Bone & Joint Research

Supplementary Material

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Patient and public involvement

Our research programme is supported by a dedicated group of patients who have previously had treatment for hip or knee periprosthetic joint infection (PJI). These patients have been involved in the conduct of all our National Joint Registry for England, Wales, Northern Ireland, the Isle of Man, and the States of Guernsey (NJR) analyses relating to PJI, including identification of the research questions, study design, conduct, and interpretation of the results. We specifically consulted the group as to what revision outcomes they considered important in the context of this analysis, and we received strong feedback that all revisions used to manage PJI from the point that it is determined that single- or two-stage revision is required should be included. They felt that if repeat first stages before a second-stage procedure were not captured, this would not adequately describe their own lived experience. Quotes from the group include "it is more realistic to include everything", "I had many complications between stages, it was not a straightforward journey between stage 1 and stage 2", and "the middle bit is the worst".

Definition of the at-risk periods

As advised by the strong preference of our patient involvement group to capture the whole treatment journey, we followed up each patient from the date of their initial revision surgery for PJI (date of first single-stage or stage 1 of 2 procedure) until the end of the observation period (31 December 2014), date of death, or the date of a re-revision. Patients re-revised with a single-stage procedure were therefore followed up until the date of this procedure. Patients re-revised with a two-stage procedure were followed up until the date of the stage 1 surgery. No stage 1 but only the stage 2 procedure was recorded for 53 patients re-revised with a two-stage procedure (53/109). The date of their stage 1 of two-stage reoperation procedure and the period they had been at risk of reoperation were therefore estimated. We initially derived the relative weight of time elapsed between the first PJI revision surgery (date of single-stage procedure or date of stage 2 operation for two-stage procedure) and stage 1 of the two-stage reoperation procedure using patients with complete information: 100 × ((length of time between stage 1 of two-stage reoperation and first PJI revision)/(length of time between stage 2 of two-stage reoperation and first PJI revision)). We then applied this weight to the length of time between the first PJI revision and stage 2 of the two-stage reoperation for those with incomplete information, to estimate the duration between their stage 1 of two-stage reoperation and the initial PJI revision surgery.

Patients with incompletely registered two-stage reoperation procedures (n = 53), i.e. only stage 2 procedure recorded, were comparable (using chi-squared test) with those with both stage 1 and stage 2 reoperation procedures recorded in the NJR (n = 56) in terms of age (≥ 80 years: 8% vs 5%; ≤ 60 years: 26% vs 39%, p = 0.442), sex (female: 47% vs 38%, p = 0.229), and American Society of Anesthesiologists (ASA)[1] Physical Status grade (> P2: 77% vs 77%, P1: 23% vs 23%, p = 0.943) reported at the time of their first revision for PJI.

A similar strategy was used to derive the date of the first revision for PJI, following the primary hip arthroplasty performed with a two-stage revision when the stage 1 procedure was not recorded in the NJR. Full details are available elsewhere.[2] Patients with incompletely registered two-stage revision procedures performed for PJI of a primary hip arthroplasty (n = 523) were also comparable from those with complete information for stages 1 and 2 (n = 1,082).

For patients revised for PJI, the time at risk of death was derived from the date of the initial revision surgery for PJI (date of first single-stage or stage 1 of 2 procedure) until the end of the observation period (31 December 2014) or date of death. For patients with a primary hip arthroplasty never revised, the time at risk of death was derived from the date of primary procedure. For patients with

a primary hip arthroplasty revised for a non-septic indication, the time at risk of death was derived from the first revision for non-septic indication.

Time-specific hazard ratios and model selection

The overall, time-averaged hazard ratios (HRs) derived from the Cox shared frailty model to produce findings comparable with the literature were supplemented with time-dependent HRs to capture time-specific disparities between PJI revision procedures. We used Poisson regression (time at risk modelled as an offset) adjusted for age, sex, and ASA grade, and modelled the baseline hazard function with restricted cubic splines. The optimum numbers of knots (two degrees of freedom (d.f.)) were identified using the most parsimonious model, minimizing both Bayesian information criteria (BIC) and Akaike information criteria (AIC) (Supplementary Table i). We modelled interaction terms between the splines and the main exposure covariate to estimate the time-varying HRs. We computed Huber-White-sandwich robust estimate of variance to account for within-hospital correlation. We used a similar approach to compare the incidence of re-revision for PJI (restricted cubic splines Poisson model with two d.f.) and the risk of mortality (restricted cubic splines Poisson model with five d.f.) between revision procedure types.

