6)	35/4778 (0.7)
Data missing on whether patient underwent surgery	1/4757 (<0.1)	3/4778 (0.1)
Medication taken within 24 hr before surgery — no. (%)		
Therapeutic-dose thrombin or factor Xa inhibitor	22 (0.5)	28 (0.6)
Therapeutic-dose vitamin K antagonist	6 (0.1)	8 (0.2)
Therapeutic-dose intravenous or subcutaneous antithrombotic agent	58 (1.2)	44 (0.9)

- 64% received DVT prophylaxis in both groups

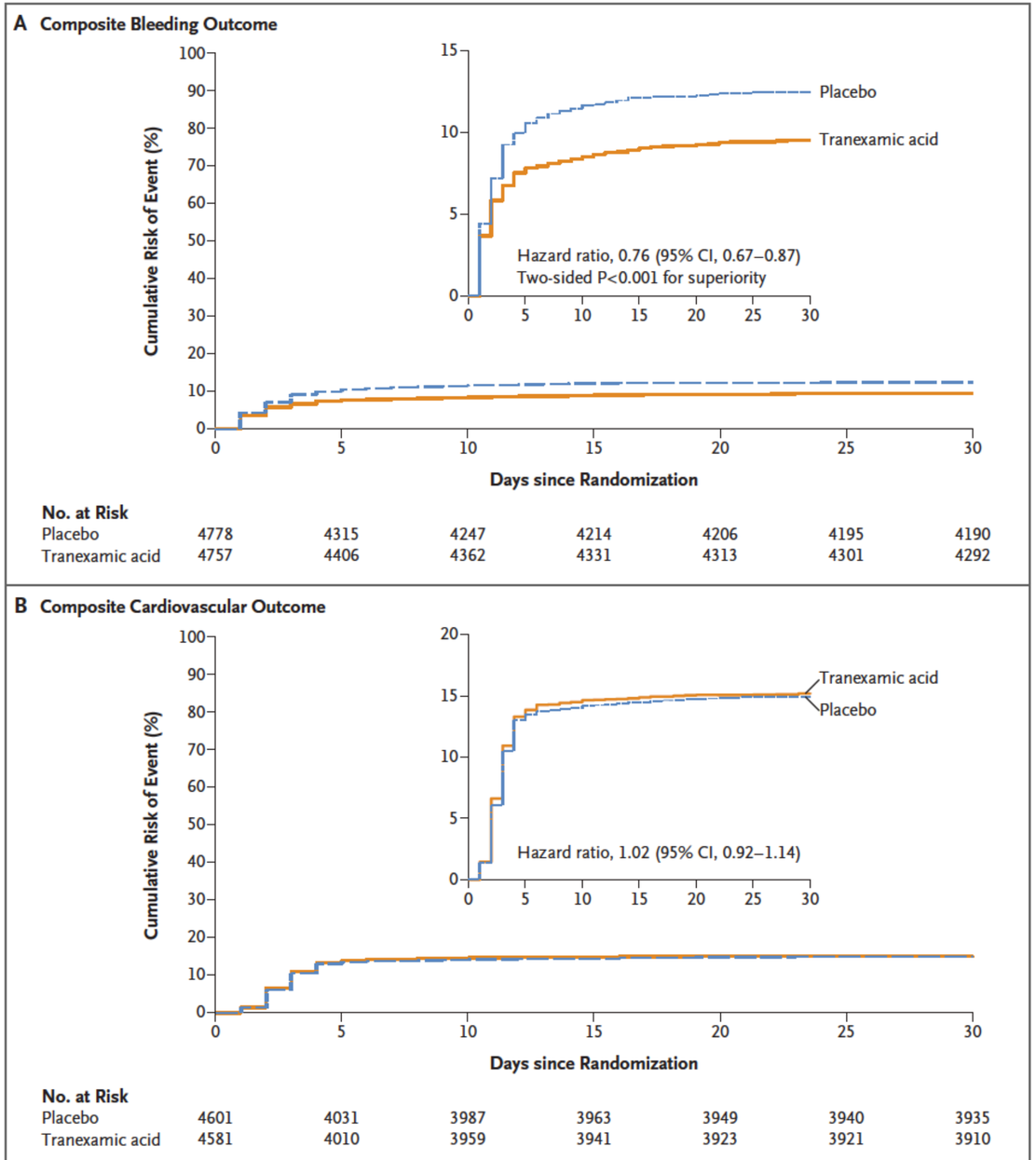

Figure 1. Kaplan–Meier Estimates of the Primary Outcomes.

