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Antibiotic-Loaded Bone Cement and Risk of Infection After Knee Arthroplasty in High-Risk Patients

A Register Based Meta-Analysis

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Background: The use of antibiotic-loaded bone cement (ALBC) in primary total knee arthroplasty (TKA) is debated. Some argue that ALBC might only be justified in high-risk patients. This study assessed the effectiveness of ALBC vs. plain bone cement (PBC) in reducing risk of revision for periprosthetic joint infection (PJI) in TKA patients considered to have a high risk of infection.

Methods: Cohort study of primary TKAs in 11 national or regional arthroplasty registries from 2010 to 2020. The 1-year risk of revision for PJI in TKAs with ALBC vs. PBC among patients with high American Society of Anesthesiologists (ASA) classification, body mass index (BMI), and/or diabetes was compared. Cumulative percent revision (1 minus Kaplan-Meier) based on 685,818 TKAs and Cox regression analyses (adjusted Hazard Rate Ratios [aHRRs]) were performed for TKAs with ALBC (reference) vs. PBC restricted to the following high-risk subgroups of patients: (1) ASA ≥3 (n = 335,612 vs. 35,997), (2) BMI ≥35 (n = 278,927 vs. 24,737), (3) ASA ≥3 and BMI ≥35 (n = 99,407 vs. 11,407), (4) diabetes (n = 38,341 vs. 21,838), and (5) ASA ≥3, BMI ≥35, and diabetes (n = 3,347 vs. 4,261). Advanced distributed meta-analyses were performed to combine all aggregate data and assess 1-year risk of revision for PJI.

Results: Each registry reported a 1-year cumulative percent revision of ≤1.6% for PJI following TKAs both for ALBC and PBC in all high-risk subgroups. Similar 1-year risks of revision for PJI were found in TKAs with ALBC (reference) and PBC among patients with ASA ≥3 (aHRR: 1.09; 95% CI, 0.90-1.31); BMI ≥35 (1.06; 0.54-2.12); ASA ≥3 and BMI ≥35 (1.12; 0.83-1.50); diabetes (0.95; 0.74-1.20); and ASA ≥3, BMI ≥35, and diabetes (1.40; 0.86-2.29).

Conclusions and Relevance: Similar 1-year revision risk of PJI was found for TKAs with ALBC vs. PBC in high-risk patients. Confirmation of the efficacy of ALBC in high-risk TKA patients needs to be evaluated in clinical trials.

Level of Evidence: Level III. See Instructions for Authors for a complete description of levels of evidence.

Introduction

Over the last 50 years, antibiotic-loaded bone cement (ALBC) has been used in arthroplasty to reduce the risk of periprosthetic joint infection (PJI), although the practice varies worldwide[1-3]. Earlier studies on the effectiveness of ALBC use in primary total knee arthroplasty (TKA) is inconclusive[4-28]. Two recent meta-analyses, including data from multiple regional/national registries, found no difference in 1-year PJI revision risk between TKAs with ALBC vs. PBC.[27,28]

Studies have reported that diabetes, body mass index (BMI) of ≥35, and American Society of Anesthesiologists (ASA) classification of ≥3 are independent risk factors of PJI[29-35]. Namba et al.[36] reported lower PJI risk among patients with diabetes who received ALBC vs. plain bone cement (PBC),

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A917).

whereas no such association was observed for patients with high BMI or high ASA class.[36]

The primary aim of this study was to assess the prophylactic effectiveness of ALBC in reducing 1-year risk of revision for PJI in assumed high-risk patients (ASA ≥3, BMI ≥35, and/or diabetes) undergoing primary TKA compared with PBC. The secondary aim was to assess risk at 5-year and 10-year follow-up.

Materials and Methods

This study was initiated by the Norwegian Arthroplasty Register (NAR) but coordinated in collaboration with Kaiser Permanente (KP). The ethical approval obtained from the Regional Committee for Research Ethics in Western Norway (registration number 2021/319783/REK Vest, dated 24.11.2021). Moreover, each participating registry acquired the necessary ethical approval in accordance with local regulations[3,27]. This study adhered to the STROBE reporting guidelines for observational studies[37].

Study Population

Overall, the study included 685,818 primary TKAs reported to 11 arthroplasty registries in Australia, Denmark, Finland, Germany, New Zealand, Norway, Sweden, Switzerland, the Netherlands, the United Kingdom, and the United States from 2010 to 2020 (Fig. 1 and Supplement Table 1).

Inclusion and Exclusion Criteria

Only registries recording information on ASA class, BMI, and/or diabetes were included (Supplement Table 1)[3]. To ensure a homogeneous study population, we only included fully cemented and/or hybrid primary TKAs for osteoarthritis (Fig. 1).

