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EVIDENCE-BASED SYSTEMATIC REVIEWS

Number of Doses of Systemic Antibiotic Prophylaxis May Be Reduced in Cemented Primary Knee Arthroplasty Irrespective of Use of Antibiotic in the Cement: A Multiregistry-Based Meta-Analysis

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Background: The use of systemic antibiotic prophylaxis (SAP) and antibiotic-loaded bone cement (ALBC) is the accepted practice to reduce the risk of periprosthetic joint infection (PJI) in primary total knee arthroplasty (pTKA). However, practice varies internationally. This study's primary aim was to compare the risk of PJI revision after pTKA with ALBC + SAP vs. plain bone cement (PBC) + SAP, and the secondary aim was to assess whether the risk of PJI revision varies with the number of SAP doses.

Methods: Cohort of 289,926 pTKAs for osteoarthritis from arthroplasty registries in Denmark, New Zealand, Norway, Romania, and United States registered from 2010 to 2020. One-year revision for PJI following pTKA with ALBC + SAP vs. PBC + SAP, and single vs. multiple SAP doses was compared. We computed cumulative percent revision (1 minus Kaplan-Meier) using distributed analysis method and adjusted hazard rate ratios (HRRs) using Cox regression analyses within each registry. Advanced distributed meta-analysis was performed to summarize HRRs from all countries.

Results: Among all pTKAs, 64.4% were performed with ALBC + SAP. Each registry reported a 1-year cumulative percent revision for PJI of <1.00% for both pTKAs with ALBC + SAP (0.34%-0.80%) and with PBC + SAP (0.54%-0.69%). The distributed meta-analysis showed HRR = 1.21; (95% confidence interval [CI], 0.79-1.87) for ALBC + SAP compared with PBC + SAP. Similar risk of PJI revision was observed between pTKAs with ALBC + single vs. multiple doses of SAP: 2 doses (0.95; 95% CI, 0.68-1.33), 3 doses (1.09; 95% CI, 0.64-1.87), and 4 doses (1.23; 95% CI, 0.69-2.21). Comparable results were found for the PBC + SAP group except for higher risk of PJI revision with 4 doses of SAP (2.74; 95% CI, 1.11-6.75).

continued

THL is the principal investigator of this study and drafted the manuscript. AMF, AS, EWP, OF, HAP, RNC, SAL, SHLL, and THL contributed to the concept and design of this study. AMF, RNC, SAL, and SHLL are coordinating statistician team in this study. All authors contributed to the acquisition, analysis, and/or interpretation of data. All authors contributed to the interpretation of the results and content of the manuscript and approved the final version to be published. THL had access to the aggregate data received from the 5 participating registries. One individual from each participating registry had full access to all their registry's data included in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis including the one minus Kaplan-Meier and Cox regression related to their registry. THL and SAL takes responsibility for the accuracy of the data analysis in the meta-analysis.

THL received a postdoctoral grant from the Western Norway Regional Health Authority. Each participating registry used its own resources. No external funding was received in support of this work. The funder had no role in the design and conduct of the study; collection, management, analysis, and data interpretation; manuscript preparation, review, or approval; and decision to submit the manuscript for publication.

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A710).

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Conclusions: ALBC and PBC entailed similar risk of PJI revision when patients received SAP in pTKA, regardless of number of SAP doses. ALBC or PBC used in combination with SAP in pTKAs, with one single preoperative dose of SAP may be sufficient without compromising the patient safety.

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

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Introduction

The use of systemic antibiotic prophylaxis (SAP) is accepted as standard practice to reduce the risk of periprosthetic joint infection (PJI)[1-3]. SAP in combination with antibiotic-loaded bone cement (ALBC) is frequently used in arthroplasty surgeries, although the practice varies internationally and the type and duration of SAP are subject to debate[1,2,4].

Two studies on primary total hip arthroplasties (THAs) from the Norwegian Arthroplasty Register (NAR) found a lower risk of revision for PJI in THAs that had SAP and ALBC compared with THAs that had SAP and plain bone cement (PBC)[5,6]. A 2021 scoping review found no significant association with postoperative SAP in preventing surgical site infection[7]. A concern with universal adoption of postoperative SAP is that excess application of antibiotics may lead to antimicrobial resistance, rendering the treatment of even common infections difficult to impossible[8,9].

In our recent meta-analysis including 10 national/regional registries, we found no difference in 1-year PJI revision risk between primary total knee arthroplasties (pTKAs) with ALBC vs. PBC[10]. However, preoperative and postoperative SAP was not considered. Using a multiregistry meta-analysis approach, the primary aim of this study was to compare the prophylactic effectiveness of ALBC + SAP vs. PBC + SAP in pTKAs on the risk of revision for PJI. Secondary aim was to assess whether the number of doses of SAP was associated with the risk of revision for PJI.

Materials and Methods

This study was primarily approved by the Regional Committee for Research Ethics in Western Norway. Furthermore, each participating registry obtained ethical approval as needed according to local regulations. This study followed strengthening the reporting of observational studies in epidemiology (STROBE) reporting guideline for observational studies[11].

Study Population

Study population comprised 289,926 cemented pTKAs for osteoarthritis reported to 5 regional/national arthroplasty registries in Denmark, New Zealand, Norway, Romania, and United States from 2010 to 2020 (Fig. 1 and Table I).

