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Extended oral antibiotic prophylaxis and PJI-free survivorship after primary total knee arthroplasty

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ABSTRACT

Introduction: Recent evidence has emerged supporting the use of extended oral antibiotic (EOA) prophylaxis after primary total knee replacement (TKA) to reduce periprosthetic joint infection (PJI) in high-risk patients. However, much of the evidence stems from single-institution series with limited sample sizes. This study aimed to explore the impact of EOA on complications and infection-free survivorship in a large cohort of patients after primary TKA.

Methods: A large national database was used to identify patients undergoing primary TKA from 2015 to 2022. Patients receiving 7–14 days of EOA were identified. Propensity-score matching, based on patient comorbidities, was used to match patients who received EOA and to control patients who did not. Three cohorts were created: any-risk, high-risk, and standard-risk. Complications at 90-days were assessed with univariate analysis and survivorship free of PJI to 2 years was analyzed with the Kaplan-Meier method and cox regression.

Results: We identified 5,701 patients who received EOA: 3,628 (64%) with high-risk comorbidities and 2,073 (36%) standard risk. There were no significant reduction in hazard of PJI at 90-days (any-risk: HR: 1.65, 95% CI: 0.90–3.04, $P = 0.11$; high-risk: HR: 1.37, 95% CI: 0.69–2.70, $P = 0.4$; standard-risk: HR: 1.51, 95% CI: 0.53–4.26, $P = 0.4$), 1 year ($P > 0.07$), or 2 years (any-risk: HR: 1.42, 95% CI: 0.98–2.05, $P = 0.065$; high-risk: HR: 1.14, 95% CI: 0.76–1.73, $P = 0.5$; standard-risk: HR: 1.51, 95% CI: 0.76–2.98, $P = 0.2$) with EOA administration.

Discussion: EOA prophylaxis was not associated with improved PJI-free survivorship at any measured time point following primary TKA in either high-risk or standard-risk risk patients. Given the observed widespread use of EOA, our study highlights the need for further investigation to delineate what specific populations may benefit from EOA prophylaxis.

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1. Introduction

Periprosthetic joint infection (PJI) is a devastating complication that occurs in an estimated 0.2–2% of cases after primary total knee arthroplasty (TKA) and is associated with increased patient morbidity and mortality [1–6]. Despite low overall incidences, PJI rates have been reported to approach 10% in certain, high-risk, populations [7]. Despite extensive preoperative optimization efforts, the risk imparted by comorbidities cannot always be completely eliminated [8,9].

Given this, along with the severe implications of PJI when they do occur, the potential role for extended oral prophylactic antibiotics (EOA) after total joint arthroplasty (TJA) has been recently explored. Recent, single institution studies have demonstrated up to four- to five-fold decreases in infection rate at both 90-days and 1 year after primary total joint arthroplasty in select, high-risk patients prescribed EOA [10–12]. However, a number of other studies have reported no differences in PJI rates following primary or revision total joint arthroplasty [10,13–17].

Considering this discrepancy among the relatively few studies exploring EOA prophylaxis, more evidence is needed to clarify the role of EOA following primary TKA. Therefore, the purpose of this study was to examine, using national data, the association of EOA prophylaxis after primary TKA with PJI-free survivorship in both high- and low-risk patients. Secondarily, we sought to determine whether patients receiving EOA prophylaxis were at an increased risk of infection from *Clostridioides difficile* (CDI). We hypothesized that rates of PJI at all time points would be decreased in patients receiving EOA prophylaxis with no significant increases in CDI.

2. Methods

2.1. Data source

The Merative MarketScan Commercial Claims and Encounters database and Medicare Supplemental and Coordination of Benefits database (Merative., Ann Arbor, MI) were utilized for this study. These databases are comprised of insurance claims data from over 300 employer-sponsored and Medicare supplemental health plans with over 245 million individual patient records. IRB approval was not needed for this study given use of deidentified data.

2.2. Patient selection

All patients undergoing primary TKA between January 1, 2015 and June 30, 2022 were identified using Current Procedural Terminology (CPT) code 27447. Patients with a prior or bilateral TKA were excluded to avoid reporting of complications that arose from a contralateral operation due to inconsistent designation of laterality in the database (n = 42,965). Additionally, patients less than 18 years of age or greater than 90 years of age (n = 354), those with a history of prior joint infection or infected orthopaedic hardware (n = 4,313), patients with an active joint or soft tissue infection at time of surgery (n = 3), and those who underwent TKA for indications of posttraumatic osteoarthritis, fracture, or conversion TKA (from prior UKA) were also excluded (n = 3393) [18,19]. We also excluded any patient without a minimum of 3 months of continuous pre- and postoperative enrollment (n = 51,006). The remaining 193,925 patients were eligible for inclusion in the study.

2.3. Extended oral antibiotic prophylaxis selection

Patients were considered to have received extended oral antibiotic prophylaxis if they received a prescription for a 7–14 day course of oral antibiotics filled between 5 days of surgery preoperatively and 3 days postoperatively. This method accounted for varying institutional prescribing protocols for perioperative prescriptions while minimizing the risk of including antibiotic prescriptions for postoperative wound or other infections as these are unlikely in the first few acute postoperative days. The following antibiotics were identified using National Drug Codes and included as they have been utilized in prior studies on EOA prophylaxis: cephalexin, cefadroxil, doxycycline, trimethoprim-sulfamethoxazole (TMP-SMX), and clindamycin. Cefdinir was excluded as this drug comprised less than 1% of all antibiotics given for EOA prophylaxis.