TABLES

The models that minimized the AIC and BIC were selected to identify the number of optimal knots for the spline function (number of degrees of freedom–1). The log of follow-up time was modelled to obtain better fitting models.

Table i. Model selection – Akaike and Bayesian information criteria by number of knots used to parametrize the spline function. Bold font indicates model with optimal number of knots.

Model	d.f.*	AIC	BIC
All-cause reoperation			
	2	2,845	2,858
	3	**2,840**	**2,855**
	4	2,842	2,861
	5	2,843	2,865
Periprosthetic joint infection reoperation-revision			
	2	**1,678**	**1,690**
	3	1,680	1,695
	4	1,682	1,700
	5	1,681	1,703
Model for mortality			
	2	99,510	99,578
	3	**99,486**	**99,565**
	4	99,486	99,577
	5	99,487	99,600

*Number of knots = d.f.–1.

AIC, Akaike information criterion; BIC, Bayesian information criterion; d.f., degrees of freedom.

Table ii. Hazard ratio of all-cause reoperation between single-stage and two-stage revision (reference) performed to manage infected primary hip arthroplasty.

Time, mths*	Unadjusted analysis			Adjusted analysis†			Sensitivity analysis†‡		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
1	3.73	2.16 to 6.45	< 0.001	3.75	2.18 to 6.45	< 0.001	3.26	1.93 to 5.51	< 0.001
3	1.97	1.13 to 3.44	0.017	1.98	1.14 to 3.43	0.015	2.09	1.18 to 3.69	0.011
6	1.32	0.86 to 2.04	0.204	1.33	0.87 to 2.04	0.182	1.30	0.86 to 1.97	0.210
9	1.07	0.74 to 1.54	0.727	1.08	0.75 to 1.55	0.681	0.98	0.67 to 1.43	0.907
12	0.95	0.64 to 1.41	0.788	0.96	0.65 to 1.42	0.829	0.84	0.55 to 1.28	0.411
24	0.87	0.59 to 1.30	0.504	0.89	0.60 to 1.31	0.546	0.84	0.56 to 1.25	0.389
36	0.96	0.61 to 1.50	0.859	0.97	0.62 to 1.52	0.909	1.02	0.60 to 1.73	0.936
48	1.07	0.55 to 2.07	0.845	1.08	0.56 to 2.10	0.809	1.25	0.58 to 2.68	0.568
60	1.18	0.48 to 2.90	0.723	1.19	0.49 to 2.94	0.697	1.49	0.55 to 4.05	0.436

*Time from first revision for periprosthetic joint infection.
†Adjusted for age, sex, American Society of Anesthesiologists grade.
‡Excluding patients with incomplete two-stage revision procedures (n = 523).
CI, confidence interval; HR, hazard ratio.

Table iii. Hazard ratio of re-revision for periprosthetic joint infection between single-stage and two-stage revision (reference) procedures performed to manage infected primary hip arthroplasty.

Time, mths*	Unadjusted analysis			Adjusted analysis†			Sensitivity analysis†‡		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
1	3.63	1.39 to 9.51	0.009	3.76	1.42 to 9.99	0.008	2.58	1.03 to 6.45	0.044
3	1.81	1.23 to 2.68	0.003	1.81	1.22 to 2.68	0.003	1.74	1.14 to 2.65	0.010
6	1.26	0.72 to 2.19	0.404	1.25	0.71 to 2.21	0.437	1.32	0.69 to 2.53	0.404
9	1.05	0.59 to 1.86	0.862	1.05	0.58 to 1.88	0.879	1.12	0.57 to 2.19	0.744
12	0.94	0.54 to 1.62	0.812	0.94	0.54 to 1.63	0.816	0.99	0.53 to 1.86	0.975
24	0.73	0.44 to 1.21	0.228	0.75	0.45 to 1.23	0.256	0.74	0.43 to 1.28	0.283
36	0.65	0.35 to 1.21	0.173	0.67	0.36 to 1.25	0.211	0.63	0.32 to 1.22	0.172
48	0.59	0.27 to 1.30	0.194	0.63	0.28 to 1.38	0.245	0.56	0.24 to 1.30	0.178
60	0.56	0.22 to 1.42	0.221	0.59	0.23 to 1.53	0.280	0.51	0.18 to 1.42	0.197

*Time from first revision for periprosthetic joint infection.