Exposure

pTKA with ALBC + SAP vs. PBC + SAP was the primary exposure. Single (one preoperative dose) vs. multiple (1 preoperative dose and 1, 2, or 3 postoperative doses on the day of surgery)

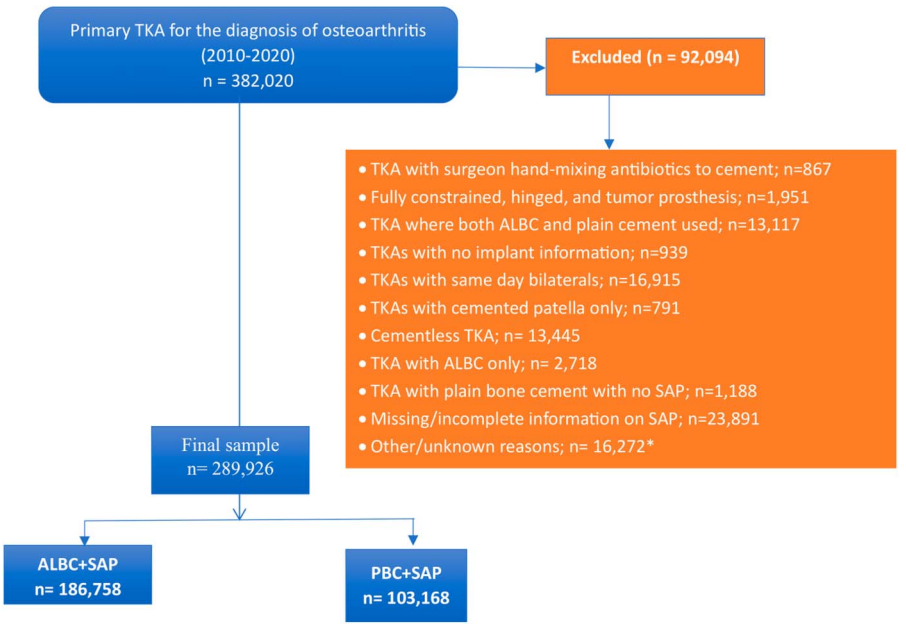

Fig. 1

Inclusion and exclusion criteria. *Excluded total knee arthroplasties (TKAs) with insufficient data to determine if inclusion criteria were met. ALBC+SAP = Antibiotic-loaded bone cement (ALBC) in combination with systemic antibiotic prophylaxis (SAP); PBC+SAP = plain bone cement with SAP.

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TABLE I Number (%) of pTKAs with ALBC + SAP vs. PBC + SAP Per Registry (2010-2020)

Registry, n (Row %)	No. of pTKA	ALBC + SAP	PBC + SAP
Total (pooled)	289,926	186,758 (64.4)	103,168 (35.6)
DKR	49,337	37,422 (75.8)	11,915 (24.2)
KP*	99,186	33,334 (33.6)	65,852 (66.4)
NAR	40,709	40,709 (100)	0 (0.0)
NZJR	70,362	57,794 (82.1)	12,568 (17.9)
RAR	30,332	17,499 (57.7)	12,833 (42.3)

*KP does not prospectively capture the specific information on SAP that was needed for the study. Instead, they retrospectively pulled the information from their integrated electronic health record specifically for this study. ALBC + SAP = ALBC in combination with SAP, ALBC = Antibiotic-loaded bone cement, DKR = The Danish Knee Arthroplasty Registry; KP = Kaiser Permanente Total Joint Replacement Registry, NAR = The Norwegian Arthroplasty Register, NZJR = The New Zealand Joint Registry, PBC + SAP = plain bone cement with SAP, pTKA = primary total knee arthroplasty, RAR = Romanian Arthroplasty Register, and SAP = systemic antibiotic prophylaxis.

SAP doses was a secondary exposure. SAP given for >4 doses and/or >1 day were excluded from the Cox regression analyses.

Outcome Variables

The outcome was risk of PJI revision following pTKAs with up to 10-year follow-up. Revision was defined as removal, addition, and/or exchange of part of a prosthesis or the whole prosthesis[10]. A standardized hierarchical list of diagnoses for revision TKA was used when reporting revisions[12]; PJI revision was the top diagnosis in this hierarchy.

Follow-up

TKAs were followed until the 1st revision or until December 31, 2021, whichever came first. The follow-ups were censored at the patient death, emigration, and/or health care membership termination time.

Data Extraction

Owing to unavailability of sharing deidentified patient-level data for privacy, security, and data ownership regulations, we used a distributed health data network that did not require centralized data storage[4,13-16]. Hence, our study population was based on aggregated data, without personal identifiable information. Detailed data collection and extraction procedures have been described previously[4,10].

Each registry reported summary statistics on patient and surgical characteristics according to the type of antibiotics prophylaxis used (ALBC + SAP vs. PBC + SAP)[4], cause and number (%) of revision surgery, cumulative percent of revision (1 minus Kaplan-Meier), and number/duration of SAP used (single vs. multiple SAP doses) using a data sharing template, which was returned to the NAR for compilation.

Afterward, NAR and Kaiser Permanente (KP) created 2 model templates for Cox regression and sent them to the participating registries for data extraction and analyses. Using a standardized design and analysis, each registry applied its own data and generated model results that were meta-analyzed across the registries[17,18]. Each registry evaluated the risk of PJI revision following pTKAs using Cox regression and returned the estimates to the NAR for meta-analysis reporting hazard rate ratios (HRRs), β coefficients, standard errors, and 95% confidence intervals (CIs)[10,17,18]. Furthermore, registries collecting data on number of SAP doses also evaluated whether the observed rate of PJI revision varied with the number of SAP doses and returned.

