Antibiotic-loaded bone cement is associated with a lower risk of revision following primary cemented total knee arthroplasty an analysis of 731 214 cases using national joint registry data

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Abstract

Aims

Antibiotic-loaded bone cements (ALBCs) may offer early protection against the formation of bacterial biofilm after joint arthroplasty. Use in hip arthroplasty is widely accepted, but there is a lack of evidence in total knee arthroplasty (TKA). The objective of this study was to evaluate the use of ALBC in a large population of TKA patients.

Materials and Methods

Data from the National Joint Registry (NJR) of England and Wales were obtained for all primary cemented TKAs between March 2003 and July 2016. Patient, implant, and surgical variables were analyzed. Cox proportional hazards models were used to assess the influence of ALBC on risk of revision. Body mass index (BMI) data were available in a subset of patients.

Results

Of 731 214 TKAs, 15 295 (2.1%) were implanted with plain cement and 715 919 (97.9%) with ALBC. There were 13 391 revisions; 2391 were performed for infection. After adjusting for other variables, ALBC had a significantly lower risk of revision for any cause (hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.77 to 0.93; $p < 0.001$). ALBC was associated with a lower risk of revision for all aseptic causes (HR 0.85, 95% CI 0.77 to 0.95; $p < 0.001$) and revisions for infection (HR 0.84, 95% CI 0.67 to 1.01; $p = 0.06$). The results were similar when BMI was added into the model, and in a subanalysis where surgeons using only ALBC over the entire study period were excluded. Prosthesis survival at ten years for TKAs implanted with ALBC was 96.3% (95% CI 96.3 to 96.4) compared with 95.5% (95% CI 95.0 to 95.9) in those implanted with plain cement. On a population level, where 100 000 TKAs are performed annually, this difference represents 870 fewer revisions at ten years in the ALBC group.

Conclusion

After adjusting for a range of variables, ALBC was associated with a significantly lower risk of revision in this registry-based study of an entire nation of primary cemented knee arthroplasties. Using ALBC does not appear to increase midterm implant failure rates.

Introduction

Prosthetic infection after total knee arthroplasty (TKA) is a rare but potentially debilitating surgical complication. Its rate has been estimated to be between 1% and 2%.[1-3] Biofilm protects infecting organisms against the host immune system and systemic antibiotics.[4,5] Patients with infected TKAs frequently require revision sur- gery,[6] which in turn leads to poorer patient outcome, longer hospitalization, and significantly increased cost.[2,7]

Adding antibiotics to the cement used in pros- thetic joint arthroplasty has been advocated for many years as a means of reducing the risk of infection as well as in the treatment of infected prostheses.[8-12] While the efficacy of antibiotic-loaded bone cement (ALBC) has been demonstrated in revision surgery for both treating prosthetic infection and as prophylaxis,[10,11,13] the evidence of its efficacy in primary prophylaxis lacks clarity[7,8,14] and has led to different practices globally.[15]

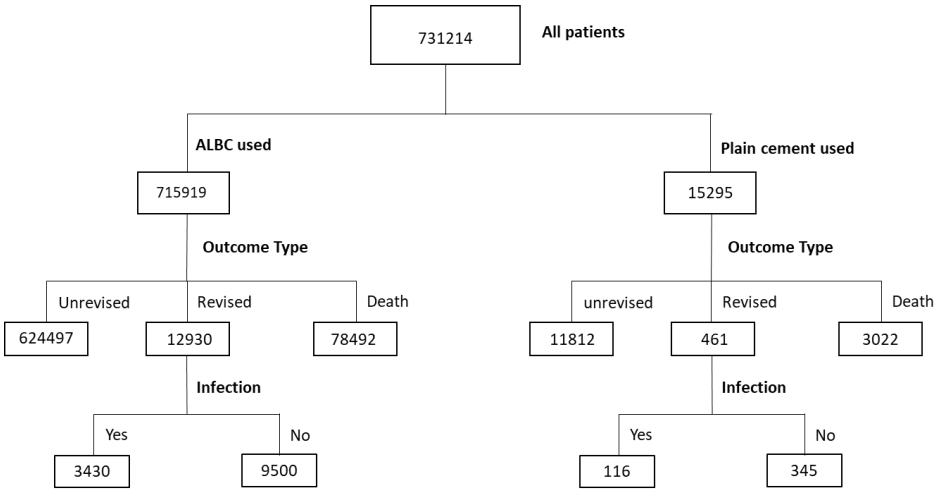


Fig.1: Distribution of number of patients before excluding patients with missing body mass index data. ALBC, antibiotic-loaded bone cement.

There are also concerns that adding antibiotics to bone cement can adversely affect its mechanical properties,[16-19] which would affect revision rates. Some authors also believe this can potentially lead to the development of resistant organisms that may complicate infection management should the prosthetic joint become infected.[4,20-23] One large study has recently shown local antibiotics in cement do not drive resistant infections.[24] Moreover, there are reports of bone cellular[25,26] and renal toxicity.[27-29] These concerns and uncertainties challenge the practice of routinely adding antibiotics to the cement in primary TKA without having strong evidence of its efficacy in reducing the risk of infection.

In this study, we sought to evaluate the hypothesis that ALBC reduces the risk of revision following primary TKA. Data from the National Joint Registry of England, Wales, Northern Ireland and the Isle of Man (NJR) were analyzed to compare the revision rate of primary TKAs performed for osteoarthritis using ALBC *versus* plain cement, in order to inform recommendations about its efficacy and the risk-benefit ratio.

Materials and Methods

A proposal was submitted to the research committee of the NJR in 2016. Approvals and data access were granted in February 2017. Data were obtained for all primary cemented TKAs recorded on the NJR dataset between 2003 and 2016. Knee arthroplasties that were not fully cemented, unicondylar knee arthroplasties, and revision procedures were excluded. Patient, implant, and surgical variables collected by the NJR were provided.

A retrospective observational registry study was carried out. The following endpoints (as recorded on the NJR minimum dataset form) were of interest: revision for infection, revision for a cause other than infection, and revision for any cause. The use of ALBC was compared with implantations undertaken with plain bone cement. For each endpoint, log- rank tests, Kaplan–Meier plots, and Cox proportional hazards models were performed to compare the groups, both unadjusted for cement variables and adjusted by stratification for patient (sex, patient age group, American Society of Anesthesiologists (ASA) grade,[30] body mass index (BMI) where available, and indication), surgical (approach, surgeon grade, thromoprophylaxis) and implant (constraint, bearing, patella) characteristics. The influence of timing of surgery (i.e. year of operation) was also explored in order to assess the influence of time-dependent unknown variables (e.g. different generations of cementation techniques). BMI data were not universally collected in the earlier years of the registry, so these data were only available in a subset of patients. Data on some factors that may influence risk of infection, such as immunosuppressing conditions and medications, as well as smoking, are not collected by the NJR and were therefore unavailable for this analysis.

The statistical models were tested to ensure the proportional hazards assumption was not violated for any of the endpoints (p-value < 0.05). For estimation of the hazard ratio (HR), a weighted Cox regression was performed to calculate an unbiased estimate. Final models were identified by stepwise selection and subjected to robustness checks (including constant proportionality over time). The Akaike Information Criterion (from the StepAIC function in the MASS package)[31] was used to select variables. Stratified Cox proportional hazard model was considered to account for year of operations.

The analysis was performed on the entire dataset (excluding BMI data) and repeated for episodes with a valid BMI (range of 15 kg/m2 $\leq$ BMI $\leq$ 50 kg/m2). Frequency and percentages were used to summarize categorical data while mean and standard deviation were used for continuous variables. A further sensitivity analysis was performed on the subgroup of cases where surgeons using ALBC during the entire data collection period were excluded.

The dataset contained 731 214 records. Figures 1 and 2 depict the distribution of the number of patients according to the type of cement used, the surgical outcome (revision or no revision), and whether infection was recorded as the cause for revision. The cement type used is recorded on the NJR data collection form. Product stickers and brand data are uploaded

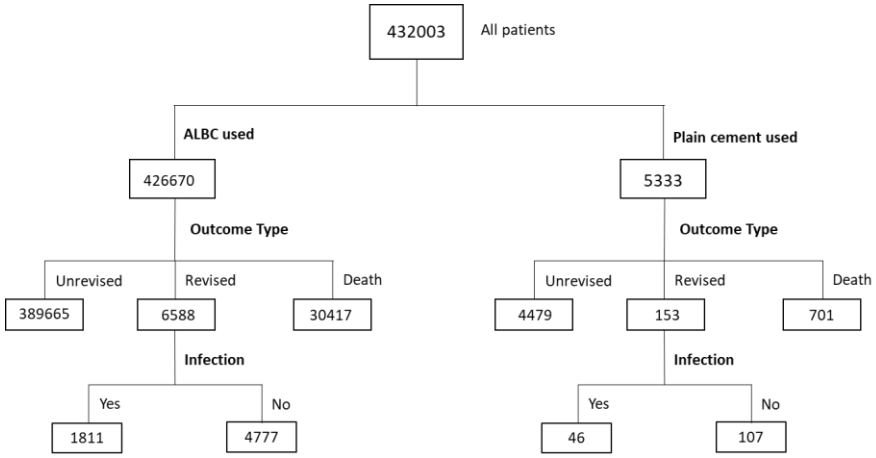


Fig.2: Distribution of number of patients after excluding patients with missing body mass index data. ALBC, antibiotic-loaded bone cement.

onto the registry and then broken down into the different types within the NJR; it is these cleaned data that were provided to use, without brand identification. The data were analyzed in three ways depending on whether the revised procedure was due to infection or not. In all the analyses, the event was defined as 'revision' and censoring was defined when there was no revision procedure as of 31 July 2016. At the time of data extraction for this study, a knee revision in the NJR was defined as removal of implants and could be categorized as 'single-stage', 'first of two stages', 'second of two stages', 'conversion to arthrodesis', and 'amputation'. There was no option to record a bearing change, washout/debridement and implant retention, or a secondary patellar resurfacing on the minimum data collection document for knee revisions prior to 2017 (although these may have been uploaded as 'single-stage revisions').