Exposure

Primary TKAs with ALBC vs. PBC was the exposure.

Outcome Variables

Revision was described as any addition, exchange, and/or removal of the whole or portion of a prosthesis[27]. Risk of revision for PJI was assessed for TKAs with ALBC vs. PBC with up to 10-year follow-up, with 1-year risk of revision as the primary outcome measure. A standardized hierarchical list of diagnoses was used when reporting revisions TKA[38] with PJI on top of this hierarchy.

High-Risk Subgroups

We restricted the cohorts for analysis of TKA patients in the following high-risk subgroups: (1) ASA ≥3, (2) BMI ≥35, (3) ASA ≥3 and BMI ≥35, (4) diabetes, and (5) ASA ≥3, BMI ≥35, and diabetes (Fig. 1 and Supplement Table 1).

Follow-up

TKAs were followed until first revision or until December 31, 2021, whichever came first. Follow-up was censored (modeled into the analysis) at time of first revision if it was for other causes than PJI, patient death, or migration and/or healthcare membership termination[27].

Data Extraction

We used a distributed health data network that did not necessitate centralized data storage[3,39-42]. Thus, this study based on aggregated data without personal identifiable information obtained from the participating registries and the data extraction was performed in 2 stages. In collaboration with KP, the NAR developed and distributed a data-sharing template to each participating registry for reporting of aggregate information for specifically defined data elements.

Stage 1

Each registry identified the eligible study sample from their data and provided summary statistics on patient and surgical attributes according to type of cement used (ALBC and PBC)[3] for the ASA ≥3, BMI ≥35, and/or diabetes (yes) subgroups of interest, and number (%) and causes of revisions using a predetermined template, and then sent it back to the NAR to compile.

Stage 2

After reviewing the data provided at stage 1, templates for 1 minus Kaplan-Meier and Cox regression were created and sent to each registry for extraction of aggregate information. Then, each registry evaluated and reported back estimated cumulative percent revision and risk of revision for PJI, reporting hazard rate ratios (HRRs), beta coefficients, standard errors, and 95% confidence intervals[27,43,44].

Statistical Analysis

Descriptive statistics, including frequencies and percentages, were used to describe each registry's study sample according to ASA class, BMI, and/or diabetes subgroups and overall (pooled) data included.

Individual Registry Analysis

Each registry used Cox regression to evaluate revision for PJI at 1-year, 5-year, and 10-year follow-up while including the covariates specified. Each registry computed HRRs with 95% CIs for risk of revision using 3 Cox models: (1) unadjusted Cox model; (2) Cox model adjusted for sex, age, and year of surgery (time period); and (3) fully adjusted Cox model for sex, age, year of surgery [time period], fixation, patella resurfacing, bearing mobility, stability, and/or systemic antibiotic prophylaxis. Ten of the 11 registries (except Danish Knee Arthroplasty Registry [DKR]) reported information on ASA class, and 10 of 11 registries (except NAR) reported information on BMI. Only the German Arthroplasty Registry and KP reported information on diabetes. Only the KP was able to extract robust data on TKA patients with all ASA ≥3, BMI ≥35, and diabetes. ALBC served as the reference group in all regression models. The results and discussion section of this study were presented based on the findings from Cox model 3. Only registries with minimum of 100 cases each in ALBC and PBC used in TKAs reported results of Cox regression analyses (excluding the Finnish, Norwegian, and Swedish registries), and/or revision cases for PJI in both ALBC and PBC groups (excluding the

