Arthroplasty Today 33 (2025) 101694

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Original Research

Extended Oral Antibiotic Prophylaxis and Periprosthetic Joint Infection—Free Survivorship After Primary Total Hip Arthroplasty

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ARTICLE INFO

Article history:
Received 4 February 2025
Received in revised form
25 March 2025
Accepted 27 March 2025
Available online xxx

Keywords:
Infection
Hip
Outcomes
Arthroplasty
Joint

ABSTRACT

Background: Several studies have presented findings in favor of using extended oral antibiotic (EOA) prophylaxis to reduce periprosthetic joint infection (PJI) after primary total hip arthroplasty (THA) in patients at high risk for infection. To date, there is a paucity of evidence examining this topic from large retrospective databases. This study explored 90-day complication rates and 2-year PJI-free survivorship in a large cohort of patients receiving EOA prophylaxis after primary THA.

Methods: A large national database was used to identify patients undergoing primary THA from 2009 to 2022. Patients receiving 7-14 days of EOA were identified and propensity score–matched based on comorbidities to controls not receiving EOA and subsequently stratified into any-risk, high-risk, and standard-risk cohorts based on infection-related risk factors. Complication rates at 90 days were examined, and 2-year PJI-free survivorship was assessed employing Kaplan-Meier curves and Cox regression analysis further adjusting for comorbidity status.

Results: A total of 4153 patients receiving EOA prophylaxis after THA were identified. Of those patients, 2154 (52%) were considered high risk for PJI, while 1999 (48%) were considered standard risk. Significant reduction in hazards of PJI with administration of EOA was not seen at 90 days (any-risk: hazard risk [HR]: 0.75, 95% confidence interval [CI]: 0.42-1.35, $P = .3$; high-risk: HR: 0.85, 95% CI: 0.39-1.85, $P = .7$; standard-risk: HR: 1.29, 95% CI: 0.44-3.77, $P = .6$), 1 year (any-risk: HR: 0.99, 95% CI: 0.68-1.44, $P > .9$; high-risk: HR: 1.24, 95% CI: 0.77-1.99, $P = .4$; standard-risk: HR: 1.56, 95% CI: 0.73-3.33, $P = .3$), or 2 years (any-risk: HR: 1.02, 95% CI: 0.73-1.42, $P > .9$; high-risk: 1.25, 95% CI: 0.82-1.91, $P = .3$; standard-risk: HR: 1.10, 95% CI: 0.61-2.00, $P = .8$).

Conclusions: No significant increase in PJI-free survivorship at 90 days, 1 year, or 2 years was seen with EOA prophylaxis following primary THA. Reported PJI rates were low across all cohorts, irrespective of baseline risk. Further evidence is needed to adjudicate the efficacy of EOA prophylaxis after THA in addition to possible risks and appropriate indications for use.

Introduction

Although outcomes are generally favorable after total hip arthroplasty (THA), periprosthetic joint infection (PJI) is a serious complication, resulting in substantial morbidity, mortality, and socioeconomic implications [1-5]. Although estimates of 90-day incidence are 1.43%, incidence may be much higher in individuals with comorbidities such as morbid obesity and diabetes [6,7]. As the volume of THA is projected to increase in future years, PJI will continue to be of significant concern for surgeons. While preoperative medical optimization is critical in reducing infection risk, some risk factors may not be easily modifiable and complete optimization before surgery may not be feasible [8-10]. Consequently, use of extended oral antibiotic (EOA) prophylaxis following THA has been theorized as an additional measure for minimizing PJI in high-risk patients.

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https://doi.org/10.1016/j.artd.2025.101694

Initial evidence highlighted the utility of EOA after 2-stage revision to reduce risk of recurrent PJI [11-13]. Further application of EOA prophylaxis after primary total joint arthroplasty (TJA) has shown 4-fold to 5-fold decreases in PJI rates at 90 days and 1 year in high-risk cohorts from several institutions, although newer evidence has contradicted these findings [14-17]. EOA prophylaxis may also play a role after aseptic revision, although results have been mixed [16,18-21]. Despite the data favoring a role for EOA prophylaxis after primary TJA, additional evidence is needed to elucidate the benefits and risks of EOA prophylaxis.

The primary aim of this study was to examine the association of EOA prophylaxis after primary THA with PJI-free survivorship among cohorts stratified by infection risk. We also examined whether patients receiving EOA prophylaxis were at an increased risk of infection from *Clostridioides difficile*. We hypothesized that rates of PJI would be decreased in high-risk patients receiving EOA prophylaxis compared to matched controls, while no significant increases in *Clostridioides difficile* infection (CDI) would be seen.

Material and methods

Data source

The Merative MarketScan Commercial Claims and Encounters database and Medicare Supplemental and Coordination of Benefits database (Merative, Ann Arbor, MI) were used as the data source. These databases compile insurance claims from more than 300 employer-sponsored health plans and Medicare supplemental plans with more than 245 million unique patient records. As these databases contain no identifiable information, institutional review board approval was not deemed necessary.