Table I summarizes the distribution of patients across all variables in the dataset before and after deleting records with missing BMI data. The ASA variable was recoded into three categories (grade 1, grade 2, and grade ≥ 3). Similarly, age was also recoded into four categories using quartiles as cut-points.

During the entire study period there were no surgical units or individual surgeons using solely plain cement. Most used a com- bination of types (272 units, 60.3% and 2626 surgeons, 94.0%). Overall, 179/451 surgical units (39.7%) and 179/2805 surgeons (6.0%) did not use plain cement at any point during the study period. The use of plain cement was mainly in the earlier years of data collection on the registry (6% in first 25 000 TKAs) (Fig. 3). Five-year and ten-year survival rates were calculated with 95% confidence intervals (CIs). The data were analyzed using SAS 9.4 (SAS Institute, Cary, North Carolina) and R 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Analyses of all patients (excluding BMI data). Survival curves comparing TKAs performed using ALBC and plain cement show lower revision rates at two years following surgery in the ALBC group (for the endpoints: all-cause revision, revision for infection, revision for aseptic causes), although the statistical significance was marginal where infection was cited as the cause of revision ($p = 0.06$, log-rank chi-squared test = 8.3, one degree of freedom) (Fig. 4).

Table II presents the univariable analysis. The following fac- tors were independently associated with a significantly increased risk of revision: male sex, younger age, lower ASA, indications other than osteoarthritis, patella unresurfaced, employing posterior-stabilized components and mobile bearings, the use of low viscosity and plain (not antibiotic-loaded) cement, and when a Factor Xa inhibitor was used for venous thromboembolic (VTE) prophylaxis. There was no evidence of significant association between the hazard of revision and other types of VTE prophylaxis used. Figure 5 shows that changes in rates of revision (HR) did not vary in a linear manner over time, irrespective of indication. Hazards of revision between the two groups varied across the operation years. In general, plain cement had higher hazard of revision than ALBC, particularly after 2007.

Table III presents multivariable analyses for the association between hazard of revision and ALBC status while adjusting for other important factors. In all the analyses, the hazard of

Table I. Characteristics of patients in the dataset

Variable	**All data**			**Data with BMI**		
	Plain cement (n = 5 295)	**ALBC (n = 715 919)**	**Total (n = 731 214)**	**Plain cement (n = 5333)**	**ALBC (n = 426670)**	**Total (n = 432 003)**
Mean age, yrs (SD)	70.62 (9.1)	70.2 (9.3)	70.2 (9.3)	70.44 (9.5)	70.08 (9.3)	70.1 (9.3)
Sex, female:male, n (%)	8859:6436 (57.9:42.1)	413 359:302 560 (57.7:42.3)	422 218:308 996 (57.7:42.3)	3159:2174 (59.2:40.8)	245 184:181 486 (57.5:42.5)	248 343:183 660 (57.5:42.5)
Mean BMI, kg/m^2 (SD)	N/A	N/A	N/A	30.45 (5.5)	30.77 (5.4)	30.8 (5.4)
ASA grade, n (%)						
1	2380 (15.6)	78 262 (10.9)	80 642 (11.0)	770 (14.4)	41 993 (9.8)	42 763 (9.9)
2	10 708 (70.0)	519 438 (72.6)	530 146 (72.5)	3713 (69.6)	312 965 (73.4)	316 678 (73.3)
3	2149 (14.1)	115 688 (16.2)	117 837 (16.1)	827 (15.5)	70 441 (16.5)	71 268 (16.5)
4	54 (0.4)	2430 (0.3)	2484 (0.3)	22 (0.4)	1252 (0.3)	1274 (0.3)
5	4 (0.0)	101 (0.0)	105 (0.0)	1 (0.0)	19 (0.0)	20 (0.0)
Indication, n (%)						
Osteoarthritis	14 883 (97.3)	695 961 (97.2)	710 844 (97.2)	5207 (97.6)	416 278 (97.6)	421 485 (97.6)
Other	412 (2.7)	19 957 (2.8)	20 369 (2.8)	126 (2.4)	10 392 (2.4)	10 518 (2.4)
Primary lead, n	1057	5757	5773	529	4968	4987
Primary consultant, n	788	2974	2984	397	2612	2618
Surgical units, n	272	451	451	165	430	431
Surgeon, n (%)						
Consultant	12 001 (78.5)	568 286 (79.4)	580 287 (79.4)	4513 (84.6)	343 700 (80.6)	348 213 (80.6)
SAS/staff	949 (6.2)	52 905 (7.4)	53 854 (7.4)	140 (2.6)	28 683 (6.7)	28 823 (6.7)
Registrar/ST	1135 (7.4)	68 155 (9.5)	69 290 (9.5)	401 (7.5)	39 045 (9.2)	39 446 (9.1)
Other	1210 (7.9)	26 573 (3.7)	27 783 (3.8)	279 (5.2)	15 242 (3.6)	15 521 (3.6)
Approach, n (%)						
Medial parapatellar	14 421 (94.3)	666 893 (93.2)	681 314 (93.2)	4996 (93.7)	398 500 (93.4)	403 496 (93.4)
Other	874 (5.7)	49 026 (6.8)	49 900 (6.82)	337 (6.3)	28 170 (6.6)	28 507 (6.6)
Cement viscosity, n (%)						
High	12 115 (79.2)	681 752 (95.2)	693 867 (94.9)	4342 (81.4)	406 993 (95.4)	411 335 (95.2)
Medium	3160 (20.7)	29 799 (4.2)	32 959 (4.5)	985 (18.5)	18 297 (4.3)	19 282 (4.5)
Low	20 (0.1)	4368 (0.6)	4388 (0.6)	6 (0.1)	1380 (0.3)	1386 (0.3)
Bearing, n (%)						
Fixed	11 122 (72.7)	591 106 (82.6)	602 228 (82.4)	3329 (62.4)	356 085 (83.5)	359 414 (83.2)
Mobile	1646 (10.8)	35 353 (4.9)	36 999 (5.1)	1153 (21.6)	17 839 (4.2)	18 992 (4.4)
Unknown	2527 (16.5)	89 460 (12.5)	91 987 (12.6)	851 (16.0)	52 746 (12.4)	53 597 (12.4)
Constraint, n (%)						
Unconstrained	8925 (58.4)	437 741 (61.1)	446 666 (61.1)	3557 (66.7)	265 472 (62.2)	269 029 (62.3)
Posterior-stabilized	3842 (25.1)	188 631 (26.3)	192 473 (26.3)	924 (17.3)	108 406 (25.4)	109 330 (25.3)
Other	2528 (16.5)	89 547 (12.5)	92 075 (12.6)	852 (16.0)	52 792 (12.4)	53 644 (12.4)