Statistical Analysis

Descriptive statistics including frequencies and percentages were used to describe each registry's study sample and overall revision rate during the study period. Each registry calculated cumulative revision percentage (rate) using 1 minus Kaplan-Meier survivorship estimates and used Cox regression to calculate the risk of PJI revision at 3 months, 1 year, 5 years, and 10 years. Each registry calculated HRRs with 95% CIs for revision risk in 3 Cox models: (1) unadjusted, (2) adjusted (sex, age, and surgery year [time period]), and (3) full-adjusted (sex, age, surgery time period, the American Society of Anesthesiologists (ASA) class, body mass index [BMI], patella resurfacing, fixation, stability, and bearing mobility). Covariates with missing values were categorized as "unknown" and included in the regression analyses. The impact of the type and dose of antibiotics added to cement and type of SAP used were not considered, although variations in these covariates were reported[4]. Only registries with n ≥ 100 pTKAs with ALBC + SAP and PBC + SAP performed Cox regression analyses.

Based on data from KP and NAR, we performed a sub–meta-analysis to evaluate whether the risk of PJI revision following pTKA with ALBC + SAP was associated with the number of SAP doses. The association of SAP doses on risk of PJI revision with PBC was assessed using Cox regression analysis based on KP data only and adjusted also for the type of SAP to consider the difference in the half-life of various antibiotic types used.

Each registry's estimates of the log HRR (the β coefficients) with standard errors from the Cox regression analyses were used to conduct the meta-analysis reported as HRR with 95% CI in forest plots. We fitted and presented the results from the random effect model (treating registries as a set of random effects), assuming some level of heterogeneity between data from individual registries[19], although it has less restricted inferences than the fixed-effects model[20]. The proportion of use of ALBC + SAP vs. PBC + SAP in pTKAs varied between participating registries[4]. A sensitivity analysis was performed to determine the influence of individual registries on the meta-analysis results[19,21]. Stata version 18 was used for the meta-analyses.

Results

Of the 289,926 pTKAs included, 186,758 (64.4%) were done with ALBC + SAP (Table I). Most patients were female (61.0%), aged 65 to 74 years (41.3%), preobese or in obese class-1 (55.3%), and with ASA class II (64.2%). The majority of the pTKAs were fully cemented (90.9%) and patella

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TABLE II Demographic and Surgical-Related Characteristics for pTKAs With ALBC + SAP vs. PBC + SAP (2010-2020) (Pooled Data)

Characteristic, n (%)	ALBC + SAP, n (% Within Group)	PBC + SAP, n (% Within Group)	Total, n (%)
No. of pTKA	186,758 (64.4)	103,168 (35.6)	289,926 (100.0)
Sex			
Male	74,728 (40.0)	38,411 (37.2)	113,139 (39.0)
Female	112,030 (60.0)	64,757 (62.8)	176,787 (61.0)
Age group (yr)			
<55	15,370 (8.2)	6,301 (6.1)	21,671 (7.5)
55-64	47,509 (25.4)	28,406 (27.5)	75,915 (26.2)
65-74	75,921 (40.7)	43,684 (42.3)	119,605 (41.3)
≥75	47,958 (25.7)	24,777 (24.0)	72,735 (25.1)
ASA score*			
ASA I	10,149 (7.7)	2,255 (2.9)	12,404 (5.9)
ASA II	84,668 (64.2)	50,252 (64.1)	134,920 (64.2)
ASA III	35,012 (26.6)	25,160 (32.1)	60,172 (28.6)
ASA IV+	454 (0.3)	305 (0.4)	759 (0.4)
Missing	1,554 (1.2)	448 (0.6)	2,002 (1.0)
BMI†			
Underweight (<18.50)	219 (0.2)	120 (0.1)	339 (0.2)
Normal (18.50-24.99)	14,253 (11.1)	10,858 (12.0)	25,111 (11.5)
Preobese (25.00-29.99)	36,157 (28.1)	28,299 (31.3)	64,456 (29.4)
Obese class 1 (30.00-34.99)	31,063 (24.2)	25,557 (28.3)	56,620 (25.9)
Obese class 2 (35.00-39.99)	16,781 (13.1)	13,620 (15.1)	30,401 (13.9)
Obese class 3 (≥40.00)	7,887 (6.1)	4,953 (5.5)	12,840 (5.9)
Missing	22,190 (17.3)	6,928 (7.7)	29,118 (13.3)
Operative side			
Right	97,799 (52.4)	53,248 (51.6)	151,047 (52.1)
Patella-resurfaced TKA	98,418 (52.7)	84,703 (82.1)	183,121 (63.2)
Time period			
2010-2014	70,255 (37.6)	45,555 (44.2)	115,810 (39.9)
2015-2020	116,503 (62.4)	57,613 (55.8)	174,116 (60.1)
Fixation			
Both/all cemented	166,298 (89.0)	97,148 (94.2)	263,446 (90.9)
Hybrid (tibial cemented)	19,612 (10.5)	4,721 (4.6)	24,333 (8.4)
Hybrid (tibial cementless)	275 (0.1)	370 (0.4)	645 (0.2)
Missing	573 (0.3)	929 (0.9)	1,502 (0.5)
Fixed bearing mobility†	77,429 (84.6)	75,262 (95.6)	152,691 (89.7)
Minimally stabilized TKA	126,442 (82.4)	35,501 (23.1)	161,943 (95.1)