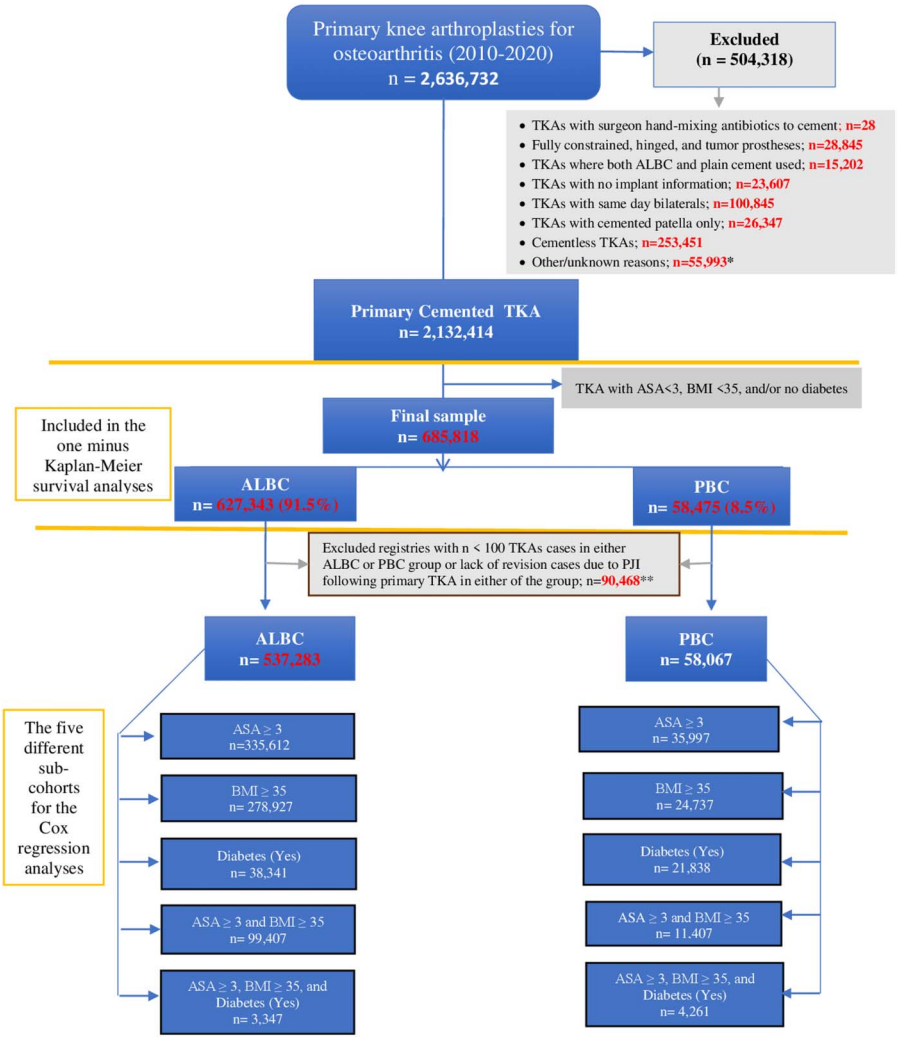

Fig. 1

Flow chart—stepwise inclusion and exclusion criteria. *Excluded TKAs with insufficient data to determine if inclusion criteria are met. ** NAR used 100% ALBC, FAR had n = 74 TKA with PBC, SAR had n = 41 TKA with PBC, and SIRIS had no revision cases due to PJI following TKA with PBC among patients with ASA ≥ 3 and BMI ≥ 35. Thus, the 4 registries (FAR, n = 23,873; NAR, n = 8,610; SAR, n = 32,804; and SIRIS, n = 25,181) were excluded from the subsequent Cox regression analyses. ALBC = antibiotic-loaded bone cement, BMI = body mass index, FAR = The Finnish Arthroplasty Register, NAR = The Norwegian Arthroplasty Register, PBC = plain bone cement, SAR = The Swedish Arthroplasty Register, and SIRIS = Swiss Implant Registry.

Swiss registry) were subsequently included in the meta-analysis (Fig. 1).

Meta-Analysis

Earlier study from the similar sample population reported variation in ALBC use ranging from 34% in the United States to 100% in Norway[27]. The study used the estimate of the log HRRs (the β coefficients) with standard errors from the Cox regression analyses performed by each registry to conduct advanced harmonized stratified meta-analysis[27]. Resulting HRRs and 95% CIs are presented in forest plots. A random-effects model was used, which treats the registries as a set of random effects and assumes certain level of heterogeneity among the data from individual registries[45]. This approach was preferred over the fixed-effects model despite having less restricted inferences[46]. Since the ratio of ALBC to PBC usage in TKAs varied across the participating registries[3], we conducted a sensitivity analysis to determine the impact of individual registries on the meta-analysis results[45,47]. The meta-analyses were performed using Stata version 18.

Results

Crude Rate of Revision for PJI

Of all 685,818 TKAs included in this study, 91.5% (627,343) were with ALBC among high-risk patients (Fig. 1 and Supplement Table 1).

Overall, 1.0% (6,375 of 627,343) of TKAs with ALBC and 1.2% (728 of 58,475) of TKAs with PBC among patients with ASA ≥3, BMI ≥35, and/or diabetes were revised due to PJI during the entire study period (Supplement Table 1). The

cumulative percent revision for PJI following TKAs with ALBC and PBC for each registry are presented in Supplement Figures 1 through 5. Each registry reported a 1-year cumulative percent revision of ≤1.6% for PJI following TKA with ALBC and PBC among patients with ASA ≥3 (ranging from 0.3% in the United Kingdom to 1.2% in Germany vs. 0.4% in the Netherlands to 0.9% in New Zealand), BMI ≥35 (0.1% in the Netherlands to 1.3% in Finland vs. 0.4% in Denmark to 1.1% in the United Kingdom), diabetes (0.7% in the United States to 1.0% in Germany vs. 0.7% in the United States to 1.6% in Germany), both ASA ≥3 and BMI ≥35 (0.4% in the United Kingdom to 1.6% in Sweden vs. 0.2% in Australia to 1.2% in New Zealand), and for ASA ≥3, BMI ≥35, and diabetes (0.9% in the United States to 1.5% in Germany, but only for the ALBC group), respectively (Supplement Figs. 1–5).