†Adjusted for age, sex, American Society of Anesthesiologists grade.

‡Excluding patients with incomplete two-stage revision procedures (n = 523).

CI, confidence interval; HR, hazard ratio.

Table iv. Hazard ratio of mortality between revision procedures performed to manage infected primary hip arthroplasty and other arthroplasty procedures.

Time, mths*	1-stage vs 2-stage (reference)			1-stage vs primary (reference)			2-stage vs primary (reference)			1-stage vs aseptic revision† (reference)			2-stage vs aseptic revision† (reference)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Unadjusted analysis															
3	1.16	0.66 to 2.07	0.598	3.26	1.98 to 5.37	< 0.001	2.80	2.05 to 3.81	< 0.001	2.51	1.51 to 4.18	< 0.001	2.16	1.55 to 3.00	< 0.001
6	1.00	0.62 to 1.61	0.986	2.35	1.52 to 3.59	< 0.001	2.34	1.87 to 2.93	< 0.001	1.92	1.24 to 2.97	0.003	1.92	1.51 to 2.44	< 0.001
12	0.76	0.47 to 1.24	0.270	1.31	0.81 to 2.10	0.478	1.71	1.45 to 2.02	< 0.001	1.19	0.73 to 1.94	0.482	1.56	1.29 to 1.87	< 0.001
24	0.58	0.31 to 1.11	0.099	0.75	0.40 to 1.38	0.352	1.28	0.98 to 1.68	0.073	0.75	0.40 to 1.41	0.366	1.28	0.95 to 1.73	0.102
30	0.61	0.35 to 1.07	0.085	0.84	0.50 to 1.42	0.524	1.38	1.07 to 1.79	0.012	0.82	0.48 to 1.41	0.468	1.35	1.01 to 1.80	0.043
36	0.69	0.41 to 1.15	0.152	1.10	0.71 to 1.73	0.661	1.60	1.26 to 2.04	< 0.001	1.02	0.65 to 1.62	0.921	1.48	1.13 to 1.95	0.004
48	0.91	0.50 to 1.64	0.751	1.68	1.00 to 2.82	0.050	1.84	1.43 to 2.38	< 0.001	1.52	0.90 to 2.58	0.123	1.67	1.27 to 2.20	< 0.001
60	1.02	0.52 to 2.02	0.946	1.30	0.70 to 2.40	0.399	1.27	0.94 to 1.71	0.124	1.44	0.76 to 2.74	0.262	1.41	1.03 to 1.94	0.032
Adjusted analysis‡															
3	1.11	0.63 to 1.96	0.723	2.70	1.63 to 4.45	< 0.001	2.43	1.78 to 3.32	< 0.001	2.01	1.21 to 3.35	0.007	1.86	1.30 to 2.65	< 0.001
6	0.96	0.60 to 1.53	0.854	1.96	1.28 to 3.00	0.002	2.05	1.63 to 2.57	< 0.001	1.54	1.00 to 2.37	0.052	1.60	1.25 to 2.06	< 0.001
12	0.73	0.45 to 1.19	0.208	1.10	0.69 to 1.77	0.688	1.50	1.27 to 1.78	< 0.001	0.94	0.58 to 1.53	0.813	1.29	1.07 to 1.55	0.007
24	0.55	0.29 to 1.05	0.069	0.63	0.34 to 1.17	0.142	1.14	0.87 to 1.49	0.328	0.58	0.31 to 1.08	0.088	1.04	0.78 to 1.40	0.777
30	0.60	0.33 to 0.99	0.046	0.71	0.42 to 1.18	0.188	1.24	0.96 to 1.60	0.093	0.62	0.36 to 1.06	0.083	1.09	0.83 to 1.45	0.529