*DKR and RAR do not collect data on ASA classes. †NAR and RAR do not collect data on BMI. ‡DKR and NZJR do not collect data on bearing mobility. ALBC + SAP = ALBC in combination with systemic antibiotic prophylaxis, ASA = American Society of Anesthesiologist's, BMI = body mass index–The BMI categories are based on the World Health Organization's classification, DKR = The Danish Knee Arthroplasty Registry, KP = Kaiser Permanente Total Joint Replacement Registry, NAR = The Norwegian Arthroplasty Register, NZJR = The New Zealand Joint Registry, PBC + SAP = plain bone cement with SAP, pTKA = primary total knee arthroplasty, and RAR = Romanian Arthroplasty Register.

resurfaced (63.2%) (Table II). There was a variation in use of ALBC + SAP among participating registries ranging from 33.6% in KP to 100% in NAR (Table I). Two-dose SAP was more common in United States (52.9% for pTKAs with ALBC and 58.6% for pTKAs with PBC), whereas 4-dose SAP was more common in Norway (80.7%) (Table II).

Crude PJI Revision Rate

Overall, 0.96% (n = 1,795) of pTKAs with ALBC + SAP and 0.98% (n = 1,011) of pTKAs with PBC + SAP were revised for PJI for the entire study period (Table III). All registries except NAR (1.2%) reported ≤1% revisions for PJI following pTKAs with ALBC + SAP, as well as for those with PBC + SAP (Table III).

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TABLE III Revision Proportion (%) for PJI Following pTKAs With ALBC + SAP vs. PBC + SAP Per Registry (2010-2020)

Register (Country)	pTKA n (% Within Register)	Revision for PJI n (% of Primary)
Total (pooled) (n = 289,926)		
ALBC + SAP	186,758 (64.4)	1,795 (0.96)
PBC + SAP	103,168 (35.6)	1,011 (0.98)
DKR (Denmark) (N = 49,337)		
ALBC + SAP	37,422 (75.8)	390 (1.0)
PBC + SAP	11,915 (24.2)	115 (1.0)
KP (US) (N = 99,186)		
ALBC + SAP	33,334 (33.6)	320 (1.0)
PBC + SAP	65,852 (66.4)	666 (1.0)
NAR (Norway)* (N = 40,709)		
ALBC + SAP	40,709 (100.0)	474 (1.2)
NZJR (New Zealand) (N = 70,362)		
ALBC + SAP	57,794 (82.1)	540 (0.9)
PBC + SAP	12,568 (17.9)	128 (1.0)
RAR (Romania) (N = 30,332)		
ALBC + SAP	17,499 (57.7)	71 (0.4)
PBC + SAP	12,833 (42.3)	102 (0.8)

*NAR (Norway) use 100% ALBC in combination with SAP in pTKA. ALBC + SAP = ALBC in combination with SAP, DKR = The Danish Knee Arthroplasty Registry, KP = Kaiser Permanente Total Joint Replacement Registry, NAR = The Norwegian Arthroplasty Register, NZJR = The New Zealand Joint Registry, pTKA = primary total knee arthroplasty, PBC + SAP = Plain bone cement with SAP, and RAR = Romanian Arthroplasty Register.

Higher PJI revision rates were observed among TKAs with ALBC with 4-dose SAP (1.22%), followed by 2-dose (0.96%), 3-dose (0.96%), and 1-dose (0.86%) SAP (Table IV). Similarly, for the pTKAs with PBC + SAP, the rate for PJI was 0.92%, 1.00%, 1.24%, and 2.06% for 1, 2, 3, and 4 doses, respectively (Table IV).

Incidence of Revision for PJI

All registries reported a cumulative 1-year revision rate of <1% for PJI with ALBC + SAP ranging from 0.34% in RAR (Romania) to 0.80% in The Danish Knee Arthroplasty Registry (DKR) (Denmark) and NAR (Norway), as well as with PBC + SAP ranging from 0.54% in The New Zealand Joint Registry (New Zealand) to 0.69% in Romanian Arthroplasty Register (RAR) (Romania) (Fig. 2).

Results of Distributed Meta-Analyses

Four registries (n = 249,217) had sufficient pTKAs (n ≥ 100) in the 2 study groups (ALBC + SAP vs. PBC + SAP) (Table I), whereas only 2 registries (n = 74,043) recorded data on number of SAP doses within 24 hours explicitly (Table IV). Individual Cox regression analyses from each registry are reported in Supplement-Tables I and II. The Cox regression–based meta-analyses showed similar 1-year risk of PJI revision after pTKA with ALBC + SAP when compared with PBC + SAP (HRR = 1.21; 95% CI, 0.79-1.87) (Fig. 3), in addition to 3 months (1.21; 95% CI, 0.63-2.32), 5 years (1.11; 95% CI, 0.85-1.45), and 10 years (1.12; 95% CI, 0.85-1.48). However, substantial heterogeneity ($I^2 \geq 75\%$; p = 0.001) was observed in the meta-analyses in all 3 Cox models (Fig. 3 and Supplement-Figures 1 and 2).

In the subanalysis on number of SAP doses, the meta-analyses based on adjusted Cox regression found similar results in 1-year risk of PJI revision when comparing TKAs with ALBC + multiple doses SAP vs. ALBC + single dose SAP: 2 doses (0.95; 95% CI, 0.68-1.33), 3 doses (1.09; 95% CI, 0.64-1.87), and 4 doses (1.23; 95% CI, 0.69-2.21) (Fig. 4). However, higher risk of revision for PJI was observed in pTKAs with PBC + 4-dose SAP compared with 1-dose SAP (2.74; 95% CI, 1.11-6.75) (Table IV).