Results of Distributed Meta-Analyses

The results from the Cox regression–based meta-analyses for the different high-risk subgroups are presented in Figures 2–5 (for full Cox model) and Supplement Figs. 6–9 (for Cox model 1 and 2). Since only KP had information on patients with all ASA ≥3, BMI ≥35, and diabetes, no meta-analysis was performed for this subcohort. The results from Cox regression analyses from each registry are reported in Supplement Tables 2–5.

Overall, the meta-analyses based on Cox regression, both unadjusted and partially adjusted (Supplement Figures 6-9)

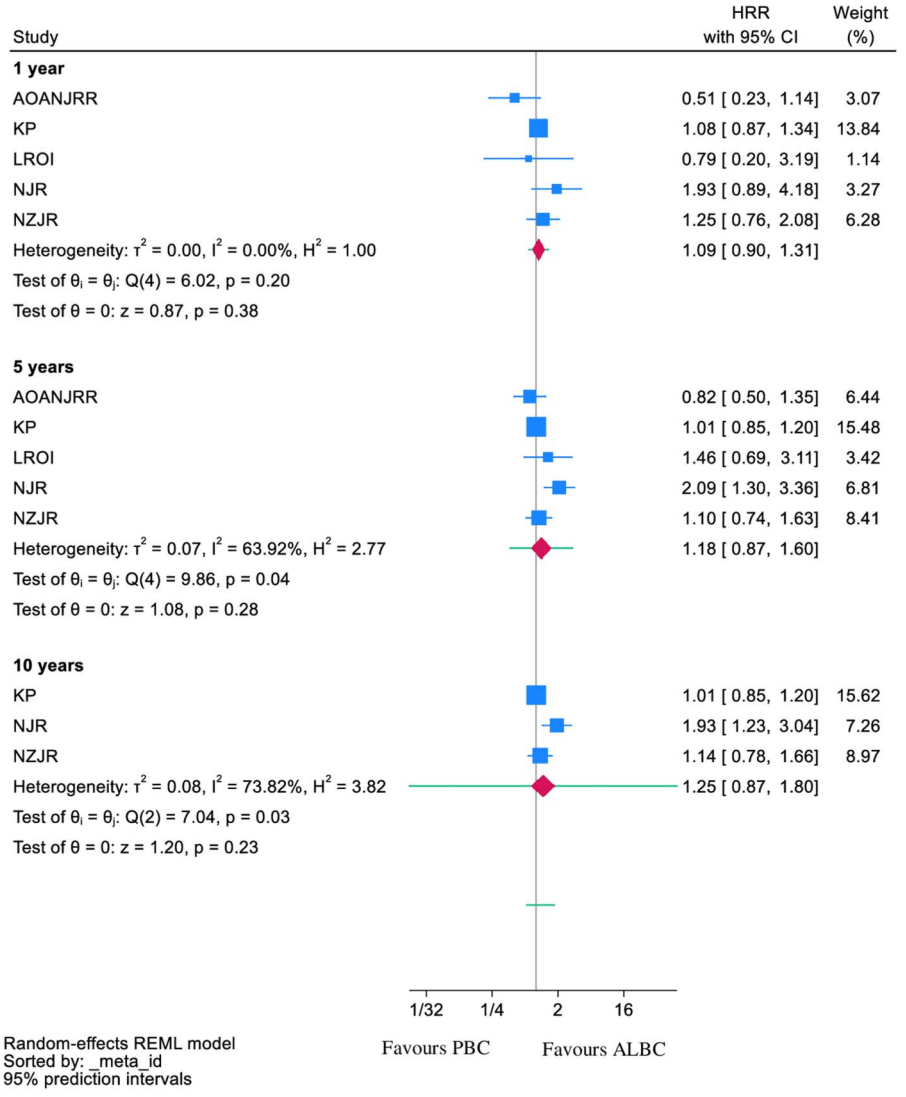

Fig. 2

Forest plots showing fully adjusted Cox regression meta-analysis on risk of revision for PJI following primary TKAs with ALBC vs. PBC among patients with ASA ≥3. ALBC was used as a reference[a,b]. [a]The meta-analysis was based on result from Cox regression analysis adjusted for age, sex, year of surgery [time period]), and all other variables available in each participating registry. [b]The size of the square in the forest plot corresponds to each registry weighted based on the number of TKA with plain bone cement in the registry (see Supplement Table 1). ASA = American Society of Anesthesiologists, ALBC = antibiotic-loaded bone cement, PBC = plain bone cement, PJI = periprosthetic joint infection, and TKA = total knee arthroplasty.

and fully adjusted (Figures 2–5), showed similar results in risk of revision for PJI following TKA with ALBC vs. PBC among patients with ASA ≥3, BMI ≥35, and/or diabetes at follow-up: 1 year, 5 year, and 10 years.