Patella resurfaced, n (%)						
No	9478 (62.0)	442 741 (61.8)	452 219 (61.8)	3004 (56.3)	259 474 (60.8)	262 478 (60.8)
Yes	5817 (38.0)	273 178 (38.2)	278 995 (38.16)	2329 (43.7)	167 196 (39.2)	169 525 (39.2)
Mechanical VTE prophylaxis, n (%)						
No	14 108 (92.2)	673 553 (94.1)	687 661 (94.0)	5197 (97.4)	405 574 (95.1)	410 771 (95.1)
Yes	1187 (7.8)	42 366 (5.9)	43 553 (6.0)	136 (2.6)	21 096 (4.9)	21 232 (4.9)
Chemical thromboprophylaxis, n (%)						
No	2532 (16.6)	43 860 (6.1)	46 392 (6.3)	1119 (21.0)	18 359 (4.3)	19 478 (4.5)
Yes	12 763 (83.4)	672 059 (93.9)	684 822 (93.7)	4214 (79.0)	408 311 (95.7)	412 525 (95.5)
Type						
LMWH, n (%)						
No	6602 (43.2)	222 871 (31.1)	229 473 (31.4)	2037 (38.2)	129 126 (30.3)	131 163 (30.4)
Yes	8693 (56.8)	493 048 (68.9)	501 741 (68.6)	3296 (61.8)	297 544 (69.7)	300 840 (69.6)
Aspirin, n (%)						
No	13 113 (85.7)	626 364 (87.5)	639 477 (87.5)	4838 (90.7)	379 405 (88.9)	384 243 (88.9)
Yes	2182 (14.3)	89 555 (12.5)	91 737 (12.6)	495 (9.3)	47 265 (11.1)	47 760 (11.1)
Direct thrombin inhibitor, n (%)						
No	15 215 (99.5)	664 433 (92.8)	679 648 (93.0)	5277 (98.8)	387 554 (90.8)	392 831 (90.9)
Yes	80 (0.5)	51 486 (7.2)	51 566 (7.1)	56 (1.1)	39 116 (9.2)	39 172 (9.1)
Factor Xa inhibitor, n (%)						
No	14 879 (99.7)	680 832 (95.9)	695 711 (96.0)	5287 (99.1)	403 411 (94.5)	408 698 (94.6)
Yes	50 (0.3)	28 828 (4.1)	28 878 (4.0)	46 (0.9)	23 259 (5.5)	23 305 (5.4)
Warfarin, n (%)						
No	15 126 (98.9)	708 211 (98.9)	723 337 (98.9)	5272 (98.9)	422 734 (99.1)	428 006 (99.1)
Yes	169 (1.1)	7708 (1.1)	7877 (1.1)	61 (1.1)	3936 (0.9)	3997 (0.9)
Pentasaccharide, n (%)						
No	15 250 (99.7)	708 774 (99.0)	724 024 (99.0)	5308 (99.5)	422 119 (98.9)	427 427 (98.9)
Yes	45 (0.3)	7145 (1.0)	7190 (1.0)	25 (0.5)	4551 (1.1)	4576 (1.1)
Other, n (%)						
No	14 686 (96.3)	666 951 (93.3)	681 637 (93.3)	5146 (96.6)	392 368 (92.0)	397 514 (92.0)
Yes	559 (3.7)	48 125 (6.7)	48 684 (6.7)	187 (3.5)	34 302 (8.0)	34 489 (8.0)
Outcome, n (%)						
Revised	461 (3.0)	12 930 (1.8)	13 391 (1.8)	153 (2.9)	6588 (1.5)	6741 (1.6)
Death	3022 (19.8)	78 492 (11.0)	81 514 (11.2)	701 (13.1)	30 417 (7.1)	31 118 (7.2)
Unrevised	11 812(77.2)	624 497 (87.2)	636 309 (87.2)	4479 (84.0)	389 665 (91.3)	394 144 (91.2)
Revisions Indication, n (%)						
Aseptic	345 (74.8)	9500 (73.5)	9845 (73.5)	107 (69.9)	4777 (72.5)	4884 (72.5)
Infection	116 (25.2)	3430 (26.5)	3546 (26.5)	46 (30.1)	1811 (27.5)	1857 (27.6)
Revision procedure type, n (%)						
Single-stage revision	340 (73.8)	9906 (76.6)	10 246 (76.5)	107 (69.9)	5095 (77.3)	5202 (77.2)
Revision 1st stage	78 (16.9)	2161 (16.7)	2239 (16.7)	34 (22.2)	1140 (17.3)	1174 (17.4)
Revision 2nd stage	42 (9.1)	821 (6.3)	873 (6.4)	11 (7.2)	342 (5.2)	353 (5.2)
Conversion	1 (0.2)	25 (0.2)	26 (0.2)	1 (0.7)	10 (0.2)	11 (0.2)
Amputation	0 (0.0)	7 (0.1)	7 (0.1)	0 (0.0)	1 (0.0)	1 (0.0)

ALBC, antibiotic-loaded bone cement; N/A, not applicable; ASA, American Society of Anesthesiologists; VTE, venous thromboembolic; LMWH, low molecular-weight heparin

revision was about 15% less likely for ALBC than plain cement after adjusting for other factors, including the year of operation.

Analyses of episodes with BMI data. There were 432 003 records with BMI data. The Kaplan–Meier curves show similar pattern to the analysis with all patients. ALBC had a lower risk of revision than plain cement (Fig. 6).

Table IV shows similar results as the analyses of all patients presented in Table II. The following factors were independently associated with a significantly increased risk of revision: male sex, younger age, lower ASA, higher BMI, patella unresurfaced, employing posterior-stabilized components and mobile bearings, the use of plain (not antibiotic-loaded) cement, and when a Factor Xa inhibitor was used for venous thromboembolic (VTE) prophylaxis. Cement viscosity and indication were not associated with revision risk.

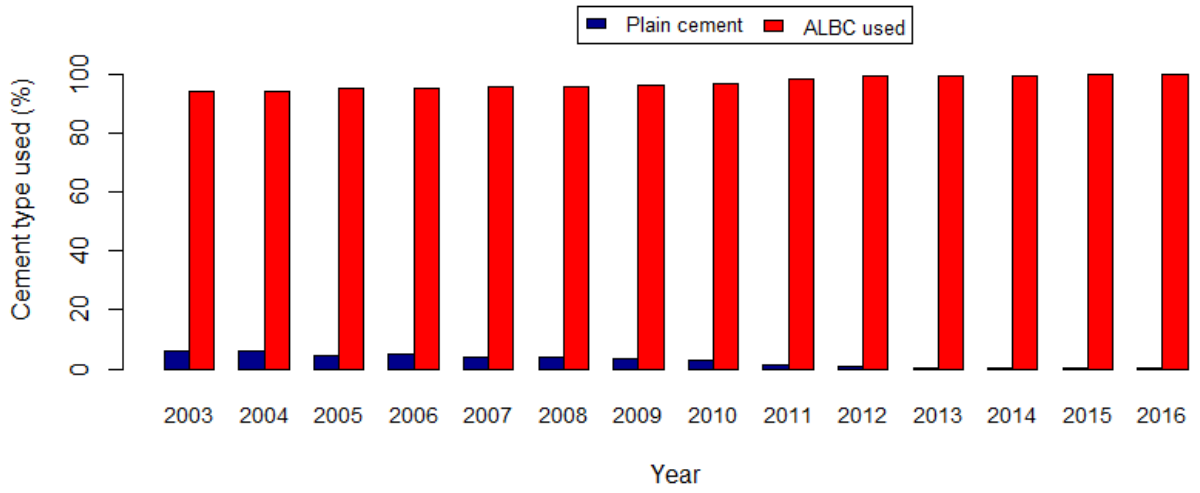


Fig.3: The proportion of cement type used by year. ALBC, antibiotic-loaded bone cement.

Multivariable analysis of the data excluding patients with missing BMI data is presented in Table V. There is significant association between the hazard of revision and ALBC usage. ALBC has about 15% less chance of revision than non-ALBC, which is similar to the results from the analysis of all patients without adjusting for BMI.

Further analysis of a subset of surgeons who used either plain or ALBC at any point during the data collection period (with those who used only ALBC excluded) demonstrated similar findings for both patients with BMI data and those without (Tables VI and VII).