Patient selection

All patients undergoing primary THA between January 1, 2009 and June 21, 2022 were identified using Current Procedural Terminology code 27130. Patients with a prior or bilateral THA were excluded to avoid reporting any complications that arose from a contralateral operation due to inconsistent laterality designators in the database (n = 31,641). Patients aged less than 18 years or more than 90 years (n = 1102), patients with a history of prior septic arthritis or infected hardware (n = 2186), patients with an active joint or soft tissue infection during index procedure (n = 95), and patients undergoing surgery for post-traumatic osteoarthritis or for acetabular or hip fracture were also excluded (n = 976). Additionally, patients without a minimum of 3 months of preoperative and postoperative enrollment were excluded (n = 91,326) to ensure a minimum follow-up of 3 months was captured. Of the 379,551 patients originally identified, 252,225 patients remained for inclusion prior to matching.

Extended oral antibiotic prophylaxis criteria

Patients were considered to have received EOA prophylaxis if they filled a prescription for a 7-14–day course of oral antibiotics within 5 days preoperatively or 3 days postoperatively. This method accounted for varying institutional protocols by capturing antibiotics filled both prior to surgery as well as immediately after surgery while minimizing risk of including prescriptions for surgical site or other infections that are unlikely to occur in this early period. Per precedence, the following antibiotics were included: cephalexin, cefadroxil, cefdinir, doxycycline, trimethoprim-sulfamethoxazole, and clindamycin [15,16,22].

Risk stratification and cohort selection

As in prior studies, patients were stratified by comorbidities conferring higher risk of PJI: body mass index > 35, diabetes mellitus, chronic kidney disease (CKD), autoimmune disease, active smoking, methicillin-resistant or methicillin-sensitive *Staphylococcus aureus* colonization, and other high-risk factors (ie, hepatitis C, chronic or recurrent cystitis, stasis dermatitis, and history of sepsis) [15]. Patients without these comorbidities were considered to be standard-risk. Patients were subsequently divided into 3 cohorts based on risk level, and each separately matched to controls—any-risk, high-risk only, and standard-risk only.

Baseline patient data and comorbidities

Baseline characteristics including sex, age, tobacco use, and alcohol use disorder were determined along with major common comorbidities such as coronary artery disease, CKD, hypertension, congestive heart failure, mood disorders, liver disease, anemia, and prior venous thromboembolism. Overall comorbidity burden was calculated using the Elixhauser Comorbidity Index (ECI) score for each patient, which employs a set of 30 comorbidities to predict morbidity and mortality [23]. International Classification of Diseases, Ninth Revision and 10th Revision codes that were assigned within 1 year of index THA were used to determine patient comorbidities.

A total of 4154 patients receiving EOA prophylaxis were obtained (Table 1). Prior to matching, EOA patients were younger (60 vs 62, $P < .001$), were composed of a higher proportion of women (53.9% vs 51.9%, $P = .01$), and had higher mean ECI (2.8 vs 2.6, $P < .001$). EOA patients also had higher rates of body mass index > 35 (21.2% vs 11.9%, $P < .001$), diabetes (20.9% vs 17.4%, $P < .001$), CKD (5.2 vs 4.4, $P = .01$), autoimmune disease (11% vs 9.1%, $P < .001$), active smoking (9.9% vs 8.6%, $P = .003$), and other high-risk comorbidities (5.2 vs 4.3, $P = .004$). After matching, ECI (2.1 vs 2.1, $P = .016$) and CKD (5.2% vs 4.1%, $P = .003$) only were significantly different between cohorts. When risk-stratified, there were 2154 matched EOAs and controls in the high-risk cohorts and 1999 matched EOAs and controls in the standard-risk cohorts (Table 2). Median follow-up time for controls was 543.5 days (interquartile range: 442) and median follow-up time for the EOA cohort was 452 days (interquartile range: 471). Median date of surgery for controls was January 6, 2018 (range: July 6, 2009-March 31, 2022) and December 7, 2018 (range: July 2, 2009-March 31, 2022) for EOA patients.

Postoperative complications

Rates of the following complications were queried at 90 days using International Classification of Diseases codes: PJI, superficial surgical site infection, CDI, noninfectious wound complications, deep vein thrombosis, pulmonary embolism, myocardial infarction (MI), pneumonia, sepsis, extended length of stay (LOS), and hospital readmission. Wound complications were defined to include diagnosis codes only related to delayed wound closure or wound dehiscence. Additionally, incidence of PJI at 2 years or latest last-known follow-up was collected.

Data analyses

Propensity score matching (1:1) was used, employing age, sex, infection-related high-risk comorbidities, coronary artery disease, hyperlipidemia, prior MI, prior ischemic stroke, and the comorbidities included in the ECI (Appendix A). Propensity scores were obtained by employing a logistic regression of the probability of

Table 1
Patient characteristics and risk factors: unmatched and matched any-risk cohorts.