The 1-year risk of revision for PJI in TKAs with PBC compared with the ALBC was similar for patients with ASA ≥3 (aHRR = 1.09; 95% CI: 0.90-1.31) (Fig. 2), for patients with BMI ≥35 (aHRR = 1.06; 95% CI: 0.54-2.12) (Fig. 3), and for patients with both ASA ≥3 and BMI ≥35 (aHRR = 1.12; 95% CI: 0.83-1.50) (Fig. 4). For patients with diabetes, the 1-year risk of revision for PJI was 0.95; 95% CI: 0.74 to 1.20 in the PBC group compared with the ALBC group (Fig. 5). For patients with ASA ≥3, BMI ≥35, and diabetes, the 1-year risk of revision for PJI was 1.40; 95% CI: 0.86 to 2.29 in the PBC group compared with the ALBC group (based on KP data only) (Supplement-Table 6). Similarly, we observed no significant differences in risk of revision for PJI between ALBC vs. PBC among patients with high ASA class and/or high BMI at 5-year and 10-year follow-up (Figures 2–5 and supplement Figures 6–9).

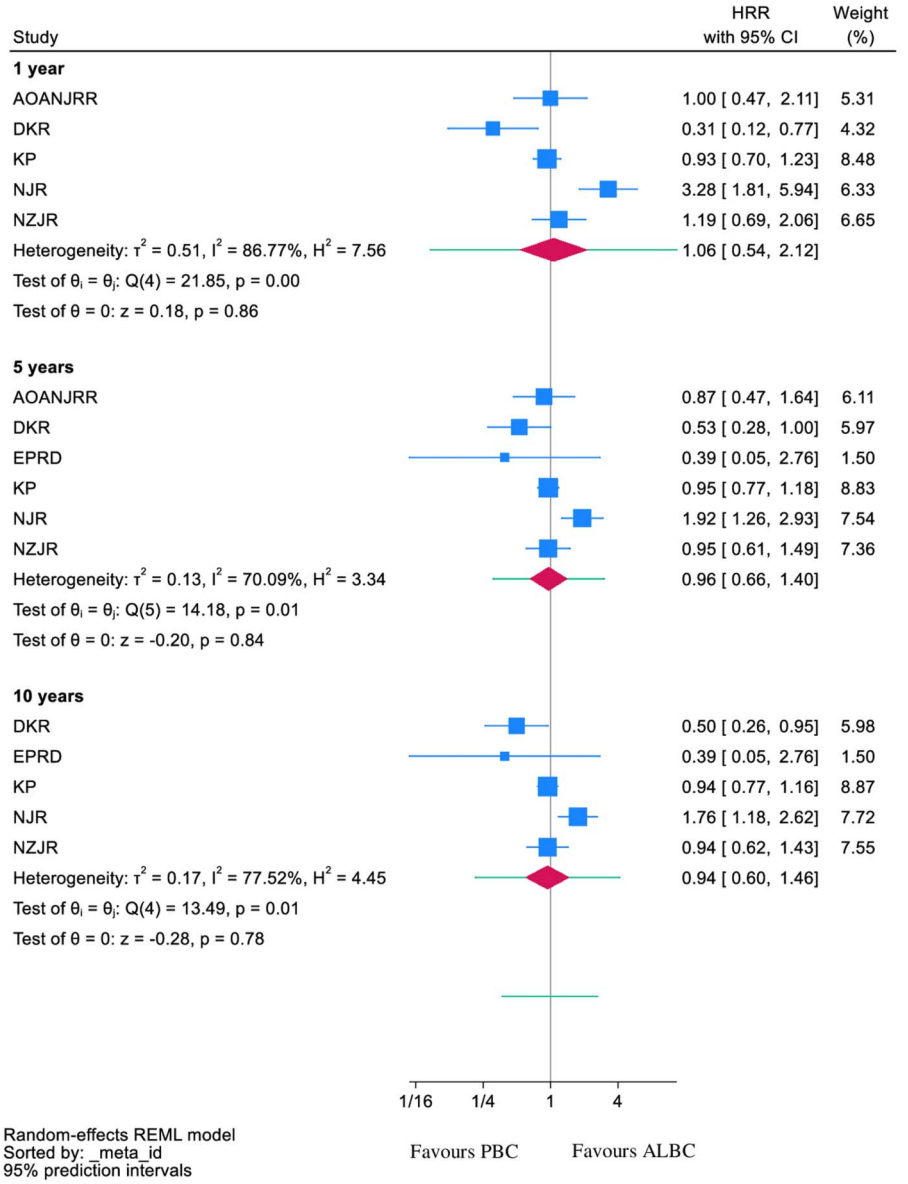

Fig. 3

Forest plots showing fully adjusted Cox regression meta-analysis on risk of revision for PJI following primary TKAs with ALBC vs. PBC among patients with BMI ≥35. ALBC was used as a reference.