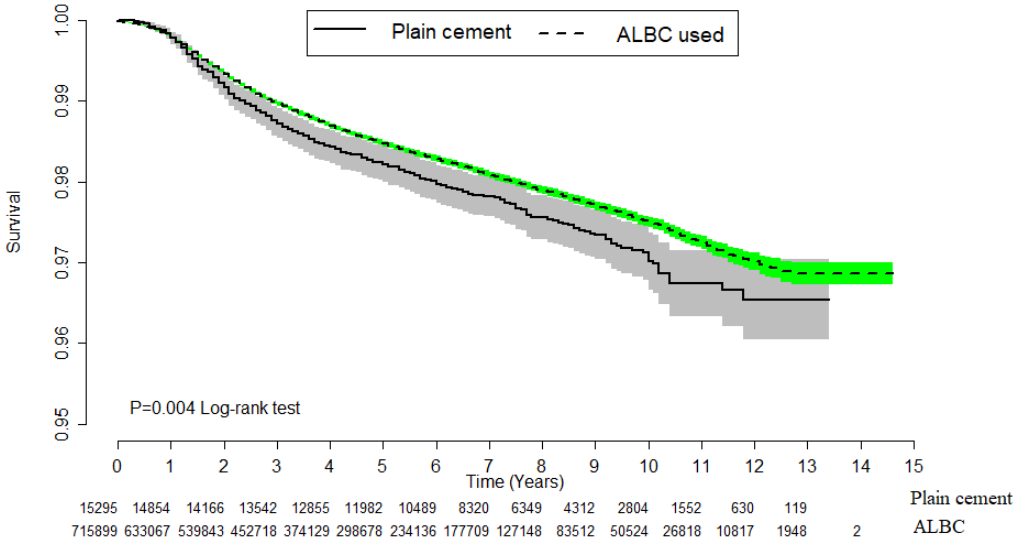


Fig. 4a

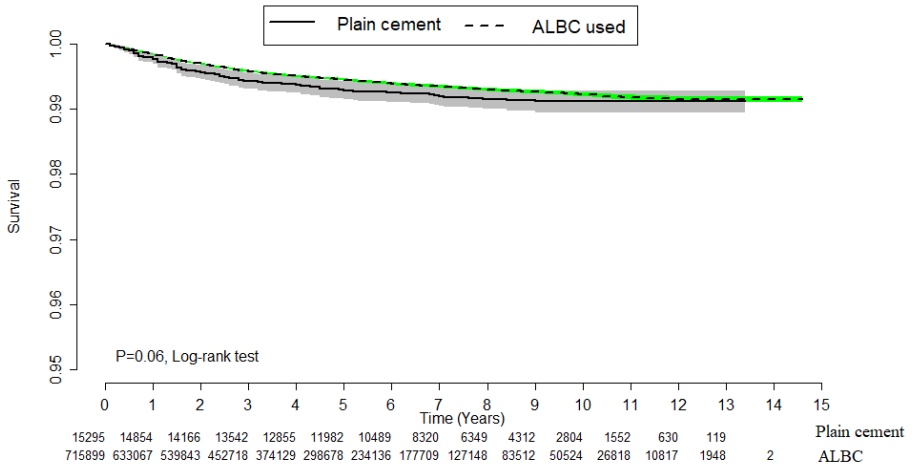
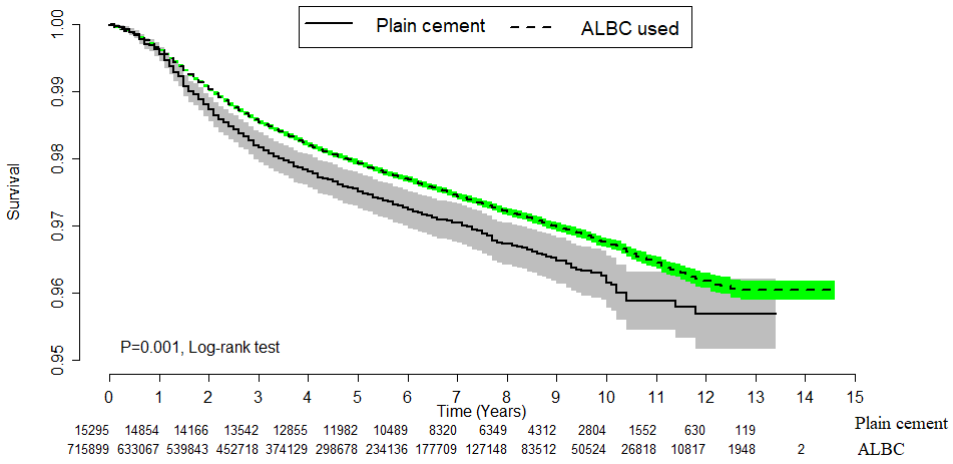


Fig. 4b



Survival curves for each revision category, stratified by cement type (all patients, n = revision events). a) Noninfection (n = 9845); b) infection (n = 3546); c) infection plus noninfection (n = 13 391). Shaded areas indicate 95% confidence intervals. ALBC, antibiotic-loaded bone cement.

Table II. Simple (unadjusted) Cox proportional hazard model analyses for the three categories of revision groups using the entire dataset. Body mass index was not included in these analyses

Variable	Revision for infection		Aseptic revision		All-cause revision	
	HR (95% CI)	p-value	HR (95% CI)	p-alue	HR (95% CI)	p-value
Age, yrs						
< 64	Reference					
64 to 71	0.79 (0.73 to 0.86)	< 0.001*	0.60(0.57 to 0.63)	< 0.001*	0.64 (0.62 to 0.67)	< 0.001*
71.1 to 77	0.63 (0.58 to 0.69)	< 0.001*	0.41 (0.39 to 0.44)	< 0.001*	0.46 (0.44 to 0.48)	< 0.001*
≥ 77.1	0.55 (0.50 to 0.60)	< 0.001*	0.26 (0.25 to 0.28)	< 0.001*	0.33 (0.31 to 0.34)	< 0.001*
Sex						
Female	Reference					
Male	1.86 (1.74 to 1.99)	< 0.001*	1.02 (0.98 to 1.06)	0.355	1.19 (1.16 to 1.24)	< 0.001*
ASA grade						
1	Reference					
2	1.06 (0.95 to 1.18)	0.276	0.85 (0.80 to 0.90)	< 0.001*	0.89 (0.85 to 0.94)	< 0.001*
≥ 3	1.48 (1.31 to 1.67)	< 0.001*	0.79 (0.73 to 0.85)	< 0.001*	0.94 (0.88 to 1.00)	0.037*
Indication						
Other	Reference					
Osteoarthritis	0.63 (0.54 to 0.74)	< 0.001*	1.05 (0.93 to 1.19)	0.401	0.90 (0.82 to 0.99)	0.026*
Operation year	1.00 (0.98 to 1.01)	0.423	1.00 (0.99 to 1.01)	0.475	1.00 (0.99 to 1.00)	0.301
Approach						
Other	Reference					
Medial parapatellar	1.06 (0.93 to 1.21)	0.384	1.00 (0.92 to 1.08)	0.931	1.01 (0.95 to 1.08)	0.71
Cement type						
Plain	Reference					
Antibiotic-loaded	0.84 (0.67 to 1.01)	0.061	0.85 (0.77 to 0.95)	0.004*	0.85 (0.77 to 0.93)	< 0.001*
Cement viscosity						
High	Reference					
Medium	1.07 (0.92 to 1.25)	0.363	0.99 (0.90 to 1.08)	0.768	1.01 (0.93 to 1.09)	0.833
Low	1.17 (0.84 to 1.63)	0.362	1.56 (1.32 to 1.83)	< 0.001*	1.46 (1.26 to 1.69)	< 0.001*
Bearing						
Fixed	Reference					
Mobile	1.14 (0.99 to 1.30)	0.062	1.44 (1.34 to 1.55)	< 0.001*	1.36 (1.28 to 1.45)	< 0.001*
Unknown	1.03 (0.94 to 1.13)	0.56	0.99 (0.93 to 1.04)	0.618	1.00 (0.95 to 1.05)	0.894
Constraint						
Unconstrained	Reference					
Posterior-stabilized	1.31 (1.21 to 1.41)	< 0.001*	1.20 (1.14 to 1.25)	< 0.001*	1.22 (1.18 to 1.27)	< 0.001*
Other	1.12 (1.01 to 1.23)	0.031*	1.02 (0.96 to 1.08)	0.631	1.04 (0.99 to 1.10)	0.129
Patellar resurfaced						
No	Reference					
Yes	1.11 (1.03 to 1.18)	0.003*	0.75 (0.72 to 0.78)	< 0.001*	0.84 (0.81 to 0.87)	< 0.001*
Mechanical VTE thrombo- prophylaxis						
None	Reference					
Yes	1.07 (0.95 to 1.22)	0.274	0.99 (0.92 to 1.07)	0.791	1.01 (0.95 to 1.08)	0.748
Chemical VTE thrombo-prophylaxis						
Yes	Reference					
None	0.95 (0.84 to 1.07)	0.411	0.95 (0.88 to 1.02)	0.138	0.95 (0.89 to 1.01)	0.090
Aspirin						
No	Reference					
Yes	1.07 (0.98 to 1.17)	0.147	0.95 (0.90 to 1.00)	0.067	0.98 (0.94 to 1.03)	0.398
LMWH						
No	Reference					
Yes	1.02 (0.95 to 1.09)	0.59	0.98 (0.94 to 1.03)	0.452	0.99 (0.96 to 1.03)	0.713
Pentasaccharide						
No	Reference					
Yes	1.14 (0.84 to 1.56)	0.393	0.95 (0.77 to 1.16)	0.61	1.00 (0.84 to 1.19)	0.995
Warfarin						

No	Reference					
Yes	1.02 (0.75 to 1.39)	0.883	0.80 (0.66 to 0.99)	0.037*	0.86 (0.73 to 1.02)	0.085
Direct thrombin inhibitor						
No	Reference					
Yes	1.04 (0.90 to 1.20)	0.586	0.95 (0.86 to 1.04)	0.234	0.97 (0.90 to 1.05)	0.476
Factor Xa inhibitor						
No	Reference					
Yes	1.02 (0.75 to 1.39)	0.886	0.52 (0.37 to 0.74)	<0.001*	0.73 (0.58 to 0.91)	0.007*

*Statistically significant. HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; VTE, venous thromboembolic; LMWH, low molecular-weight heparin

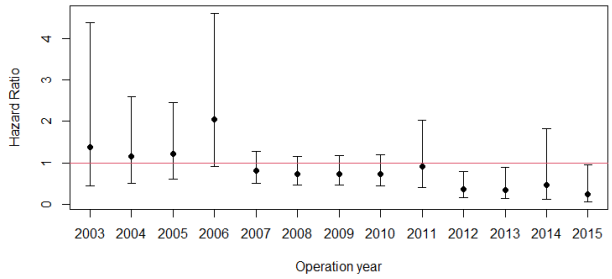


Fig. 5a

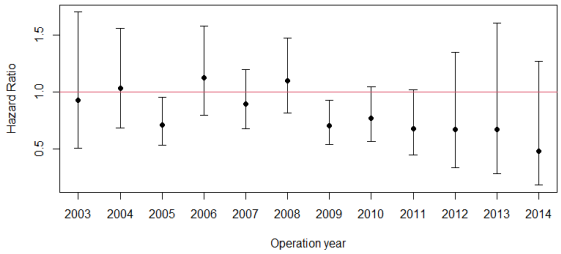


Fig. 5b

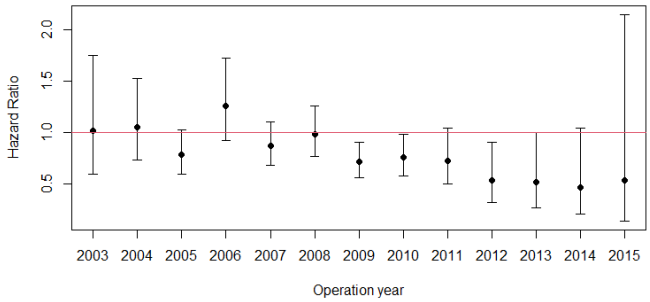


Fig. 5c

Line charts describing the association between the hazard ratios of revision and the year of operations for each revision category: a) infection event; b)noninfection event; c) infection plus noninfection event. The horizontal line corresponds to a hazard ratio equal to one.