Total	Unmatched cohorts			Matched cohorts		
	Control	EOA	*P* value[a]	Control	EOA	*P* value[a]
	248,071	4154		4153	4153	
Age (mean, range)	62 (19, 89)	60 (19, 89)	**<.001**	59 (20, 89)	60 (23, 89)	.5
Sex (n, %)			**.01**			.7
Male	119,225 (48.1)	1913 (46.1)		1900 (45.8)	1913 (46.1)	
Female	128,846 (51.9)	2241 (53.9)		2253 (54.2)	2240 (53.9)	
Elixhauser score (mean, SD)	2.6 (2.1)	2.8 (2.1)	**<.001**	2.7 (2.1)	2.8 (2.1)	**.016**
BMI > 35 (n, %)	29,605 (11.9)	880 (21.2)	**<.001**	894 (21.5)	880 (21.2)	.7
Diabetes (n, %)	43,267 (17.4)	868 (20.9)	**<.001**	829 (20.0)	867 (20.9)	.3
CKD (n, %)	10,863 (4.4)	216 (5.2)	**.01**	172 (4.1)	216 (5.2)	**.02**
Autoimmune (n, %)	22,614 (9.1)	457 (11.0)	**<.001**	407 (9.8)	456 (11.0)	.078
Active smoking (n, %)	21,205 (8.6)	410 (9.9)	**.003**	395 (9.5)	410 (9.9)	.6
MRSA/MSSA colonization (n, %)	1691 (0.7)	34 (0.8)	.3	30 (0.7)	34 (0.8)	.6
Other high risk (n, %)[b]	10,654 (4.3)	216 (5.2)	**.004**	194 (4.7)	215 (5.2)	.3

BMI, body mass index; CKD, chronic kidney disease; EOA, extended oral antibiotic; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SD, standard deviation.
Bolding is *P* value that achieved statistical significance ($P < .05$).
[a] Welch *t*-test, *Chi*-square test.
[b] Other high risk = hepatitis C, chronic cystitis, stasis dermatitis, or history of sepsis.

receiving EOA prophylaxis against the covariates listed above. All standardized mean differences were well below 0.1 after matching, indicating that adequate matching between cohorts was achieved, although small but statistically significant differences in ECI remained.

Patient characteristics and comorbidities data were compared using *Chi*-square tests for all categorical variables and independent 2-sample *t*-tests for all quantitative variables. Complication rates at 90 days were analyzed via McNemar's tests for matched pairs' design [24].

Survivorship curves were constructed using Kaplan-Meier analysis with significance determined by log-rank tests. Censoring took place at date of first PJI diagnosis or at the time of last available follow-up. Number of patients at risk was also included at interval increments of 6 months to report loss to follow-up. Differences in survival at 90 days, 1 year, and 2 years were assessed using Cox proportional hazards regression while employing ECI as an additional covariate in the models. The validity of the Cox proportional hazards models as well as the absence of significant interaction between covariates for all models were verified. All analyses used $P < .05$ as the significance threshold, and RStudio, version 4.2.3 was used to carry out data analysis (PBC, Boston, MA).

Results

At 90 days, PJI rates were not statistically significant between EOA or controls in any of the 3 cohort comparisons (Table 3) (any-risk: 1.4% vs 1.2%, $P = .44$; high-risk: 1.8% vs 1.3%, $P = .21$; standard-risk: 1.0% vs 0.6%, $P = .20$). There were also no significant differences in rates of superficial surgical site infection (any-risk: 1.2% vs 1.0%, $P = .45$; high-risk: 1.3% vs 1.3%, $P = > .9$; standard-risk: 1.0% vs 0.6%, $P = .38$) or CDI in any of the cohort comparisons (any-risk: 0.1% vs < 0.1%, $P = .72$; high-risk: < 0.1% vs < 0.1%, $P = > .9$; standard-risk: 0.2% vs 0%, $P =$ NA). In all 3 cohorts, rates of extended LOS were lower in EOA patients vs controls (extended LOS: any-risk: 10.4% vs 13.4%, $P < .001$; high-risk: 13.3% vs 16%, $P = .014$; standard-risk: 7.2% vs 10.8%, $P < .001$). There were no significant differences in wound complications,

Table 2
Patient characteristics and risk factors: matched high-risk and standard-risk cohorts.

Variable	High risk			Standard risk		
	Control	EOA	*P* value[a]	Control	EOA	*P* value[a]
	2154	2154		1999	1999	
Age (mean, range)	60 (21, 88)	60 (19, 89)	>.9	59 (19, 89)	60 (21, 89)	.5
Sex (n, %)			.7			.4
Male	948 (44.0)	961 (44.6)		950 (47.5)	952 (47.6)	
Female	1206 (56.0)	1193 (55.4)		1049 (52.5)	1047 (52.4)	
Elixhauser score (mean, SD)	3.6 (2.2)	3.8 (2.2)	.08	1.8 (1.4)	1.9 (1.5)	**.027**
BMI > 35 (n, %)	925 (42.9)	880 (40.9)	.2	0 (0)	0 (0)	-
Diabetes (n, %)	873 (40.5)	867 (40.2)	.9	0 (0)	0 (0)	-
CKD (n, %)	215 (10.0)	216 (10.0)	> .9	0 (0)	0 (0)	-
Autoimmune (n, %)	440 (20.4)	456 (21.2)	.5	0 (0)	0 (0)	-
Active smoking (n, %)	411 (19.1)	410 (19.0)	> .9	0 (0)	0 (0)	-
MRSA/MSSA colonization (n, %)	21 (1.0)	34 (1.6)	.08	0 (0)	0 (0)	-
Other high risk[b] (n, %)	191 (8.9)	215 (10.0)	.2	0 (0)	0 (0)	-