The composite bleeding outcome (Panel A) was a composite of life-threatening bleeding, major bleeding, and bleeding into a critical organ at 30 days. The composite cardiovascular outcome (Panel B) was a composite of myocardial injury after noncardiac surgery, nonhemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days. The insets show the same data on an expanded y axis.

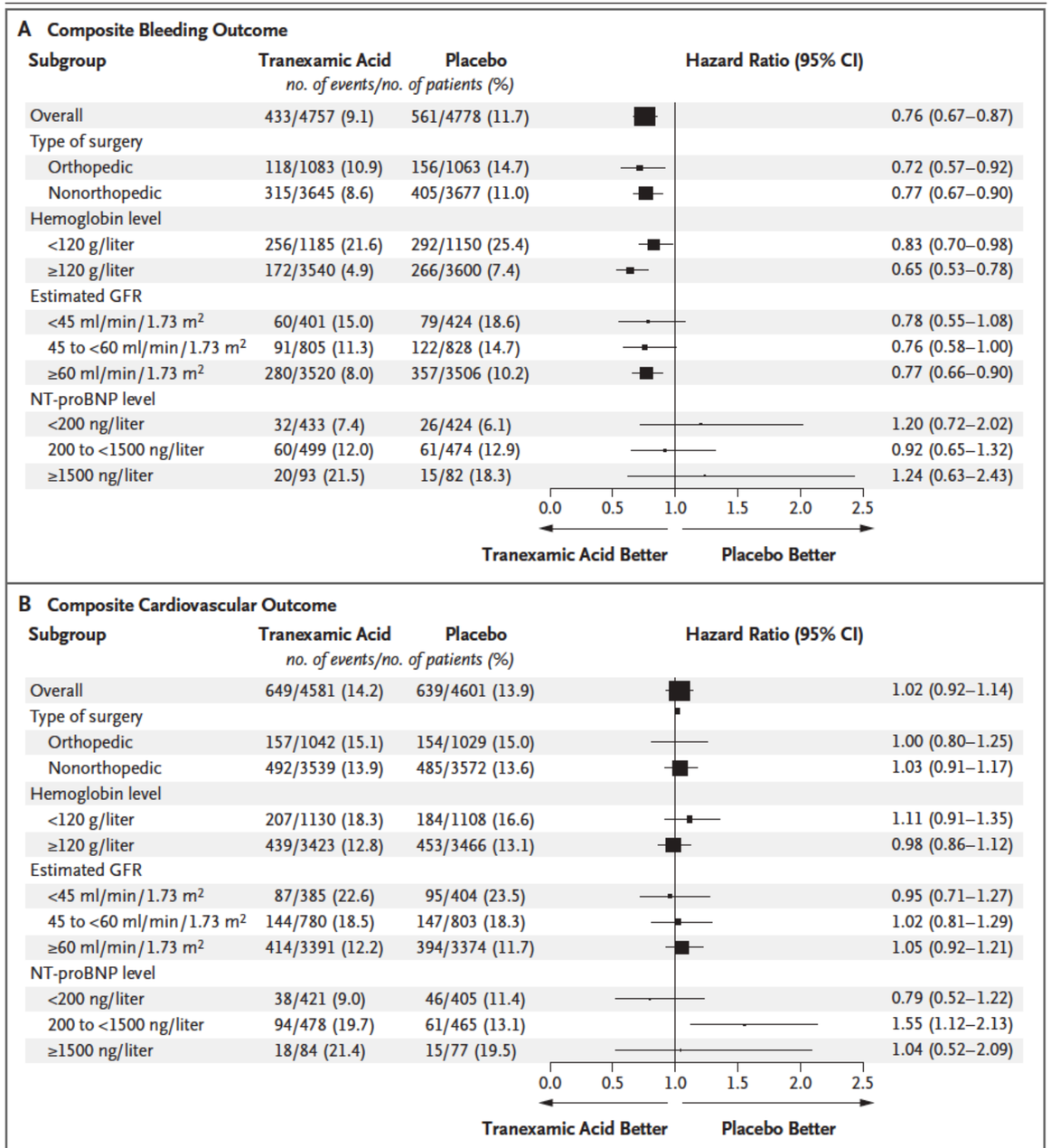

Figure 2. Prespecified Subgroup Analyses.

The size of the boxes is proportional to the number of patients with events. GFR denotes glomerular filtration rate, and NT-proBNP N-terminal pro–brain natriuretic peptide.