Summary. TKAs implanted with ALBC had a five-year revision rate of 2.34% (95% CI 2.30 to 2.39) and a ten-year rate

of 3.66% (3.59 to 3.75) compared with 3.02% (95% CI 2.72 to 3.34) and 4.53% (95% CI 4.10 to 4.99) when plain cement was employed, after adjusting for patient and surgical variables. This equates to an absolute ten-year revision risk reduction of 0.87% and a relative risk reduction of 19.2% when ALBC was used. The number of patients needed to treat in one year with ALBC to prevent one revision is 115. On a population level, where 100 000 TKAs are performed annually, this difference represents 870 fewer revisions at ten years in the ALBC group.

Table III. Multivariable (adjusted) analysis of association between revision rate (all-cause) and the use of antibiotic-loaded bone cement (ALBC), adjusting for other factors (including year of operation) using unstratified and stratified Cox proportional hazard models. Only variable categories with significant influences included. Body mass index not included in these analyses.

Variable	**Unstratified analysis**				**Stratified analysis**			
	All patients		**Excluding dead**		**All patients**		**Excluding dead**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age, yrs								
< 64	Reference							
64 to 71	0.64 (0.61 to 0.67)	<0.001*	0.66 (0.64 to 0.69)	< 0.001*	0.64 (0.61 to 0.67)	< 0.001*	0.66 (0.64 to 0.69)	< 0.001*
71.1 to 77	0.46 (0.44 to 0.48)	< 0.001*	0.51 (0.49 to 0.54)	< 0.001*	0.46 (0.44 to 0.48)	< 0.001*	0.51 (0.49 to 0.54)	< 0.001*
≥ 77.1	0.32 (0.30 to 0.34)	< 0.001*	0.42 (0.40 to 0.45)	< 0.001*	0.32 (0.31 to 0.34)	< 0.001*	0.43 (0.41 to 0.45)	< 0.001*
Sex								
Female	Reference							
Male	1.15 (1.11 to 1.19)	< 0.001*	1.18 (1.14 to 1.22)	< 0.001*	1.15 (1.11 to 1.19)	< 0.001*	1.19 (1.15 to 1.23)	< 0.001*
ASA grade								
1	Reference							
2	1.06 (1.00 to 1.11)	0.035*	1.051 (1 to 1.105)	0.052	1.05 (1.00 to 1.10)	0.06	1.08 (1.02 to 1.13)	0.0055*
≥ 3	1.22 (1.14 to 1.30)	< 0.001*	1.29 (1.21 to 1.37)	< 0.001*	1.21 (1.14 to 1.29)	< 0.001*	1.33 (1.25 to 1.41)	< 0.001*
Indication								
Other	Reference							
Osteoarthritis	1.04 (0.95 to 1.14)	0.423	0.99 (0.90 to 1.09)	0.867	1.04 (0.94 to 1.14)	0.455	1.00 (0.91 to 1.10)	0.975
Cement type								
Plain	Reference							
Antibiotic-loaded	0.84 (0.77 to 0.92)	< 0.001*	0.81 (0.73 to 0.89)	< 0.001*	0.85 (0.77 to 0.93)	< 0.001*	0.85 (0.77 to 0.93)	< 0.001*
Cement viscosity								
High	Reference							
Medium	1.04 (0.96 to 1.13)	0.322	1.05 (0.97 to 1.14)	0.211	1.04 (0.96 to 1.13)	0.3	1.05 (0.96 to 1.13)	0.286
Low	1.61 (1.39 to 1.86)	< 0.001*	1.75 (1.51 to 2.02)	< 0.001*	1.62 (1.40 to 1.88)	< 0.001*	1.62 (1.40 to 1.88)	< 0.001*
Bearing								
Fixed	Reference							
Mobile	1.25 (1.17 to 1.33)	< 0.001*	1.27 (1.19 to 1.35)	< 0.001*	1.24 (1.16 to 1.32)	< 0.001*	1.23 (1.15 to 1.31)	< 0.001*
Unknown	0.85 (0.27 to 2.63)	0.772	0.87 (0.28 to 2.70)	0.806	0.84 (0.27 to 2.61)	0.764	0.82 (0.26 to 2.56)	0.738
Constraint								
Unconstrained	Reference							
Posterior-stabilized	1.28 (1.23 to 1.33)	< 0.001*	1.29 (1.24 to 1.34)	< 0.001*	1.28 (1.23 to 1.33)	< 0.001*	1.28 (1.23 to 1.33)	< 0.001*
Other	1.30 (0.42 to 4.05)	0.648	1.29 (0.41 to 4.00)	0.662	1.30 (0.42 to 4.04)	0.649	1.33 (0.43 to 4.12)	0.624
Patellar resurfaced								
No	Reference							
Yes	0.81 (0.79 to 0.84)	< 0.001*	0.81 (0.78 to 0.84)	< 0.001*	0.81 (0.76 to 0.84)	< 0.001*	0.82 (0.76 to 0.85)	< 0.001*

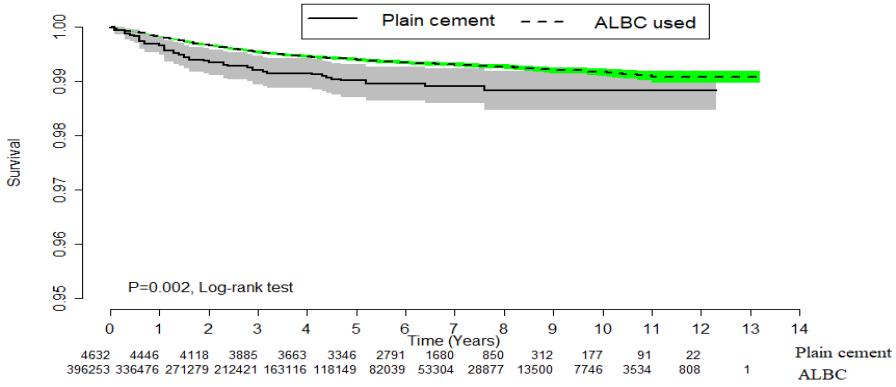


Fig. 6a

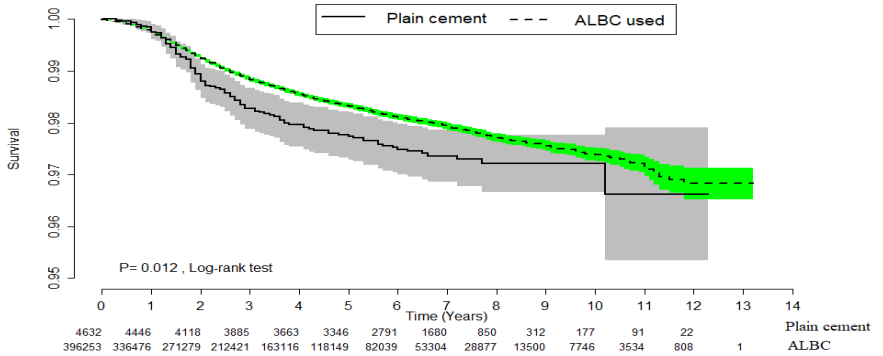


Fig. 6b

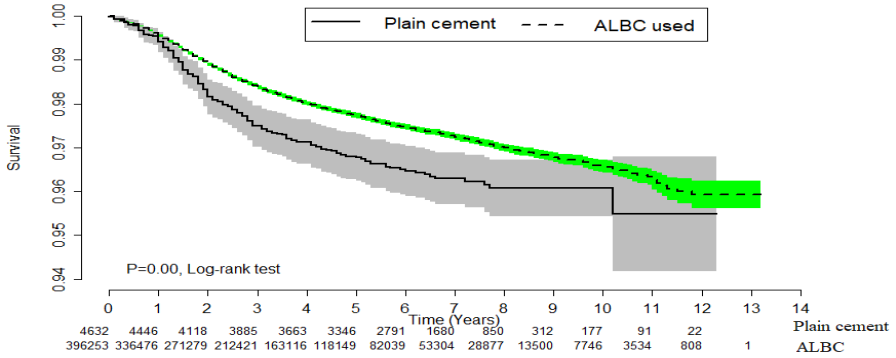


Fig. 6c

Survival curves for each revision category, stratified by cement type (patients with valid BMI data only, n=revision events): a) infection (n = 1857); b) noninfection (n = 4884); c) infection plus noninfection (n = 6741). Shaded areas indicate 95% confidence intervals. ALBC, antibiotic-loaded bone cement.