Sensitivity Analysis

The sensitivity analysis demonstrated that the results of the meta-analysis were consistent as individual registries were stepwise removed from the meta-analysis for risk of revision for PJI following pTKA (Supplement-Table III).

Discussion

This meta-analysis revealed similar risk of revision for PJI following pTKA with ALBC + SAP vs. PBC + SAP. In addition, similar risk of revision for PJI was observed in pTKAs when comparing ALBC + single vs. multiple doses of SAP, whereas higher risk of revision for PJI was observed in pTKAs with PBC + 4-dose SAP compared with 1-dose SAP.

The existing literature on the effectiveness of ALBC + SAP and the number of SAP doses used in primary joint arthroplasty remains inconclusive[5,6,22-25]. Two Norwegian register studies by Espehaug et al.[5] and Engesaeter et al.[6], involving 10,905 and 22,170 primary THAs, respectively, found that the use of ALBC + SAP reduced the risk of revision compared with PBC + SAP. Parvizi et al.[26], in their meta-analysis including 21,445 THAs, found that ALBC reduced the infection rate by approximately 50% compared with PBC. However, these studies are over 15 years old. Knowledge on importance of timing of SAP preoperatively[27], half-life of the antibiotic[28], reporting of revision for PJI, and the influence of tourniquet use and SAP has improved[27-30]. This time-dependent confounding may be some of the explanation for why our results, including the last decade, differ from earlier studies.

The present meta-analysis, however, revealed no difference in risk of PJI revision following TKAs between ALBC + SAP and PBC + SAP. In agreement with this study, 3 earlier studies[23,24,31] did not find reduced infection rates with ALBC compared with PBC. This lack of effectiveness of ALBC in reducing the risk of infection following pTKA was also shown in a large registry study by Bohm et al[25]. All patients in the abovementioned studies received SAP[23-25,31].

In contrast to this study, in their study on primary THAs from the NAR, Engesaeter et al.[6] reported the lowest risk of any revision for patients who received 4 doses of SAP, compared with patients who received 1, 2, or 3 doses. Several more

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TABLE IV Number (%) of Doses of SAP Used in pTKA With ALBC + SAP as Reported by KP and NAR (2010-2020)*

	KP				NAR		Pooled (KP + NAR)	
	ALBC + SAP		PBC + SAP		ALBC + SAP		ALBC + SAP	
No. of SAP Doses	Primary, n (%)	Revision for PJI, n (% Out of Primary)	Primary, n (%)	Revision for PJI, n (% Out of Primary)	Primary, n (%)	Revision for PJI, n (% Out of Primary)	Primary, n (%)	Revision for PJI, n (% Out of Primary)
Total, N	33,334	320 (0.96)	65,852	666 (1.01)	40,709	474 (1.16)	74,043	794 (1.07)
One day 1 dose (preoperatively)	8,052 (24.2)	69 (0.86)	20,726 (31.5)	190 (0.92)	1,780 (4.4)	16 (0.90)	9,832 (13.3)	85 (0.86)
One day 2 doses	17,648 (52.9)	173 (0.98)	38,583 (58.6)	386 (1.00)	1,374 (3.4)	10 (0.73)	19,022 (25.7)	183 (0.96)
One day 3 doses	3,915 (11.7)	37 (0.95)	2,668 (4.1)	33 (1.24)	2,017 (5.0)	20 (0.99)	5,932 (8.0)	57 (0.96)
One day 4 doses	1,586 (4.8)	13 (0.82)	291 (0.4)	6 (2.06)	32,853 (80.7)	407 (1.24)	34,439 (46.5)	420 (1.22)
One day ≥5 doses	211 (0.6)	3 (1.42)	124 (0.2)	4 (3.23)	1,547 (3.8)	19 (1.23)	1,758 (2.4)	22 (1.25)
Multiple dose (≥2-day doses)	1,922 (5.8)	25 (1.30)	3,459 (5.3)	47 (1.36)			1,922 (2.6)	25 (1.30)
Unknown					1,138 (2.8)	2 (0.18)	1,138 (1.5)	2 (0.18)

*ALBC = Antibiotic-loaded bone cement, KP = Kaiser Permanente Total Joint Replacement Registry, PBC = plain bone cement, PJI = periprosthetic joint infection, pTKA = primary total knee arthroplasty, NAR = The Norwegian Arthroplasty Register, and SAP = systemic antibiotic prophylaxis.