BMI, body mass index; CKD, chronic kidney disease; EOA, extended oral antibiotic; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; SD, standard deviation.
Bolding is *P* value that achieved statistical significance ($P < .05$).
[a] Welch *t*-test, *Chi*-square test.
[b] Other high risk = hepatitis C, chronic cystitis, stasis dermatitis, or history of sepsis.

Table 3
Univariate analysis of 90-day complication rates—stratified by infection risk.

Complication	Any risk			High risk			Standard risk		
	Control, n = 4153	EOA, n = 4153	*P* value[a]	Control, n = 2154	EOA, n = 2154	*P* value[a]	Control, n = 1999	EOA, n = 1999	*P* value[a]
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
PJI	49 (1.2)	58 (1.4)	.44	28 (1.3)	39 (1.8)	.21	11 (0.6)	19 (1.0)	.20
Superficial SSI	40 (1.0)	48 (1.2)	.45	28 (1.3)	29 (1.3)	> .9	13 (0.6)	19 (1.0)	.38
CDI	3 (<0.1)	5 (0.1)	.72	1 (<0.1)	1 (<0.1)	> .9	0 (0)	4 (0.2)	-
Wound complication	38 (0.9)	57 (1.4)	.06	28 (1.3)	40 (1.9)	.18	17 (0.8)	17 (0.8)	> .9
DVT	91 (2.2)	81 (2.0)	.49	64 (3.0)	48 (2.2)	.15	28 (1.4)	33 (1.6)	.61
PE	28 (0.7)	43 (1.0)	.09	22 (1.0)	30 (1.4)	.32	8 (0.4)	13 (0.6)	.38
MI	14 (0.3)	14 (0.3)	> .9	7 (0.3)	11 (0.5)	.48	3 (0.1)	3 (0.3)	> .9
Pneumonia	50 (1.2)	58 (1.4)	.49	39 (1.8)	40 (1.9)	> .9	19 (1.0)	18 (0.9)	> .9
Sepsis	28 (0.7)	34 (0.8)	.52	16 (0.7)	21 (1.0)	.51	5 (0.2)	13 (0.6)	.10
Extended LOS	557 (13.4)	430 (10.4)	**< .001**	344 (16.0)	286 (13.3)	**.014**	216 (10.8)	144 (7.2)	**< .001**
Readmission	300 (7.2)	264 (6.4)	.12	190 (8.8)	174 (8.1)	.41	105 (5.2)	90 (4.5)	.30

CDI, *Clostridioides difficile* infection; DVT, deep vein thrombosis; EOA, extended oral antibiotic; LOS, length of stay; MI, myocardial infarction; PE, pulmonary embolism; PJI, periprosthetic joint infection; SSI, surgical site infection.
Bolding is *P* value that achieved statistical significance ($P < .05$).
[a] McNemar's test.

deep vein thrombosis, pulmonary embolism, MI, pneumonia, sepsis, or readmission at 90 days in any of the cohorts.

Figures 1-3 depict Kaplan-Meier survivorship curves for the any-risk, high-risk, and standard-risk cohorts, respectively. The curves all demonstrated no statistically significant differences in survival at maximum follow-up of 2 years (Log-rank tests: any-risk: $P = .9$; high-risk: $P = .3$; low-risk: $P = .8$). Number at risk dropped precipitously from 1-2 years due to loss of follow-up. Cox regression models controlling for ECI (Tables 7-9) did not find a significant difference in adjusted hazard ratios (HRs) for PJI with administration of EOA prophylaxis at 90 days, 1 year, or 2 years (Table 4). In the any-risk cohorts, ECI was associated with increased hazards for PJI at all time points (90 days: HR: 1.18, 95% confidence interval [CI]: 1.08-1.28, $P < .001$; 1 year: HR: 1.17, 95% CI: 1.09-1.24, $P < .001$; 2 year: HR: 1.14, 95% CI: 1.07-1.21, $P < .001$). At 90 days, increasing ECI also had increased hazards for PJI in the standard-risk comparison (HR: 1.21, 95% CI: 1.03-1.41, $P = .019$). At 2 years, increasing ECI was also significant in the high-risk cohort (HR: 1.11, 95% CI: 1.02-1.22, $P = .023$).