Table IV. Simple (unadjusted) Cox proportional hazard model analyses for the three categories of revision groups using the dataset where body mass index data was available

Variable	**Revision for infection**		**Aseptic revision**		**All-cause revision**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age, yrs						
< 64	Reference					
64 to 71	0.71 (0.63 to 0.80)	< 0.001*	0.57 (0.53 to 0.61)	< 0.001*	0.61 (0.57 to 0.64)	< 0.001*
71.1 to 77	0.59 (0.52 to 0.67)	< 0.001*	0.43 (0.40 to 0.47)	< 0.001*	0.47 (0.44 to 0.50)	< 0.001*
≥ 77.1	0.57 (0.50 to 0.65)	< 0.001*	0.30 (0.27 to 0.33)	< 0.001*	0.37 (0.34 to 0.39)	< 0.001*
Sex						
Female	Reference					
Male	1.93 (1.76 to 2.12)	< 0.001*	1.01 (0.96 to 1.07)	0.69	1.21 (1.15 to 1.27)	< 0.001*
ASA grade						
1	Reference					
2	1.11 (0.95 to 1.31)	0.201	0.80 (0.74 to 0.88)	< 0.001*	0.87 (0.80 to 0.93)	< 0.001*
≥ 3	1.72 (1.43 to 2.06)	< 0.001*	0.77 (0.70 to 0.86)	< 0.001*	0.97 (0.88 to 1.06)	0.468
Body mass index	1.05 (1.04 to 1.05)	< 0.001*	1.02 (1.02 to 1.03)	< 0.001*	1.03 (1.03 to 1.03)	< 0.001*
Indication						
Other	Reference					

Osteoarthritis	0.59 (0.47 to 0.75)	< 0.001*	1.02 (0.85 to 1.23)	0.808	0.86 (0.74 to 0.99)	0.031*
Operation year	0.98 (0.97 to 1.00)	0.082	0.98 (0.96 to 0.99)	< 0.001*	0.98 (0.97 to 0.99)	< 0.001*
Approach						
Other	Reference					
Medial parapatellar	0.99 (0.83 to 1.19)	0.928	0.96 (0.86 to 1.07)	0.452	0.97 (0.88 to 1.06)	0.491
Cement type						
Plain	Reference					
Antibiotic-loaded	0.65 (0.49 to 0.87)	0.004*	0.81 (0.67 to 0.98)	0.029*	0.76 (0.65 to 0.89)	< 0.001*
Cement viscosity						
High	Reference					
Medium	1.12 (0.91 to 1.38)	0.292	0.95 (0.83 to 1.09)	0.495	1.00 (0.89 to 1.12)	0.976
Low	1.13 (0.61 to 2.11)	0.694	1.06 (0.73 to 1.54)	0.762	1.08 (0.78 to 1.48)	0.645
Bearing						
Fixed	Reference					
Mobile	1.14 (0.94 to 1.39)	0.174	1.42 (1.28 to 1.58)	< 0.001*	1.34 (1.23 to 1.47)	< 0.001*
Unknown	0.94 (0.82 to 1.08)	0.385	0.99 (0.91 to 1.07)	0.75	0.97 (0.91 to 1.05)	0.466
Constraint						
Unconstrained	Reference					
Posterior-stabilized	1.33 (1.20 to 1.47)	< 0.001*	1.16 (1.09 to 1.23)	< 0.001*	1.20 (1.14 to 1.27)	< 0.001*
Other	1.02 (0.89 to 1.18)	0.744	1.01 (0.93 to 1.10)	0.835	1.01 (0.94 to 1.09)	0.723
Patellar resurfaced						
No	Reference					
Yes	1.07 (0.98 to 1.18)	0.132	0.71 (0.66 to 0.75)	< 0.001*	0.80 (0.76 to 0.84)	< 0.001*
Mechanical VTE thromboprophylaxis						
None	Reference					
Yes	1.12 (0.93 to 1.35)	0.249	1.04 (0.92 to 1.17)	0.526	1.06 (0.96 to 1.17)	0.254
Chemical VTE thromboprophylaxis						
Yes	Reference					
None	0.94 (0.77 to 1.15)	0.577	0.97 (0.86 to 1.09)	0.618	0.96 (0.87 to 1.07)	0.475
Aspirin						
No	Reference					
Yes	1.09 (0.96 to 1.25)	0.177	0.91 (0.84 to 0.99)	0.035*	0.96 (0.90 to 1.03)	0.265
LMWH						
No	Reference					
Yes	1.02 (0.93 to 1.13)	0.619	1.05 (0.97 to 1.11)	0.131	1.04 (0.99 to 1.10)	0.122
Pentasaccharide						
No	Reference					
Yes	1.14 (0.76 to 1.71)	0.52	1.05 (0.81 to 1.36)	0.714	1.08 (0.87 to 1.34)	0.516
Warfarin						
No	Reference					
Yes	0.97 (0.59 to 1.58)	0.889	0.88 (0.64 to 1.20)	0.413	0.90 (0.69 to 1.18)	0.442
Direct thrombin inhibitor						
No	Reference					
Yes	1.01 (0.85 to 1.19)	0.941	0.92 (0.83 to 1.03)	0.133	0.95 (0.86 to 1.03)	0.218
Factor Xa inhibitor						
No	Reference					
Yes	0.83 (0.58 to 1.21)	0.334	0.40 (0.26 to 0.63)	< 0.001*	0.58 (0.44 to 0.77)	< 0.001*

*Statistically significant. HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; VTE, venous thromboembolic; LMWH, low molecular-weight heparin

Table V. Multivariable (adjusted) analysis of association between revision rate (all-cause) and the use of antibiotic-loaded bone cement (ALBC), adjusting for other factors (including year of operation) using unstratified and stratified Cox proportional hazard models. Only variable categories with significant influences included

Variable	**Unstratified analysis**				**Stratified analysis**			
	All patients		**Excluding dead**		**All patients**		**Excluding dead**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age, yrs								
< 64	Reference							
64 to 71	0.61 (0.58 to 0.65)	< 0.001*	0.62 (0.59 to 0.66)	< 0.001*	0.61 (0.58 to 0.65)	< 0.001*	0.63 (0.59 to 0.66)	< 0.001*
71.1 to 77	0.48 (0.45 to 0.51)	< 0.001*	0.51 (0.48 to 0.55)	< 0.001*	0.48 (0.45 to 0.51)	< 0.001*	0.51 (0.48 to 0.55)	< 0.001*
≥ 77.1	0.38 (0.35 to 0.41)	< 0.001*	0.45 (0.42 to 0.49)	< 0.001*	0.38 (0.35 to 0.41)	< 0.001*	0.46 (0.42 to 0.50)	< 0.001*
Sex								
Female	Reference							
Male	1.19 (1.13 to 1.25)	< 0.001*	1.21 (1.16 to 1.27)	< 0.001*	1.19 (1.13 to 1.25)	< 0.001*	1.22 (1.16 to 1.28)	< 0.001*
ASA grade								
1	Reference							
2	1.01 (0.94 to 1.09)	0.753	1.02 (0.95 to 1.10)	0.608	1.02 (0.94 to 1.10)	0.688	1.03 (0.96 to 1.11)	0.427
≥ 3	1.20 (1.09 to 1.32)	< 0.001*	1.27 (1.16 to 1.40)	< 0.001*	1.21 (1.10 to 1.33)	< 0.001*	1.29 (1.17 to 1.42)	< 0.001*
Body mass index	1.01 (1.01 to 1.02)	< 0.001*	1.01 (1.01 to 1.02)	< 0.001*	1.01 (1.01 to 1.02)	< 0.001*	1.01 (1.01 to 1.02)	< 0.001*
Indication								
Other	Reference							
Osteoarthritis	0.95 (0.83 to 1.10)	0.502	0.93 (0.81 to 1.07)	0.327	0.95 (0.83 to 1.10)	0.496	0.93 (0.81 to 1.08)	0.348
Cement type								
Plain	Reference							
Antibiotic-loaded	0.75 (0.64 to 0.89)	0.001*	0.73 (0.62 to 0.86)	< 0.001*	0.78 (0.67 to 0.92)	0.003*	0.78 (0.66 to 0.92)	0.003*
Cement viscosity								
High	Reference							
Medium	1.05 (0.93 to 1.18)	0.444	1.05 (0.94 to 1.18)	0.387	1.05 (0.94 to 1.18)	0.386	1.05 (0.94 to 1.18)	0.397
Low	1.29 (0.93 to 1.77)	0.122	1.37 (0.99 to 1.88)	0.057	1.25 (0.90 to 1.72)	0.178	1.241 (0.9 to 1.71)	0.187
Bearing								
Fixed	Reference							
Mobile	1.24 (1.13 to 1.36)	< 0.001*	1.26 (1.14 to 1.38)	< 0.001*	1.21 (1.10 to 1.32)	< 0.001*	1.20 (1.09 to 1.31)	< 0.001*
Unknown	0.57 (0.14 to 2.27)	0.422	0.56 (0.14 to 2.23)	0.407	0.56 (0.14 to 2.25)	0.413	0.53 (0.13 to 2.13)	0.371
Constraint								
Unconstrained	Reference							
Posterior-stabilized	1.27 (1.20 to 1.34)	< 0.001*	1.28 (1.21 to 1.35)	< 0.001*	1.26 (1.19 to 1.33)	< 0.001*	1.26 (1.20 to 1.33)	< 0.001*
Other	1.91 (0.48 to 7.67)	0.36	1.98 (0.49 to 7.92)	0.336	1.91 (0.48 to 7.65)	0.363	2.01 (0.50 to 8.07)	0.324
Patellar resurfaced								
No	Reference							
Yes	0.77 (0.73 to 0.81)	< 0.001*	0.77 (0.73 to 0.81)	< 0.001*	0.78 (0.74 to 0.82)	< 0.001*	0.77 (0.74 to 0.82)	< 0.001*

*Statistically significant. HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; BMI, body mass index

Table VI. Multivariable (adjusted) analysis of association between revision rate (all-cause) and the use of antibiotic-loaded bone cement (ALBC), adjusting for other factors (including year of operation) using unstratified and stratified Cox proportional hazard models. Only variable categories with significant influences included. Body mass index not included in these analyses. Cases carried out by surgeons who only used ALBC during entire study excluded