Time*	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value
36	0.63	0.39 to 1.03	0.067	0.91	0.59 to 1.41	0.680	1.45	1.13 to 1.85	0.003	0.76	0.49 to 1.20	0.243	1.21	0.93 to 1.58	0.162
48	0.81	0.46 to 1.42	0.458	1.35	0.82 to 2.24	0.235	1.68	1.28 to 2.19	< 0.001	1.12	0.67 to 1.88	0.669	1.39	1.05 to 1.83	0.020
60	0.91	0.47 to 1.74	0.776	1.06	0.59 to 1.89	0.840	1.17	0.87 to 1.57	0.305	1.09	0.60 to 1.99	0.791	1.19	0.87 to 1.63	0.270
Sensitivity analysis‡§															
3	0.89	0.498 to 1.60	0.693				3.04	2.19 to 4.24	< 0.001				2.27	1.59 to 3.26	< 0.001
6	0.82	0.50 to 1.33	0.422				2.39	1.88 to 3.04	< 0.001				1.88	1.44 to 2.45	< 0.001
12	0.71	0.43 to 1.17	0.177				1.55	1.26 to 1.91	< 0.001				1.33	1.06 to 1.66	0.010
24	0.60	0.30 to 1.18	0.144				1.05	0.76 to 1.46	0.754				0.96	0.68 to 1.36	0.828
30	0.60	0.33 to 1.07	0.079				1.18	0.89 to 1.57	0.257				1.04	0.76 to 1.42	0.811
36	0.62	0.38 to 1.03	0.062				1.46	1.13 to 1.89	0.003				1.23	0.93 to 1.62	0.154
48	0.70	0.40 to 1.23	0.221				1.92	1.46 to 2.53	< 0.001				1.59	1.21 to 2.09	< 0.001
60	0.78	0.40 to 1.54	0.483				1.36	0.95 to 1.93	0.092				1.39	0.97 to 1.99	0.078

*Time from first revision for periprosthetic joint infection for the 'single-stage' and 'two-stage' group, from the primary hip arthroplasty for the 'primary' group, or from the revision for a non-septic indication for the 'aseptic revision' group.

†Aseptic revision: revision surgery performed for indication other than an infection.

‡Adjusted for age, sex, and American Society of Anesthesiologists grade.

§Excluding patients with incomplete two-stage revision procedures (n = 523).

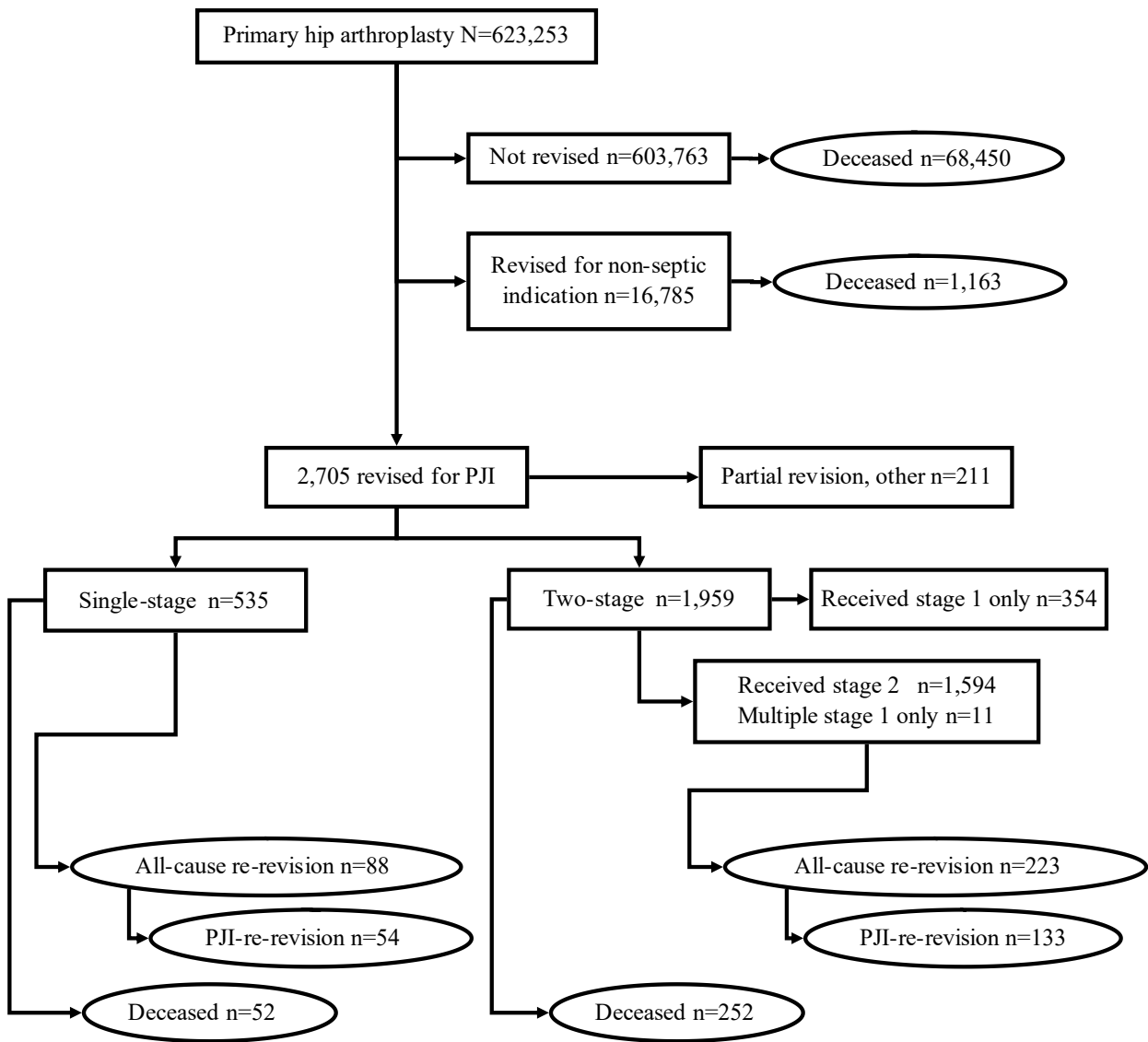CI, confidence interval; HR, hazard ratio.