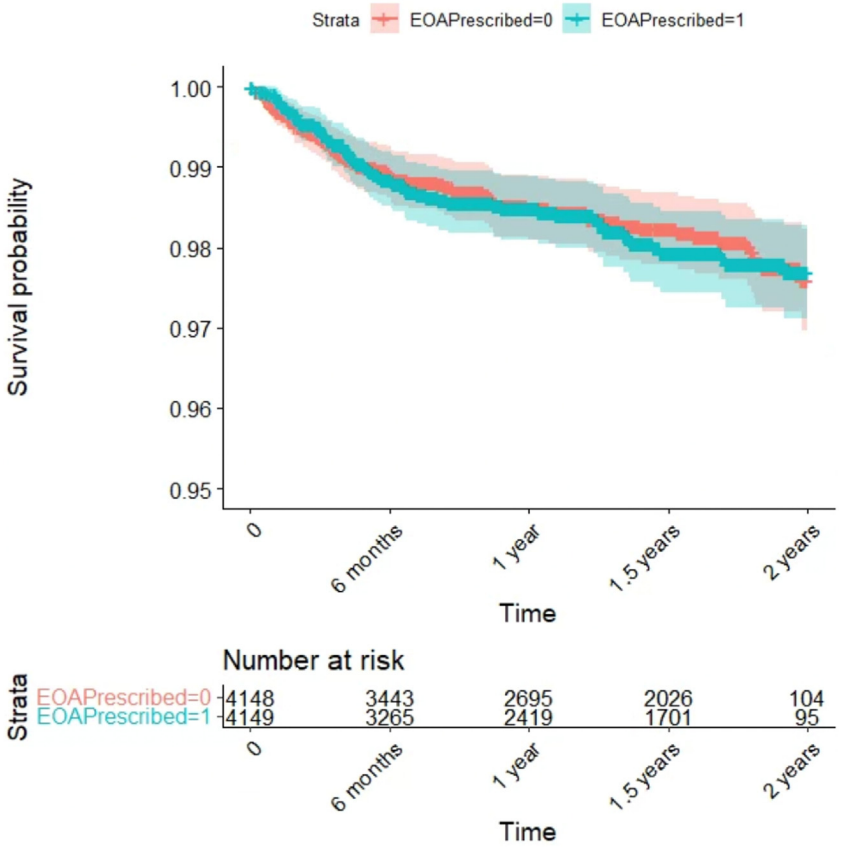

Figure 1. Two-year PJI-free survival curve—any-risk cohorts. PJI, periprosthetic joint infection.

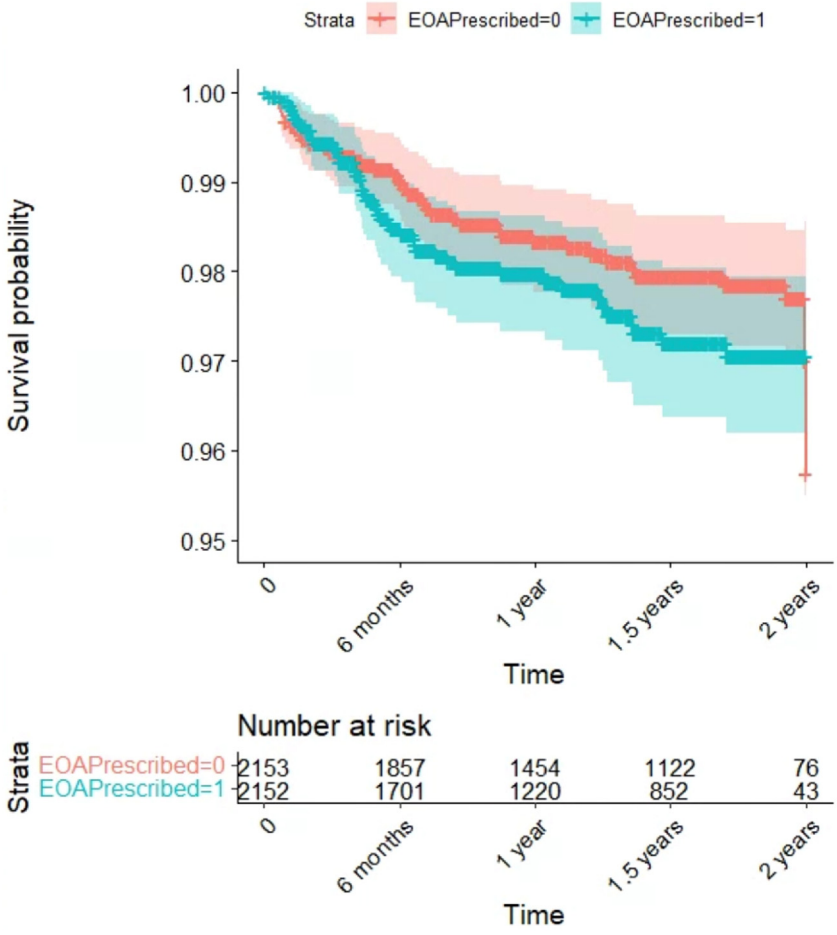

Figure 2. Two-year PJI-free survival curve—high-risk cohorts. PJI, periprosthetic joint infection.