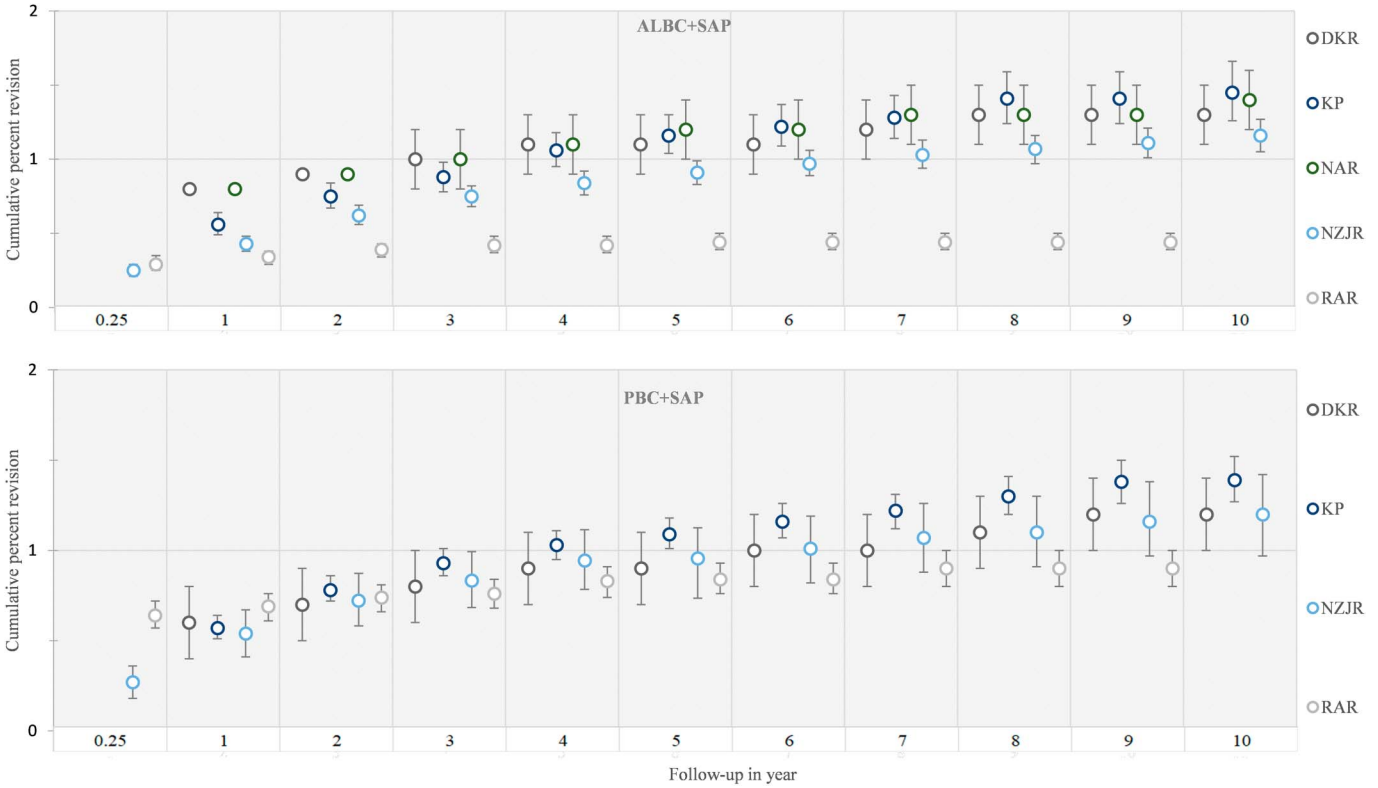

Fig. 2

Cumulative percent revision (one minus Kaplan-Meier) revision for PJI following pTKA with ALBC + SAP vs. PBC + SAP (2010-2020).[a] [a]NAR use 100% ALBC in combination with SAP. ALBC = Antibiotic-loaded bone cement, PBC = plain bone cement, PJI = periprosthetic joint infection, pTKA = primary total knee arthroplasty, and SAP = systemic antibiotic prophylaxis.

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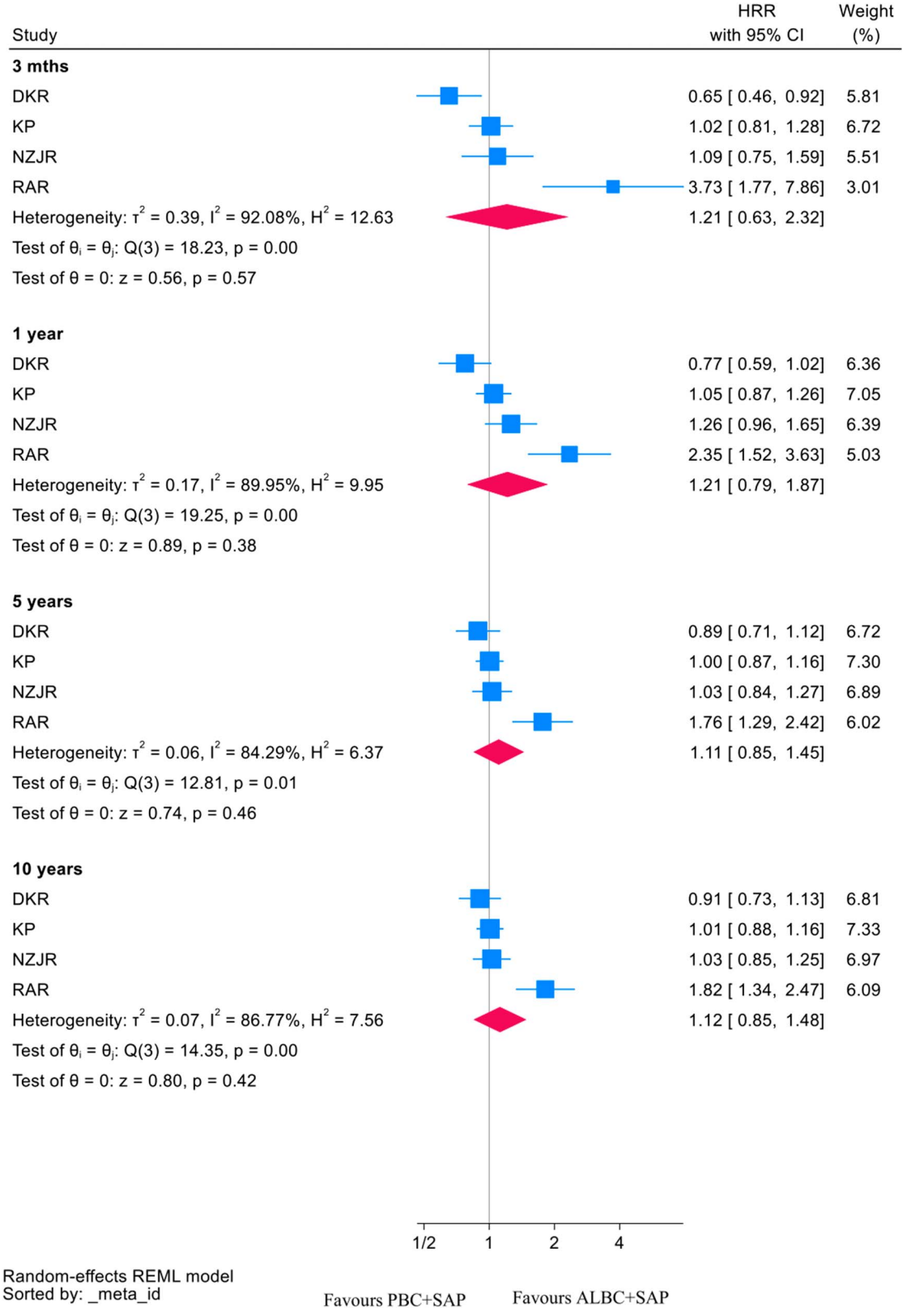