[a,b] PBC favors, ALBC favors. [a]The meta-analysis was based on result from Cox regression analysis adjusted for age, sex, year of surgery [time period]), and all other variables available in each participating registry. [b]The size of the square in the forest plot corresponds to each registry weighted based on the number of TKA with plain bone cement in the registry (see Supplement Table 1). ALBC = antibiotic-loaded bone cement, PBC = plain bone cement, PJI = periprosthetic joint infection, and TKA = total knee arthroplasty.

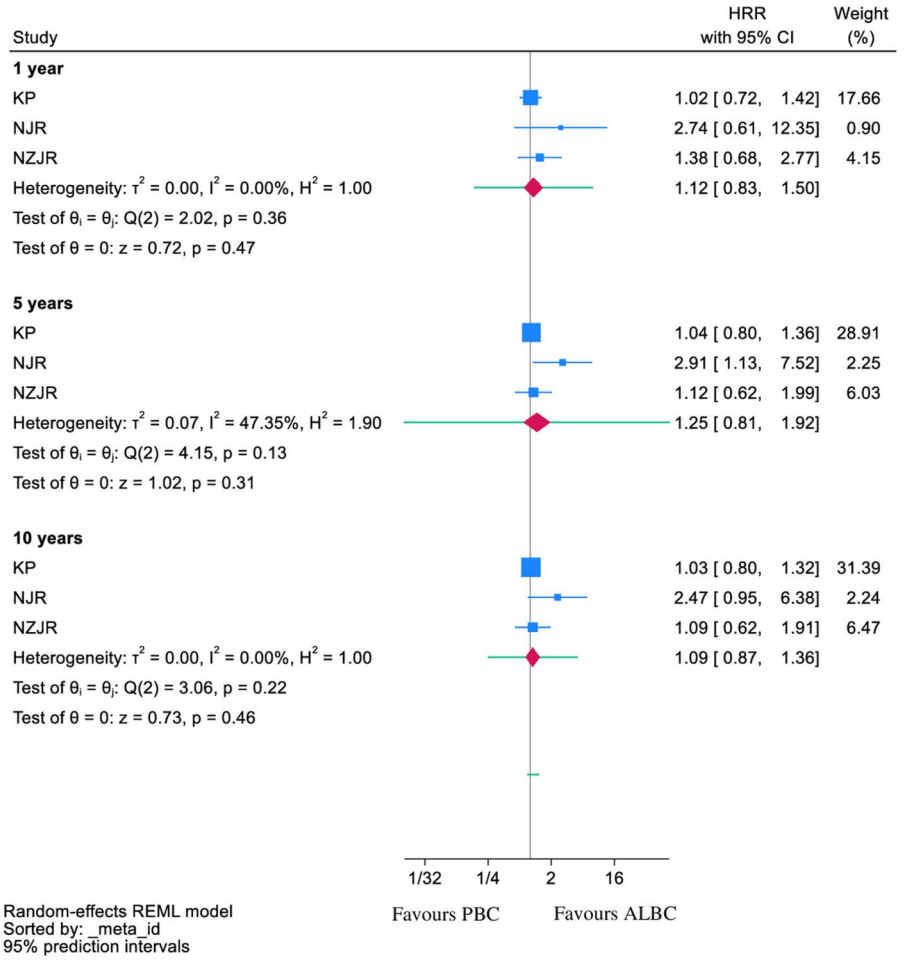

Fig. 4

Forest plots showing fully adjusted Cox regression meta-analysis on risk of revision for PJI following primary TKAs with ALBC vs. PBC among patients with ASA ≥3 and BMI ≥35. ALBC was used as a reference[a,b,c]. [a]The data were from the KP, NJR, and NZJR only. PBC favors. ALBC favors. [b]The meta-analysis was based on result from Cox regression analysis adjusted for age, sex, year of surgery [time period]), and all other variables available in each participating registry. PBC favors, ALBC favors. [c]The size of the square in the forest plot corresponds to each registry weighted based on the number of TKA with plain bone cement in the registry (see Supplement Table 1). ALBC = antibiotic-loaded bone cement, BMI = body mass index, PBC = plain bone cement; PJI = periprosthetic joint infection, and TKA = total knee arthroplasty.