Breakdown of antibiotics prescribed for EOA prophylaxis is included in Figure 4. The most commonly used antibiotic was cephalexin (39.0%) followed by cefadroxil (25.7%). Cefdinir was the least commonly used antibiotic (1.9%).

Discussion

In this large database study, we found no association of EOA prophylaxis with a significant increase in PJI-free survivorship at 90 days, 1 year, or 2 years after primary THA. Additionally, no signal was noted for significantly increased rates of CDI following administration of EOA prophylaxis.

Despite vastly improved quality of life and hip function in a majority of patients after THA, the development of PJI is associated with extensive morbidity and mortality [5,25]. In a concerted effort to reduce infection rates, EOA prophylaxis after TJA has become a promising intervention of focus in orthopaedic literature. Since 2018, several institutions have reported a clinically significant reduction in PJI with administration of EOA prophylaxis in high-risk individuals. Two studies found a 4-fold and 3.4-fold increase in PJI rates at 90 days and 1 year, respectively, in high-risk patients who did not receive EOA prophylaxis [14,15]. Other institutions have followed suite, some reporting congruent findings [16] and others reporting no difference [17]. Given the potential harms associated with increased antibiotic use and evidence limited to relatively small, institutional data, further data are needed to adjudicate the role of this protocol in joint arthroplasty.

This study did not find a significant association with reduced PJI rates at 90 days, 1 year, or 2 years with administration of EOA prophylaxis. Overall infection rates were observed to be well in line with the literature; however, rates in the high-risk cohorts were only moderately increased compared to the standard-risk cohorts (high-risk at 90 days: 1.3% and 1.8% in controls and EOA, respectively, vs standard risk at 90 days: 0.6% and 1.0%). In contrast, 2 of the major studies examining EOA reported PJI rates of 4.3% in high-risk patients not receiving EOA vs 1.1% in high-risk EOA patients at 90 days after THA [14,15]. The lack of concordance in PJI rates observed in high-risk patients between studies is unexpected as similar criteria were used to determine risk level between studies. Potential explanation for these differences may include difference in the severity of high-risk conditions among the cohorts between studies, yielding substantially different infection rates. Their influence has been shown to have numerous mediating factors such as illness severity, duration, or disease control that modulates infection risk and likely varies among study cohorts [26-30]. The low PJI rates in our study may also be a result of decreased sensitivity for PJI using an insurance claims database, although they are in line with most estimates in the literature outside of studies examining EOA prophylaxis and recent evidence has demonstrated excellent accuracy for identification of infection in similar databases [31,32]. The exceptionally high rates of PJI in cohorts described by studies supporting the use of EOA may also be a reflection of relatively smaller sample sizes and regression to the mean as more recent evidence has been mixed on the topic [17,19,20].

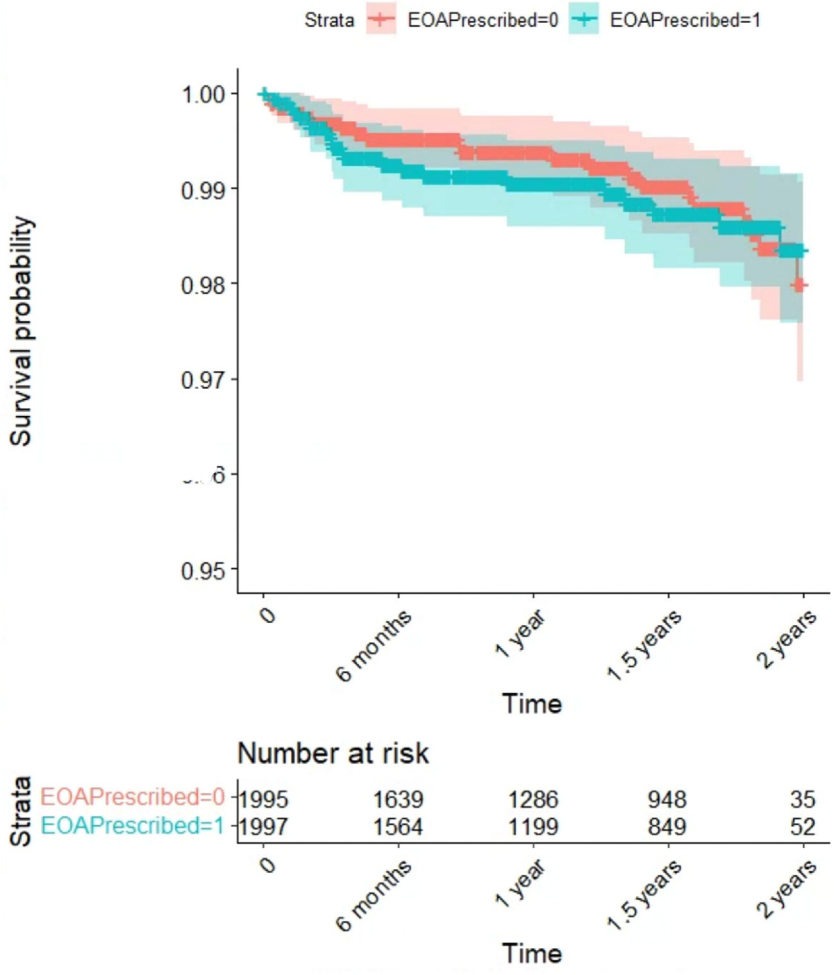

Figure 3. Two-year PJI-free survival curve—standard-risk cohorts. PJI, periprosthetic joint infection.