Table 2. Effects of Tranexamic Acid on 30-Day Outcomes.*

Outcome	Tranexamic Acid (N = 4757)	Placebo (N = 4778)	Hazard Ratio (95% CI)†	P Value
Primary efficacy outcome: composite bleeding outcome — no. (%)‡	433 (9.1)	561 (11.7)	0.76 (0.67–0.87)	<0.001§
Individual components of composite bleeding outcome — no. (%)				
Life-threatening bleeding¶	78 (1.6)	79 (1.7)	0.99 (0.73–1.36)	
Major bleeding¶	363 (7.6)	496 (10.4)	0.72 (0.63–0.83)	
Bleeding into a critical organ¶	12 (0.3)	21 (0.4)	0.57 (0.28–1.16)	
Primary safety outcome: composite cardiovascular outcome — no./total no. (%)‖	649/4581 (14.2)	639/4601 (13.9)	1.02 (0.92–1.14)	0.04**
Individual components of composite cardiovascular outcome — no. (%)				
MINS¶	608 (12.8)	602 (12.6)	1.02 (0.91–1.14)	
Nonhemorrhagic stroke††	24 (0.5)	16 (0.3)	1.51 (0.80–2.84)	
Peripheral arterial thrombosis††	22 (0.5)	23 (0.5)	0.96 (0.53–1.72)	
Symptomatic proximal venous thromboembolism††	32 (0.7)	28 (0.6)	1.15 (0.69–1.91)	
Other secondary outcomes — no. (%)				
Bleeding independently associated with death after noncardiac surgery	416 (8.7)	541 (11.3)	0.76 (0.67–0.87)	
MINS not fulfilling the universal definition of myocardial infarction	549 (11.5)	549 (11.5)	1.01 (0.89–1.13)	
Myocardial infarction	67 (1.4)	53 (1.1)	1.27 (0.89–1.82)	
Net risk–benefit outcome‡‡	983 (20.7)	1046 (21.9)	0.94 (0.86–1.02)	

Table 3. Effects of Tranexamic Acid on 30-Day Tertiary Outcomes.*

Outcome	Tranexamic Acid (N=4757)	Placebo (N=4778)	Hazard Ratio (95% CI)†
Major bleeding according to ISTH criteria — no. (%)	315 (6.6)	415 (8.7)	0.75 (0.65 to 0.87)
Transfusion of ≥1 unit of packed red cells — no. (%)	449 (9.4)	574 (12.0)	0.77 (0.68 to 0.88)‡
Death from any cause — no. (%)	52 (1.1)	57 (1.2)	0.92 (0.63 to 1.33)
Death from cardiovascular cause — no. (%)	25 (0.5)	30 (0.6)	0.84 (0.49 to 1.42)
Hemorrhagic stroke — no. (%)	2 (<0.1)	0	—
Amputation — no. (%)	14 (0.3)	21 (0.4)	0.67 (0.34 to 1.31)
Symptomatic pulmonary embolism — no. (%)	24 (0.5)	17 (0.4)	1.42 (0.76 to 2.64)
Symptomatic proximal deep venous thrombosis — no. (%)	11 (0.2)	13 (0.3)	0.85 (0.38 to 1.90)
Any symptomatic or asymptomatic proximal venous thromboembolism — no. (%)	32 (0.7)	28 (0.6)	1.15 (0.69 to 1.91)
Cardiac revascularization — no. (%)	12 (0.3)	13 (0.3)	0.93 (0.42 to 2.03)
Acute kidney injury — no. (%)§	672 (14.1)	655 (13.7)	1.03 (0.93 to 1.15)
New renal-replacement therapy — no. (%)	19 (0.4)	16 (0.3)	1.19 (0.61 to 2.32)
Rehospitalization for cardiovascular reasons — no. (%)	84 (1.8)	75 (1.6)	1.13 (0.82 to 1.54)
Seizure — no. (%)	10 (0.2)	3 (0.1)	3.35 (0.92 to 12.20)
Infection — no. (%)	499 (10.5)	487 (10.2)	1.03 (0.91 to 1.17)
Sepsis — no. (%)	68 (1.4)	63 (1.3)	1.08 (0.77 to 1.53)
Median length of hospital stay (IQR) — days	4.0 (2.1 to 7.1)	4.0 (2.1 to 7.1)	0 (–0.1 to 0.1)¶
Median no. of days alive at home (IQR)	25 (22 to 28)	25 (21 to 28)	0 (–0.4 to <0.1)¶
Disability — no. (%)	1408 (31.9)	1407 (31.6)	1.02 (0.92 to 1.13)‖