Fig. 3

Meta-analysis on risk of revision for PJI following pTKA with ALBC + SAP vs. PBC + SAP.[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 registeries weighted based on the number of cemented pTKA in the registry with PBC+SAP. ALBC = Antibiotic-loaded bone cement, PBC = plain bone cement, PJI = periprosthetic joint infection, pTKA = primary total knee arthroplasty, and SAP = systemic antibiotic prophylaxis.

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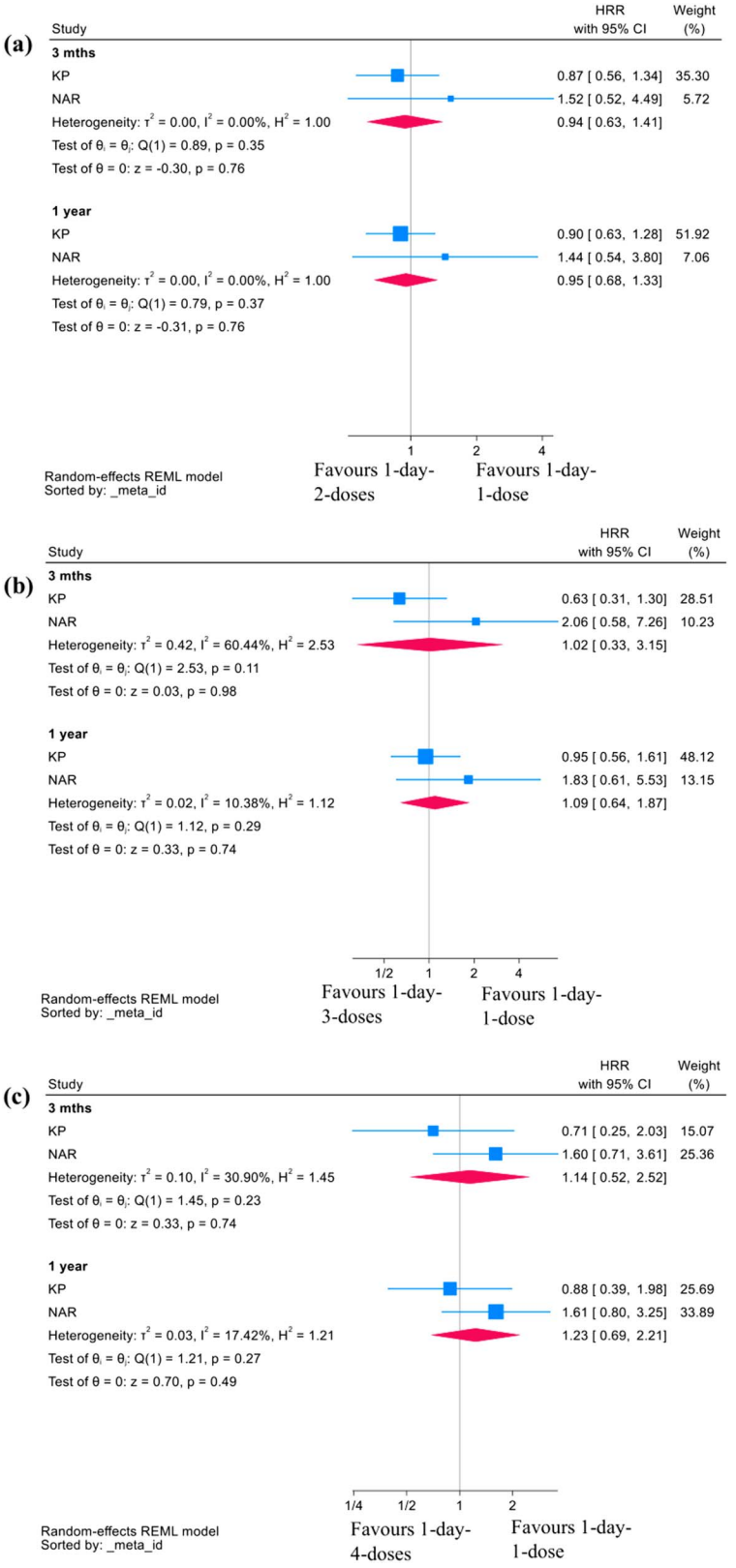

Fig. 4

Meta-analysis on risk of revision for PJI following pTKA with ALBC + SAP stratified for SAP doses.[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 registeries weighted based on the number of cemented pTKA in the registry with PBC+SAP. ALBC = Antibiotic-loaded bone cement, PJI = periprosthetic joint infection, pTKA = primary total knee arthroplasty, and SAP = systemic antibiotic prophylaxis.