Despite the potential benefits, concerns exist regarding the rapid expansion of extended antibiotic use leading to increased antibiotic resistance and cases of CDI [15]. Antibiotic resistance is a theoretical concern in patients who develop PJI despite EOA prophylaxis. Prior exposure to extended courses of antibiotics might alter the microbiology and treatment of subsequent infections [33,34]. Using a retrospective database design, we were unable to determine whether antimicrobial resistance was seen in PJI cases following EOA administration in this study. While prior studies on this topic have not found substantially increased resistance profiles following EOA prophylaxis, further work is needed to better understand this risk [22]. Furthermore, although CDI is a rare complication of primary TJA, with an approximate incidence of 0.1%, even single doses of a third-generation cephalosporin have been reportedly shown to increase risk after surgery [35]. As patients who receive EOA prophylaxis are likely to possess multiple

Table 4
Cox proportional hazards regression models for risk of PJI after TKA—stratified by infection risk.

Characteristic	90 days			1 year			2 years		
	HR[a]	95% CI[b]	*P* value	HR[a]	95% CI[b]	*P* value	HR[a]	95% CI[b]	*P* value
Any risk									
EOA prescribed	0.75	0.42-1.35	.3	0.99	0.68-1.44	> .9	1.02	0.73-1.42	> .9
ECI	1.18	1.08-1.28	< **.001**	1.17	1.09-1.24	< **.001**	1.14	1.07-1.21	< **.001**
High risk									
EOA prescribed	0.85	0.39-1.85	.7	1.24	0.77-1.99	.4	1.25	0.82-1.91	.3
ECI	1.10	0.95-1.27	.2	1.10	0.99-1.22	.076	1.11	1.02-1.22	**.023**
Standard risk									
EOA prescribed	1.29	0.44-3.77	.6	1.56	0.73-3.33	.3	1.10	0.61-2.00	.8
ECI	1.21	1.03-1.41	**.019**	1.03	0.87-1.23	.7	0.98	0.82-1.18	.9

CI, confidence interval; ECI, Elixhauser Comorbidity Index; EOA, extended oral antibiotic; HR, hazard ratio; PJI, periprosthetic joint infection; TKA, total knee arthroplasty. Bolding is *P* value that achieved statistical significance ($P < .05$).

[a] Hazard ratio.

[b] Confidence interval.

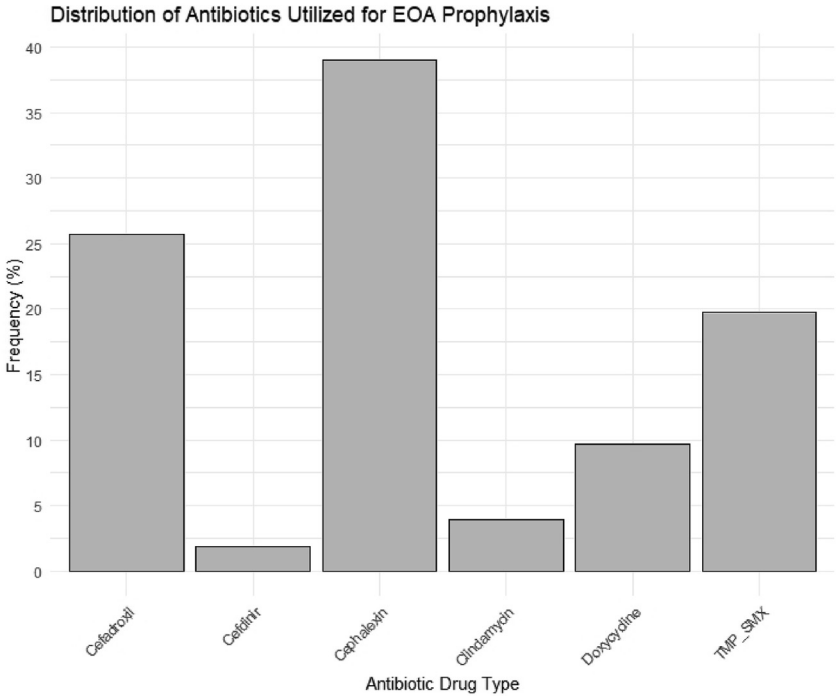

Figure 4. Distribution of antibiotics given for EOA prophylaxis by drug type. EOA, extended oral antibiotic.

comorbidities that place them at elevated baseline risk for CDI, EOA could further increase risk of these severe infections [36]. Fortunately, both past evidence and present study have not found increased rates of CDI following EOA administration, suggesting that this is not a substantial concern, especially given antibiotics generally used [37]. However, surgeons using EOA prophylaxis in their practice should remain vigilant for this complication and consider use of antibiotics with lower risk of CDI as appropriate [37].