Sensitivity Analysis

The sensitivity analysis demonstrated that the results of the meta-analysis for ASA ≥3, BMI ≥35, and ASA ≥3 and BMI ≥35 were consistent as individual registries were stepwise removed from the meta-analysis for risk of revision for PJI following TKAs (Supplement-Table 7).

Discussion

This is the largest registry-based meta-analysis performed to date evaluating the prophylactic effectiveness of ALBC use in TKAs for osteoarthritis on risk of revision for PJI in patients considered to have high-risk of infection. We observed similar 1-year PJI revision risks after TKAs with ALBC vs. PBC in patients with ASA ≥3, BMI ≥35, and/or diabetes. Similarly, no significant differences for risk at 5 years and 10 years following TKA with ALBC vs PBC were observed. The prophylactic effectiveness of ALBC use in TKA is still subjected to debate. While some studies reported ALBC to reduce the risk of revision for PJI[4-10], other studies have reported similar results for ALBC and PBC[11-25,27,28,36].

This study findings are in agreement with 2 previous studies[25,36]. However, other studies have reported that ALBC use is associated with both reduced and increased risk of revision for PJI[10,15,22,26]. Ricciardi et al.[48], based on American Joint Replacement Registry data, reported a higher 90-day PJI revision rate of the ALBC group compared with PBC after TKA in patients with high BMI (>35). Possible explanations for this difference may be attributed to differences in patient-related and surgery-related characteristics, study size, or of follow-up length.

We also found a similar PJI revision risk in patients with diabetes. By contrast, a US-based register study[36] and a

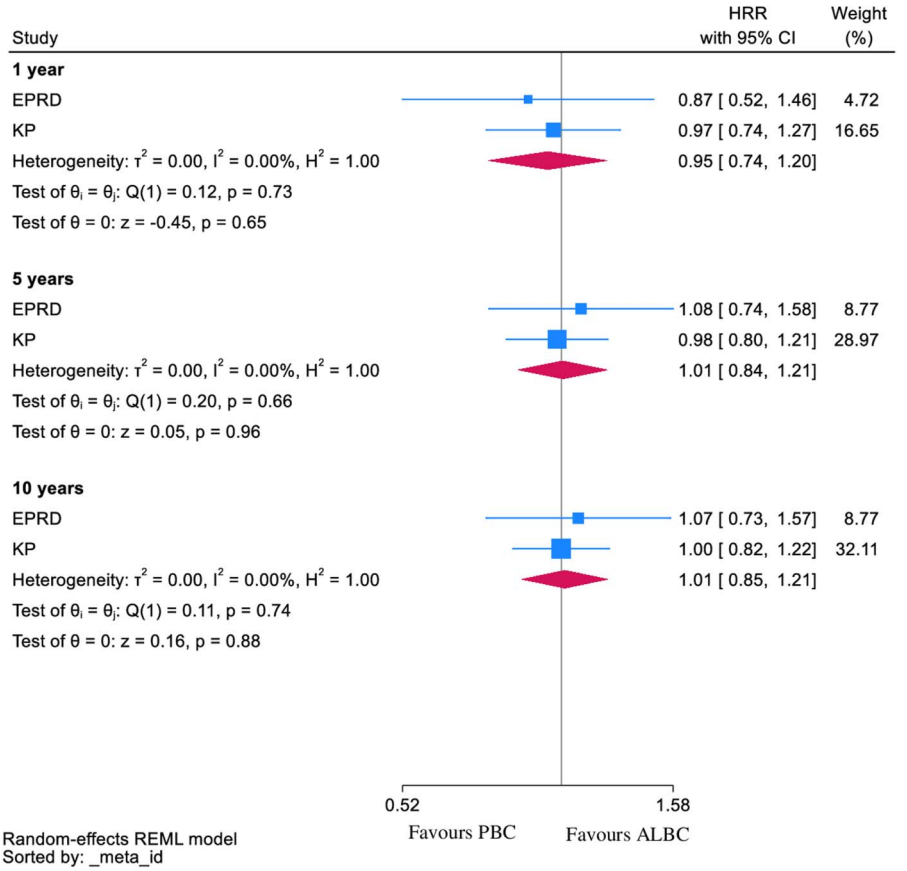

Fig. 5

Forest plots showing fully adjusted Cox regression meta-analysis on risk of revision for PJI following primary TKAs with ALBC vs. PBC among patients with diabetes. ALBC was used as a reference[a,b,c]. [a]The data were from the EPRD and KP only. [b]The meta-analysis was based on result from Cox regression analysis adjusted for age, sex, year of surgery [time period]), and all other variables available in each participating registry. [c]The size of the square in the forest plot corresponds to each registry weighted based on the number of TKA with plain bone cement in the registry (see Supplement Table 1). ALBC = antibiotic-loaded bone cement, KP = Kaiser Permanente, PBC = plain bone cement, PJI = periprosthetic joint infection, and TKA = total knee arthroplasty.