Variable	**Unstratified analysis**				**Stratified analysis**			
	All patients		**Excluding dead**		**All patients**		**Excluding dead**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age, yrs								
< 64	Reference							
64 to 71	0.64 (0.6 to 0.67)	<	0.66 (0.63 to 0.69)	< 0.001*	0.64 (0.61 to 0.67)	< 0.001*	0.66 (0.63 to 0.69)	<

		0.001*						0.001*
71.1 to 77	0.47 (0.44 to 0.5)	< 0.001*	0.52 (0.5 to 0.56)	< 0.001*	0.47 (0.44 to 0.5)	< 0.001*	0.53 (0.5 to 0.56)	< 0.001*
≥ 77.1	0.33 (0.31 to 0.35)	< 0.001*	0.44 (0.41 to 0.47)	< 0.001*	0.33 (0.31 to 0.35)	< 0.001*	0.44 (0.41 to 0.47)	< 0.001*
Sex								
Female	Reference							
Male	1.14 (1.1 to 1.19)	< 0.001*	1.18 (1.13 to 1.23)	< 0.001*	1.14 (1.1 to 1.19)	< 0.001*	1.18 (1.14 to 1.23)	< 0.001*
ASA grade								
1	Reference							
2	1.05 (0.99 to 1.11)	0.094	1.05 (0.99 to 1.11)	0.111	1.04 (0.98 to 1.11)	0.147	1.07 (1.01 to 1.14)	0.023
≥ 3	1.2 (1.11 to 1.29)	< 0.001*	1.28 (1.18 to 1.37)	< 0.001*	1.19 (1.11 to 1.28)	< 0.001*	1.31 (1.22 to 1.41)	< 0.001*
Indication								
Other	Reference							
Osteoarthritis	1.05 (0.94 to 1.17)	0.409	1 (0.9 to 1.12)	0.974	1.04 (0.94 to 1.17)	0.442	1.01 (0.91 to 1.13)	0.853
Cement type								
Plain	Reference							
Antibiotic-loaded	0.83 (0.76 to 0.92)	< 0.001*	0.8 (0.73 to 0.88)	< 0.001*	0.84 (0.76 to 0.92)	< 0.001*	0.84 (0.76 to 0.92)	< 0.001*
Cement viscosity								
High	Reference							
Medium	1.06 (0.97 to 1.16)	0.164	1.07 (0.98 to 1.17)	0.136	1.07 (0.98 to 1.17)	0.148	1.06 (0.97 to 1.16)	0.163
Low	1.38 (1.15 to 1.66)	< 0.001*	1.49 (1.24 to 1.79)	< 0.001*	1.39 (1.16 to 1.67)	< 0.001*	1.39 (1.16 to 1.67)	< 0.001*
Bearing								
Fixed	Reference							
Mobile	1.24 (1.15 to 1.33)	< 0.001*	1.26 (1.17 to 1.36)	< 0.001*	1.23 (1.14 to 1.32)	< 0.001*	1.22 (1.13 to 1.32)	< 0.001*
Unknown	0.69 (0.22 to 2.14)	0.518	0.7 (0.23 to 2.18)	0.54	0.68 (0.22 to 2.12)	0.506	0.67 (0.21 to 2.07)	0.483
Constraint								
Unconstrained	Reference							
Posterior-stabilized	1.32 (1.26 to 1.38)	< 0.001*	1.33 (1.27 to 1.39)	< 0.001*	1.31 (1.25 to 1.37)	< 0.001*	1.31 (1.26 to 1.38)	< 0.001*
Other	1.67 (0.54 to 5.19)	0.375	1.66 (0.53 to 5.15)	0.383	1.68 (0.54 to 5.22)	0.371	1.71 (0.55 to 5.33)	0.351
Patellar resurfaced								
No	Reference							
Yes	0.83 (0.79 to 0.87)	< 0.001*	0.83 (0.8 to 0.87)	< 0.001*	0.83 (0.8 to 0.87)	< 0.001*	0.83 (0.8 to 0.87)	< 0.001*

*Statistically significant. HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; BMI, body mass index

Table VII. Multivariable (adjusted) analysis of association between revision rate (all-cause) and the use of antibiotic-loaded bone cement (ALBC), adjusting for other factors (including year of operation) using unstratified and stratified Cox proportional hazard models. Only variable categories with significant influences included. Cases carried out by surgeons who only used ALBC during entire study excluded

Variable	**Unstratified analysis**				**Stratified analysis**			
	All patients		**Excluding dead**		**All patients**		**Excluding dead**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age, yrs								
< 64	Reference							
64 to 71	0.6 (0.55 to 0.65)	< 0.001*	0.61 (0.56 to 0.66)	< 0.001*	0.6 (0.55 to 0.65)	< 0.001*	0.61 (0.57 to 0.67)	< 0.001*
71.1 to 77	0.49 (0.44 to 0.53)	< 0.001*	0.52 (0.47 to 0.57)	< 0.001*	0.49 (0.44 to 0.53)	< 0.001*	0.52 (0.48 to 0.57)	< 0.001*
≥ 77.1	0.39 (0.35 to 0.44)	< 0.001*	0.47 (0.42 to 0.52)	< 0.001*	0.39 (0.35 to 0.44)	< 0.001*	0.48 (0.43 to 0.53)	< 0.001*
Sex								
Female	Reference							
Male	1.21 (1.13 to 1.29)	< 0.001*	1.24 (1.16 to 1.32)	< 0.001*	1.21 (1.13 to 1.29)	< 0.001*	1.24 (1.16 to 1.33)	< 0.001*
ASA grade								

1	Reference							
2	1.03 (0.93 to 1.14)	0.621	1.04 (0.94 to 1.15)	0.488	1.03 (0.93 to 1.14)	0.598	1.05 (0.94 to 1.16)	0.389
≥ 3	1.18 (1.04 to 1.33)	0.012*	1.25 (1.1 to 1.42)	< 0.001*	1.18 (1.04 to 1.34)	0.009*	1.27 (1.12 to 1.44)	< 0.001*
Body mass index	1.02 (1.01 to 1.02)	< 0.001*	1.01 (1.01 to 1.02)	< 0.001*	1.02 (1.01 to 1.02)	< 0.001*	1.01 (1.01 to 1.02)	< 0.001*
Indication								
Other	Reference							
Osteoarthritis	0.95 (0.79 to 1.14)	0.547	0.92 (0.77 to 1.11)	0.386	0.94 (0.78 to 1.13)	0.507	0.92 (0.77 to 1.11)	0.381
Cement type								
Plain	Reference							
Antibiotic-loaded	0.75 (0.64 to 0.89)	0.001*	0.74 (0.63 to 0.87)	< 0.001*	0.79 (0.67 to 0.93)	0.005*	0.79 (0.67 to 0.93)	0.005*
Cement viscosity								
High	Reference							
Medium	1.03 (0.9 to 1.17)	0.652	1.04 (0.91 to 1.18)	0.604	1.04 (0.92 to 1.19)	0.528	1.04 (0.91 to 1.19)	0.544
Low	1.26 (0.88 to 1.8)	0.198	1.34 (0.94 to 1.91)	0.107	1.23 (0.86 to 1.76)	0.262	1.22 (0.85 to 1.75)	0.275
Bearing								
Fixed	Reference							
Mobile	1.25 (1.1 to 1.42)	0.001*	1.27 (1.11 to 1.44)	< 0.001*	1.23 (1.08 to 1.41)	0.002*	1.23 (1.08 to 1.4)	0.002*
Unknown	0.67 (0.09 to 4.8)	0.691	0.63 (0.09 to 4.47)	0.641	0.69 (0.1 to 4.92)	0.709	0.62 (0.09 to 4.44)	0.635
Constraint								
Unconstrained	Reference							
Posterior-stabilized	1.32 (1.22 to 1.42)	< 0.001*	1.33 (1.24 to 1.44)	< 0.001*	1.31 (1.22 to 1.41)	< 0.001*	1.32 (1.22 to 1.42)	< 0.001*
Other	1.64 (0.23 to 11.67)	0.623	1.78 (0.25 to 12.7)	0.564	1.6 (0.22 to 11.38)	0.641	1.77 (0.25 to 12.59)	0.571
Patellar resurfaced								
No	Reference							
Yes	0.78 (0.73 to 0.84)	< 0.001*	0.78 (0.73 to 0.84)	< 0.001*	0.79 (0.73 to 0.84)	< 0.001*	0.79 (0.73 to 0.84)	< 0.001*

*Statistically significant. HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; BMI, body mass index

Discussion

This retrospective cohort study provides the largest analysis of ALBC in primary knee arthroplasty patients. All-cause revision, revision for aseptic causes, and revision where infection was cited as a cause were all significantly lower in the ALBC group compared with plain cement. There were similar findings when BMI variable was included and excluded from the models, and when cases carried out by surgeons using only ALBC during the entire study were excluded. Crucially, revision risk for aseptic causes was significantly lower when ALBC was used. Concerns regarding greater mechanical instability with the use of ALBC are therefore unfounded in this population-based mid- term study.

However, there are limitations. Data on proven risk factors for prosthetic joint infection, such as diabetes, smoking, and length of surgery,[32] were unavailable in this study. ASA grade, while crude, was therefore used as a surrogate for comorbidity in statistical models, although there are issues with data validity as the registry data includes some patients graded as ASA 5. BMI (known to influence risk of infection) data are incomplete within the NJR, although rates of collection have improved in recent years. Despite this, our analyses demonstrated little difference between the cohort with BMI data and the full dataset, when BMI was excluded from the statistical models. ALBC was associated with a significant reduction in revisions, irrespective of BMI.