FIGURES

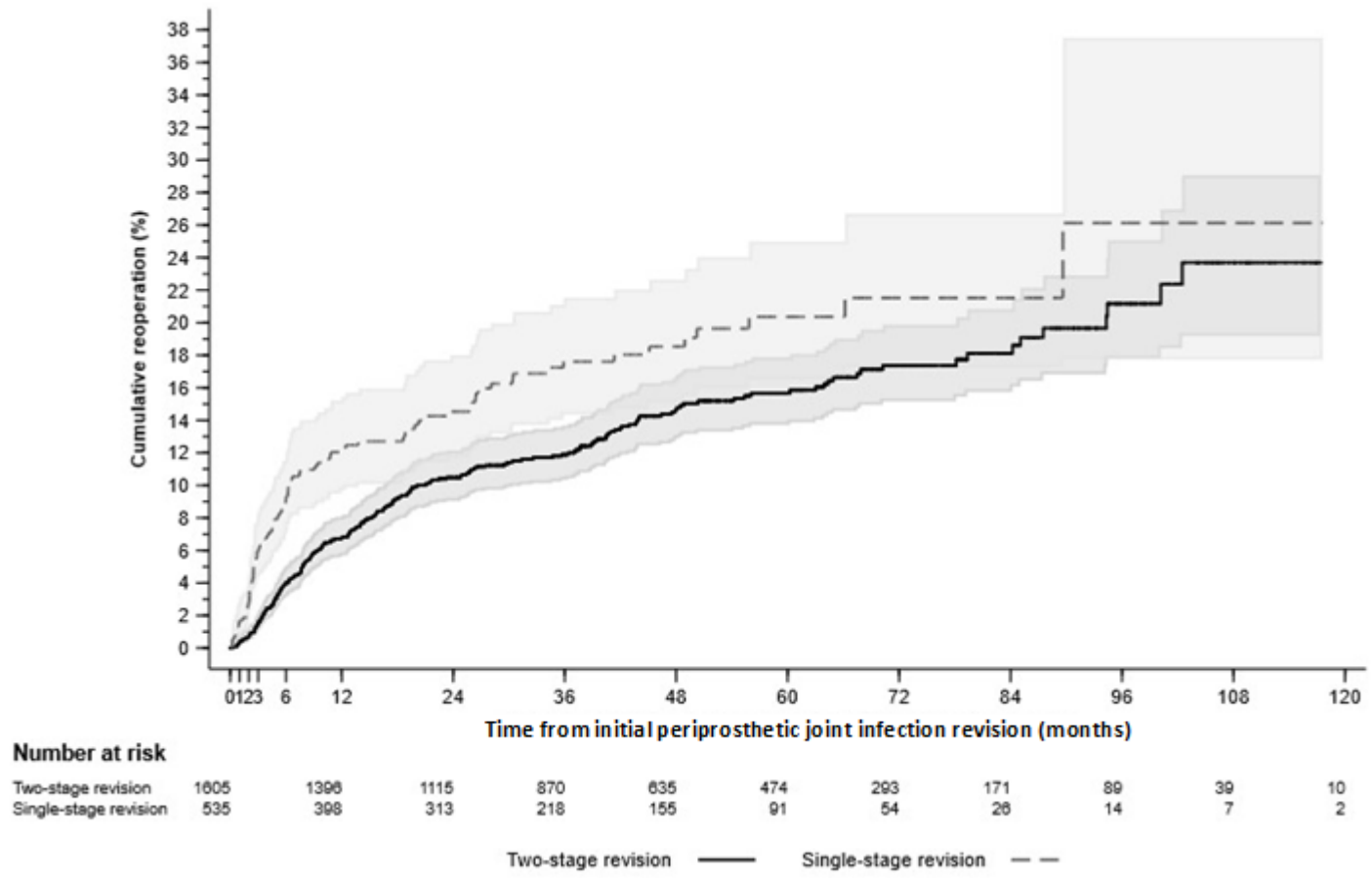**Fig a.** Participants flow diagram. PJI, periprosthetic joint infection.