randomized study including 78 TKAs from Taiwan reported that ALBC use in TKAs lowered the risk of infection among patients with diabetes. Plausible explanations for this difference could be selection bias, as ALBC probably was used in high-risk patients e.g. in the United States, as well as limitations of data and methodology, in that the results were based on crude estimates of few patients and p-values only calculated in the Taiwan study.

Study Strength and Limitations

Our study demonstrates good external validity due to the large cohort size which can help identify small differences in event rates, addressing variation in ALBC utilization and inclusion of different settings (different regional/national joint registry data).

The study has some limitations. The proportion of TKAs with PBC in this study was only 8.5%, which might result in skewed distribution. Nevertheless, earlier studies from similar data reported no differences in risk of revision for PJI between ALBC vs. PBC despite the mismatched group sizes[4,5]. Registries rely on PJI data collection at the time of surgery, resulting in potential misclassification and underreporting. For example, revisions reported as aseptic loosening may represent low-grade PJI and the diagnosis will likely not be corrected after results from routinely collected bacterial samples. Besides, some of the registries participating in this study reported a cumulative percent revision of ≤0.5% for PJI at 1 year which might indicate an underreporting of events. Recent registry studies have reported 87% accuracy of surgeon-reported revisions for PJI after hip arthroplasty in NAR[49], 58% sensitivity of PJI revisions in the DKR[50], and 75% accuracy of reporting of PJI in AOANJRR.[51]

How revision for PJI following TKAs were recorded, as well as the completeness of reporting revisions due to PJI, may differ between the participating registries. In addition, reoperations for infections, where no prosthetic components were changed, removed, or added, were not included in the analysis. Participating registries used a standardized hierarchical

diagnoses list for revision TKA[38] when reporting revisions. PJI was at top of the hierarchy and should therefore not be missed if reported.

Our study included data from different national and/or regional registries, possibly with different patient characteristics, perioperative protocols, and surgical techniques that inherently make it difficult to account for all confounders. However, we used random-effects models for the meta-analysis, considering the difference in number of procedures each registry contributes has a minor influence on the findings, diminishing potential inequality from the larger volume registries[46,52]. In addition, the sensitivity analyses confirmed the heterogeneity among participating registries did not diminish the reliability of our findings.

Data on ASA classification, BMI, and diabetes were incomplete within the participating registries. Thus, we chose to perform the analyses stratified for separate variables though we acknowledge that ASA classification and BMI, as well as diabetes, are theoretically inter-related. Jämsen et al.[34] reported that only hyperglycemia and morbid obesity (BMI >40) was associated with higher risk of PJI, not diabetes. We lack information on glycemia in this study.

While we were not able to identify an association between ALBC and risk of PJI, we lacked detailed information on the type and dosage of the antibiotics in the cement, and type, timing, dosage, and duration of systemic antibiotic prophylaxis though variation in these covariates were reported among registries[3]. Thus, we could not reveal any information on whether certain antibiotics are more effective than others. However, in an earlier study with ALBC or PBC in combination with systemic antibiotic prophylaxis with different half-lives, we found no statistically significant difference[28].

Implications and Clinical Relevance

We found no statistically significant evidence that use of ALBC in cemented TKAs is associated with a reduced risk of revision for PJI compared with PBC when restricting to ASA, BMI, and/or diabetes subgroups considered higher risk for infection. Excessive antibiotic use may potentially lead to selection of antibiotic-resistant bacterial strains and, subsequently, high costs to the healthcare system. Cost-burden[16,21,24,53] and the potential to develop antimicrobial resistance[54,55] that may complicate the management of an infected implant are some of the concerns regarding the use of ALBC in TKAs. Further studies on the potential for antimicrobial resistance to develop from ALBC use and cost-effectiveness of ALBC use in TKAs are needed.

Conclusion and Relevance

A similar 1-year revision risk of PJI was found for TKAs with ALBC and PBC in high-risk patients. However, the assumption that high-risk patients benefit from the use of ALBC in TKA cannot be ruled out based on this study. Thus, a prospective, multicenter register-based randomized controlled trial studying the clinical benefits of ALBC use in high-risk patients undergoing TKA could be warranted, although studying differences between patients and surgical procedures within or between countries remains complex.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A918). This content was not copyedited or verified by JBJS. ■

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