Registries rely on data collection at time of surgery, resulting in some inaccuracies in stated reason for revision. For example, revisions apportioned to aseptic loosening may ultimately be driven by low-grade infection. As linked microbiological data are unavailable, registry analyses are likely to under-report infection as a cause of revision. Moreover, the NJR does not record any information on superficial infections that are treated conservatively and (in the time period of this study) did not specifically record cases of infection where the treatment was a debridement, antibiotics, and implant retention (although this may be recorded as single-stage revision). However, there would be no logical reason why the use of one type of cement may be more associated with registry process issues than the comparator.

While we were able to identify an association between ALBC and lower infection risk, we lacked detailed information on the type and dosage of the antibiotics added to the cement, antibiotic prophylaxis used, and treatment duration. We could not, therefore, produce any useful information on whether certain antibiotics are more effective than others. Furthermore, we have no data on antimicrobial resistance profiles in those patients who were revised for infection following original implantation with ALBC.

Finally, the proportion of knee arthroplasties implanted using plain cement in this study was only 2%, and most were implanted in the earlier years of the registry. Nevertheless, this still accounts for over 15 000 cases and differences in revision rates between cement types were significant despite these relative mismatched group sizes. Subset analyses with BMI data included, and where cases where excluded when performed by a surgeon who only used ALBC during the entire study, further strengthen the findings. Prosthetic joint infection is a serious complication following TKA, frequently requires revision surgery, and leads to poor patient outcome and increased cost.[2,7] ALBC has been used for prophylaxis purposes in primary and revision TKA and also as part of the treatment in revision surgery for infected TKA.[8-11] It is the most frequently used local antibiotic delivery system in joint arthroplasty.[33] Acting as a carrier for topical delivery of antibiotics, ALBC is thought to reduce the risk of prosthetic infection not addressed by systemic antibiotics due to impaired blood supply, and therefore low local antibiotic concentrations at the surgical site in the immediate postoperative period.[14,34]

There is strong evidence of the efficacy of ALBC in treating prosthetic TKA infection and as a means of prophylaxis in revision knee surgery. However, its efficacy in providing prophylaxis in primary TKA has been a matter of debate. In fact, the current evidence is so conflicting that while in some studies ALBC was found to reduce the risk of primary TKA infection,[13,14,35-42] other studies have shown no difference[43-52] or even an increased risk of primary TKA infection because of ALBC.[53,54] We are aware of four recent joint arthroplasty registry-based studies that examined this subject. Namba et al,[54] in their study of an American total joint registry, identified the use of ALBC in primary TKA as a risk factor for causing deep surgical site infection, but also found that adding antibiotics to the irrigation solution was protective against deep surgical site infection. Tayton et al[53] also found ALBC increased the risk of revision for infection at six months in their review of over 60 000 primary knee arthroplasties on the New Zealand joint registry. The use of laminar flow and surgical helmets was also associated with greater infection risk. However, a significant limitation to their study was that they did not take into account revisions performed after one year from the primary operation.[53] In both the American and New Zealand registry studies, the authors proposed an explanation for this: the observed paradoxical increase in the rate of infection with the use of ALBC could be a result of selection bias, as ALBC was not routinely used in their countries and potentially was

selectively used in patients who were identified by the surgeons to have high risk factors for infection. On the contrary, in Finland where ALBC is routinely used in primary TKA, Jämsen et al,[13] in their analysis of the Finnish Arthroplasty Register, found the risk of infection was 1.3 times greater when plain cement was used in primary TKA, and this increased to 2.1 times in revision TKA. Bohm et al[46] analyzed the Canadian Joint Arthroplasty Registry and compared the revision rates (at two-year follow-up) of primary TKA performed using ALBC and plain cement, finding no statistically significant difference in the rate of revision for all causes. Interestingly, a statistically significant doubling of the rate of revision for aseptic loosening was found in the plain cement group.[46] However, limitations included selection bias (as ALBC may have been used in higher risk patients) and inclusion bias (infections treated with washout and implant retention were not included).[46] In their systematic review and meta-analysis of randomized controlled trials that investigated the efficacy of ALBC in reducing infection in primary TKA and total hip arthroplasty (THA), Wang et al[14] concluded that compared with plain bone cement and the use of systemic antibiotics alone, ALBC effectively reduced the rate of deep wound infection in THA and TKA patients. In the United Kingdom, ALBC is routinely used in primary TKA, and we found that it was associated with an overall 15% reduction in the rate of revision for all causes in primary TKA, although the statistical significance was only marginal when we used the revision for infection as the endpoint ($p = 0.06$). This decrease in the rate of revision for all causes, more clearly than the rate of revision for infection, may be due to subclinical infections that were not detected and were diagnosed and recorded as aseptic loosening or revision for other noninfection causes. This was theorized to have been the case in the study by Bohm et al[46] where ALBC was found to reduce the revision rate for aseptic loosening rather than that for infection, and in a study by Havelin et al[55] on hip arthroplasties from the Norwegian Arthroplasty Register, where the authors found a trend toward lower revision rate due to aseptic loosening in the hip arthroplasties performed using ALBC cement compared with those performed using plain.

Several patient characteristics, comorbidities, and hospital and surgeon-related characteristics have been identified in previous arthroplasty registry-based studies as risk factors for developing prosthetic infection after primary TKA. These risk factors are: male sex,[3,13,54,56] background of diabetes mellitus,[54,57] primary TKA indication being rheumatoid arthritis,[13,58] osteonecrosis[54] or post-traumatic arthritis,[13,54] high BMI,[13,53,54,56] increased ASA score,[3,54,59] high-volume hospitals,[54,60] quadriceps release exposure,[54] constrained and hinged knee prostheses,[13] and long operative time.[3,54,59]

The use of ALBC has been shown to be effective at reducing the rate of infection following primary TKA performed in diabetic patients,[42] in patients whose indication for TKA was rheumatoid arthritis,[40] and where the primary TKA was performed without 'clean-air' measures.[37,39]

One of the concerns regarding the use of ALBC for infection prophylaxis in primary joint arthroplasty is the potential for the ALBC to develop resistant organisms that may further complicate infection management should the implant become infected;[4,20-23] or complicate the reliability of joint fluid and tissue cultures during revision surgery.[61,62] However, in a study by Hansen et al[63] of primary TKAs and THAs performed using ALBC *versus* plain cement in the United States, the authors found no change in the patterns of the infecting organisms, and no notable increase in the proportion of resistance of the organisms found at revision surgery. They concluded that the routine prophylactic use of ALBC did not lead to a change in the

profile of the infecting pathogen and did not lead to increased resistance of the infecting organisms. Tyas et al[24] studied the rate of deep surgical site infection in hip hemiarthroplasty performed using high-dose dual-antibiotic cement and those performed using low-dose single-antibiotic cement. While they found a significantly lower rate of infection in patients who received the high-dose dual-antibiotic cement, they also found no increase in the cases of bacterial resistance to antibiotics in the high-dose dual-antibiotic cement group.[24]

Another concern is that adding antibiotics to bone cement can adversely affect its mechanical properties.[16-19] However, none of the available arthroplasty registry-based studies found evidence of adverse effect of ALBC on the revision rate for noninfective causes. In contrast, Bohm et al[46] found that ALBC actually improved the revision rate for aseptic loosening in primary TKAs. Havelin et al[55] found a trend toward higher revision rate for aseptic loosening in the hip arthroplasties performed using plain cement rather than those performed using ALBC. We accept that these studies report short-term results and did not assess the longer-term effect. Several studies have also reported incidents of bone cellular[25,26] and renal toxicity[27-29] with ALBC. A cost-effectiveness analysis estimated that a reduction of TKA infection rate by at least 1.2% as a result of ALBC is required to recover the cost and therefore justify the routine use of ALBC in TKA in the United States.[15] In this current study of NJR data, there was an overall reduction in revision risk at ten years of 0.87%. However, costs of ALBC vary across markets, with United States health providers often paying many times the costs in the United Kingdom. Therefore, cost-effectiveness analyses in the United States are likely to overestimate thresholds, and it should also be noted that a wholesale switch to ALBC in the United States would significantly reduce ALBC costs. Finally, the NJR annual report states that 75% of patients with TKA are alive at ten years following surgery.[64] It is entirely feasible that risk reduction over the lifetime of these implants will be greater than 0.87%.

While we believe this paper presents data to justify its use, there may be specific groups of patients who are more likely to benefit from ALBC than others, and further work on risk factors is needed to stratify risk and contain costs.

In conclusion, after adjusting for a range of variables, ALBC was associated with a 19% lower risk of revision in this large registry-based study of over 700 000 primary TKAs. Using ALBC does not increase midterm implant failure rates.

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Acknowledgements:

The authors would like to thank the patients and staff of all the hospitals in England, Wales, and Northern Ireland who have contributed data to the National Joint Registry (NJR). We are grateful to the Healthcare Quality Improvement Partnership (HQIP), the NJR Research Sub-committee, and staff at the NJR Centre for facilitating this work. The authors have conformed to the NJR's standard protocol for data access and publication. The views expressed represent those of the authors and do not necessarily reflect those of the NJR Steering Committee or the HQIP who do not vouch for how the information is presented.