Fig b. All-cause re-revision by single-stage or two-stage revision procedure for infected primary hip arthroplasty – Kaplan-Meier cumulative failure function.
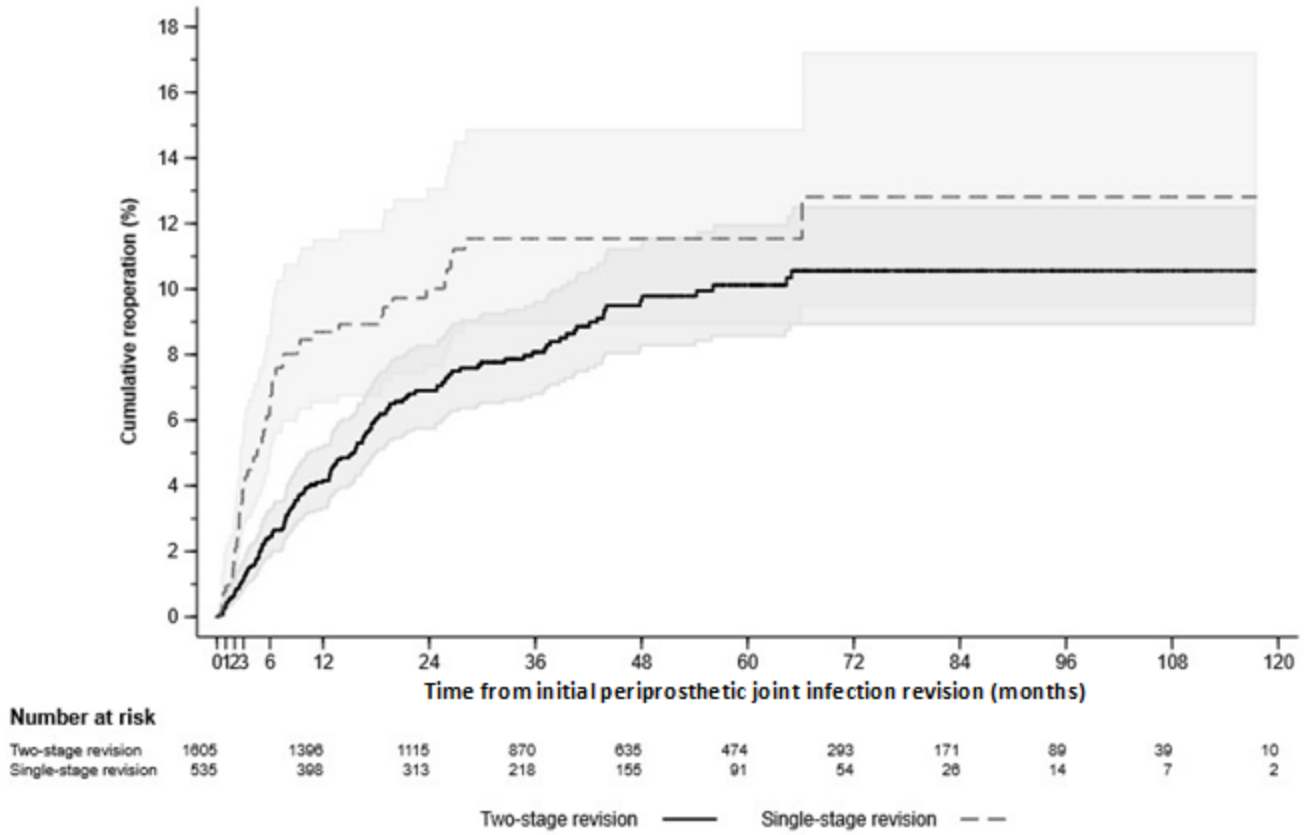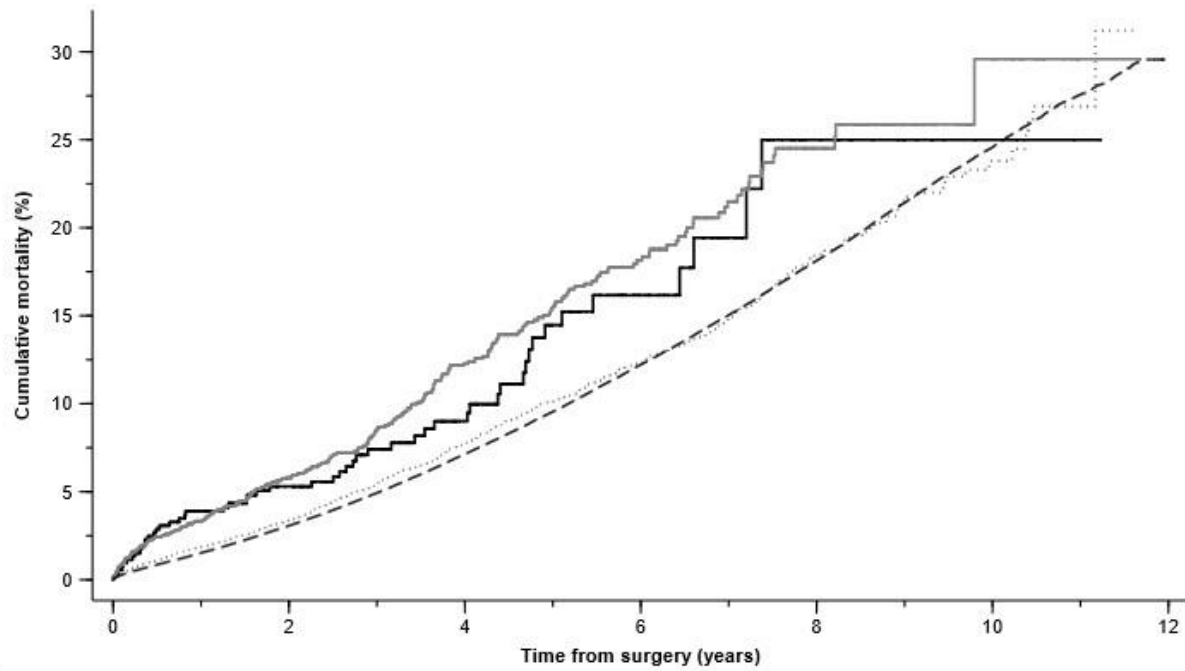
Fig c. Re-revision for periprosthetic joint infection by single-stage or two-stage revision procedure for infected primary hip – Kaplan-Meier cumulative failure function.

Number at risk

Single-stage revision	535	368	114	70	34	3	0
Two-stage revision	1,959	1,436	639	410	240	19	0
Non-septic rev.	16,446	11,011	3,593	2,339	1,392	142	0
Primary	603,762	509,229	279,789	213,870	152,811	30,136	0

Single-stage revision ——— Two-stage revision ——— Non-septic revision ········ Primary — —

Fig d. Mortality by revision procedures performed to manage infected primary hip arthroplasty or other arthroplasty procedures – Kaplan-Meier cumulative failure function.

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2. **Lenguerrand E, Whitehouse MR, Beswick AD, et al.** Risk factors associated with revision for prosthetic joint infection after hip replacement: a prospective observational cohort study. *Lancet Infect Dis*. 2018;18(9):1004-1014.