Unexpectedly, rates of extended LOS were consistently lower in the EOA cohorts compared to controls. While reasons for readmission were not examined, patients who were prescribed EOA prophylaxis did undergo surgery more recently than controls due to the relatively newer implementation of this protocol. Over the past decade, efforts have been made to decrease LOS and increase same-day discharges after TJA [38]. Consequently, the decreased extended LOS observed in the EOA cohorts might be due to the recency of surgery rather than by the influence of EOA prophylaxis itself, particularly given that no other significant differences in 90-day outcomes were seen between cohorts.

This study is the first to our knowledge examining association of EOA prophylaxis with infection rates after primary THA in a large database, leading to increased power and external validity. Another notable strength of this study is the use of robust statistical methods to control for established infection-related risk factors that were not accounted for in previous studies including cardiovascular disease, alcohol use disorder, anemia, malnutrition, and depression [15]. Comorbidity-matched cohorts and further adjustment for overall comorbidity status allowed a better analysis of EOA prophylaxis in patients of similar risk. Survivorship analysis to 2 years was also conducted, which is the longest follow-up period investigated by contemporary studies on this topic, to our knowledge.

However, there are critical limitations from this study design to consider when drawing conclusions from this study. Use of a database to determine incidence of PJI may have resulted in underestimation of PJI rates due to reduced sensitivity, which has been well described in the literature [7]. Furthermore, the authors lacked access to critical clinical data regarding the severity of comorbidities, preventing precise matching based on true risk level. As a result, patients receiving EOA prophylaxis may have been at substantially higher risk of infection than matched patients in the control group, resulting in the absence of any observable correlation seen between EOA protocols and reduced PJI rates. Similarly, clinical data related to specific institutional infection prevention protocols and infection outcomes such as intravenous antibiotic regimens, use of antibiotic-loaded bone cement, culture results, and antibiotic sensitivity profiles were not available for analysis, which are critical in assessing possible hidden confounders as well as other potential risks of EOA after primary THA. Finally, as noted in the survival analysis, significant loss to follow-up was observed in all cohorts between 1 and 2 years, likely due to the relative recency of surgery in patients receiving EOA. However, secondary analysis revealed that informative censoring did not occur between control and EOA cohorts and loss to follow-up was similar between cohorts. Nevertheless, slightly imbalanced loss to follow-up among patients receiving EOA prophylaxis due to intrinsically poorer health may have decreased the internal validity of the survivorship analysis.

Conclusions

No observable association was seen between administration of EOA prophylaxis and a significant reduction in PJI-free survivorship to 2 years after primary THA in this study. In light of prior evidence supporting its ability to reduce infection rates in high-risk

populations and the inherent limitations of this study design, the findings of this research do not preclude the potential efficacy of EOA prophylaxis in lowering PJI rates in specific patient populations. However, given the mixed evidence regarding the efficacy of EOA prophylaxis, additional research in the form of randomized controlled trials is needed to assess the true risks and benefits of EOA prophylaxis and clarify the appropriate indications for its use. Considering the paucity of current evidence supporting its use in standard-risk patients, the potential benefits of EOA prophylaxis must be carefully weighed against the potential risks associated with increased antibiotic exposure.

Conflicts of interest

Jacob M. Wilson is a paid consultant for Zimmer Biomet and holds stock or stock options in Accupredict. Ajay Premkumar holds stock or stock options in Accujoint, Osgenic, and Azra Care. All other authors declare no potential conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2025.101694.

CRediT authorship contribution statement

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Appendix

Appendix A
Variables entered in propensity score match.

Age	HTN
Sex	Paralysis
CHF	Neurological disorders
Arrhythmia	Chronic pulmonary disease
Valvular disease	Diabetes mellitus
Pulmonary circulation disorders	Hypothyroidism
PVD	Renal failure
Alcohol use	Drug use
Active smoking	CKD
Chronic cystitis	Stasis dermatitis
HLD	Prior ischemic stroke
Liver disease	Alcohol use
PUD	Obesity
HIV/AIDS	Weight loss
Lymphoma	Fluid/electrolyte disorders
Metastatic cancer	Depression
Solid tumor	Blood loss anemia
Obesity	Iron deficiency anemia
Psychosis	Autoimmune disease
MRSA/MSSA colonization	Hepatitis C
History of sepsis	CAD
Prior MI	Elixhauser Comorbidity Index

AIDS, acquired immunodeficiency syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; HIV, human immunodeficiency virus; HLD, hyperlipidemia; HTN, hypertension; MI, myocardial infarction; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PUD, peptic ulcer disease; PVD, peripheral vascular disease.