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recent systematic reviews and meta-analyses on THAs and TKAs have not found evidence whether additional postoperative SAP doses are more efficient than one single preoperative dose in reducing the rates of PJI[3,32,33]. Recent studies from the Dutch Arthroplasty Register[34] and from the United States[35] reported no difference in the PJI rate between patients who received a single vs. multiple doses of SAP. In agreement with these studies[34-36], this study found a similar risk of PJI revision in TKAs with ALBC in combination with single dose vs. multiple doses of SAP. For pTKAs with PBC, we found that patients who received 4-dose SAP had higher risk of PJI revision compared with 1-dose SAP. Thornley et al.[3] in their systematic review and meta-analysis found higher incidence of PJI for multiple doses (3.1%) than a single dose (2.3%) SAP and concluded that additional postoperative SAP doses did not reduce the rates of infections. The plausible explanation for such higher risk of infection in pTKAs with PBC + 4-dose SAP could be attributed to a selection of high-risk cases to this group. This study, however, is consistent with World Health Organization and the US Center for Disease Control and Prevention recommendations against the usage of postoperative SAP and advocate for a single dose of SAP preoperatively[37,38].

Study Strength and Limitations

This is the largest international multi–register-based meta-analysis on use of ALBC + SAP vs. PBC + SAP in pTKAs ensuring the statistical power and generalizability of our findings. The study has several limitations. First, the completeness and validity of PJI revisions in the registries varied due to registration practice; however, it is unlikely differential related to exposure status. A recent study from the NAR found, however, high (87%) accuracy of surgeon-reported PJI revisions after hip arthroplasty[39], and the sensitivity of PJI revisions in the DKR was 58%[40].

Second, it is possible that there was a selection bias to use ALBC + SAP in pTKAs patients with higher risk of infection, which could potentially skew the results. However, we restricted our study population to only patients with osteoarthritis, to reduce the possible bias of ALBC being used selectively in patients at higher risk of infection, like those with rheumatoid arthritis or other inflammatory conditions. In addition, we adjusted for important confounders associated with the risk of PJI to compensate for this potential bias. However, the RAR lacked information on ASA and BMI, and the results from RAR was not controlled for these 2 clinically important risk factors of PJI. Patient case-mix may therefore be an explanation for the findings of ALBC effect in the RAR. In that case, it indicates that high-risk patients may benefit from ALBC.

Third, this study included data from different national registries with potentially different patient characteristics, comorbidities, surgical techniques, and perioperative protocols. This inherently makes it difficult to account for all confounding variables. Moreover, the 4 registries included in the meta-analyses all had high heterogeneity (I^2) ≥75. We used the random-effects models for meta-analysis considering that the number of procedures each registry contributes has a minor influence on the findings, diminishing potential inequality from the larger volume registries[20,41]. In addition, we assessed the meta-analysis results with sensitivity analysis of the individual registries[41] and found no change in estimates. Thus, we believe that heterogeneity between registries should not diminish the certainty of the findings.

Fourth, the registry data were reported immediately after surgery. This may result in misdiagnoses in reported cause for revision, e.g., revisions for aseptic loosening may be due to low-grade PJI; thus, revision for PJI is underreported[42]. PJI treated without exchange of tibia polyethylene (debridement, antibiotic, irrigation, and retention of the implant) is not reported[43,44]. However, we have no reason to believe that the misdiagnosis or underreporting affects the ALBC or PBC groups differently.

Finally, we had no information on type and dosage of the antibiotics in cement, timing and dosage of each dose of SAP, and whether the registries used stickers with bar codes and product numbers to identify the type of cement. Besides, the PBC + SAP dose analysis only included KP data. Furthermore, the study also lacks information on the cost of ALBC and SAP. Namba et al.[45] reported an extra cost of $308 for 2 bags of ALBC compared with PBC. In the United States, with 790,000 knee joint replacements annually and 30% ALBC use, one may save over $72 million yearly. Thus, there will be a need for further studies incorporating these variables.

Conclusion and Clinical Relevance

We found no evidence for effectiveness of ALBC + SAP use in pTKAs on reducing the risk of PJI revision compared with PBC + SAP. In addition, we found similar results for single and multiple SAP doses on the risk of PJI revision in pTKAs when used in combination with ALBC. Reduction of the use of postoperative SAP in pTKAs, without compromising the patient safety, will pose many advantages, including reduction of potential adverse events, such as drug allergy, drug intolerance, drug interaction, selection of resistant bacterial strains, and changes in the gut microbiota. No postoperative doses of SAP will also simplify patient logistics and subsequent cost. When SAP is used in combination with either ALBC or PBC, one single dose of SAP may be sufficient. However, further prospective, multicenter pragmatic randomized controlled trials investigating if the number of SAP doses can be reduced when ALBC or PBC is used in pTKAs or in uncemented pTKAs should be done. In addition, high-quality cost-effectiveness studies on the use of ALBC are warranted.

Appendix

eA Supporting material provided by the author is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A709). This content has not been copyedited or verified. ■

NOTE: The authors are grateful to all the registries participating in this study. The authors also thank all TKA patients for approving inclusion of personal information in respective registry databases as well as all the orthopedic surgeons for reporting their surgical cases to their respective registries.

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