2.4. Risk stratification and cohort selection

Patients were stratified by risk identified by the presence of diagnosis codes for comorbidities conferring higher risk of PJI per precedence [12]. Patients were assigned to the high risk cohort if they possessed one or more of the following comorbidities: body mass index (BMI) > 35, an active diagnosis of diabetes mellitus, chronic kidney disease (CKD), autoimmune disease, active smoking, methicillin resistant (MRSA) or methicillin sensitive (MSSA) *Staphylococcus aureus* colonization, or other high risk factors (i.e. hepatitis C, chronic or recurrent cystitis, stasis dermatitis, and history of sepsis) [12]. Patients without these comorbidities were labeled as standard risk. Patients were subsequently divided into 3 different cohorts for comparisons and each separately matched to controls (i.e. patients who did not receive EOA) – any-risk (both high- and standard-risk patients), high-risk only, and standard-risk only.

2.5. Baseline patient data and comorbidities

Baseline characteristics including sex, age, and tobacco and alcohol use were extracted from the database along with common comorbidities such as coronary artery disease (CAD), chronic kidney disease (CKD), hypertension (HTN), congestive heart failure (CHF), mood disorders, liver disease, and prior venous thromboembolism (VTE). Overall comorbidity burden was determined by calculating the Elixhauser Comorbidity Index (ECI) score for each patient, which employs a set of 30 comorbidities to stratify patient comorbid status [20]. ICD codes active within 1 year of the index operation were used to assign comorbidities.

Among included patients, 5,702 (3%) received EOA and 188,223 did not (Table 1). Prior to matching, there were small, but significant differences between cohorts. EOA patients were younger (61 vs 62, $P < 0.001$), more often men (42 vs 40%, $P = 0.003$), and had statistically higher Elixhauser Comorbidity Index (ECI) scores (3.3 vs 3.2, $P < 0.001$). EOA patients also had higher rates of BMI > 35 (34 vs 25%, $P < 0.001$), diabetes (27 vs 24%, <0.001), autoimmune disease (12 vs 10%, $P < 0.001$), and active smoking (7.9 vs 7.1%, $P = 0.013$). Following matching, 5,701 EOA patients were matched to 5,701 controls in the any-risk cohort. Only Elixhauser Comorbidity Index 3.3 vs 3.1, $P < 0.001$) and other high-risk comorbidities (6.2 vs 4.9%, P = 0.003) were significantly different between cohorts after matching. When stratified by risk, there were 3,628 matched EOAs and controls in the high-risk cohort and 2,073 matched EOAs and controls in the standard-risk cohort (Table 2).

2.6. Postoperative complications

Complication rates of the following were queried at 90-days using ICD-10 diagnostic codes: prosthetic joint infection (PJI), superficial surgical site infection (SSI), C. *difficile* infection (CDI), noninfectious wound complications, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), pneumonia, sepsis, extended length of stay (LOS), and readmission. Wound complications were defined as delayed wound closure or wound dehiscence. Occurrence of PJI was collected out to 2 years or until last known follow-up in those without available 2-year follow-up.

2.7. Data analyses

Propensity score matching (1:1) was used to match EOA patients and controls based on the following: age, sex, infection-related high-risk comorbidities, coronary artery disease (CAD), hyperlipidemia, prior MI, prior ischemic stroke, and the comorbidities included in the Elixhauser comorbidity index (Appendix A) [21]. After matching, all standardized mean differences were below 0.1, indicating that adequate matching was achieved. Despite this, small but statistically significant differences in ECI remained.

Collected demographic and comorbidities data was compared using *Chi*-square test for categorical variables and independent two-sample *t*-tests for quantitative variables. Similarly, postoperative outcomes at 90 days were analyzed using *McNemar's* tests for matched pairs design [22].

Survivorship free of PJI was evaluated using Kaplan-Meier analysis, and significance was determined via log-rank tests. Patients were censored at occurrence of PJI or at the time of last available follow-up. The number of patients remaining at risk were also included at interval increments of 6 months. Differences in survival at 90 days, 1 year, and 2 years were assessed using Cox proportional hazards regression accounting for ECI as an additional covariate. Due to violations of the proportionality assumptions for ECI in the any-risk cohort, a time-transformed ECI covariate was added to the final models

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

	Unmatched			Matched Cohorts		
	Control	EOA	*P*-value	Control	EOA	*P*-Value
Total	188,223	5,702		5,701	5,701	
Age (Mean, range)	62 (19,89)	61 (23,89)	**<0.001**	61 (19,89)	61 (23,89)	0.5
Sex (*n*, %)			**0.003**			0.7
Male	76,133 (40)	2,418 (42)		2,400 (42)	2,418 (42)	
Female	112,090 (60)	3,284 (58)		3,301 (58)	3,283 (58)	
Elixhauser Score (mean, sd)	3.2 (2.1)	3.3 (2.2)	**<0.001**	3.1 (2.1)	3.3 (2.2)	**<0.001**
BMI > 35 (*n*, %)	46,955 (25)	1,933 (34)	**<0.001**	1,963 (34)	1,932 (34)	0.5
Diabetes (*n*, %)	44,862 (24)	1,555 (27)	**<0.001**	1,476 (26)	1,554 (27)	0.10
CKD (*n*, %)	10,833 (5.8)	357 (6.3)	0.11	366 (6.4)	357 (6.3)	0.7
Autoimmune (*n*, %)	19,453 (10)	675 (12)	**<0.001**	656 (12)	674 (12)	0.6
Active Smoking (*n*, %)	13,278 (7.1)	451 (7.9)	**0.013**	452 (7.9)	451 (7.9)	> 0.9
MRSA/MSSA colonization (*n*, %)	2,223 (1.2)	70 (1.2)	0.7	54 (0.9)	70 (1.2)	0.15
Other High Risk (*n*, %)	11,480 (6.1)	355 (6.2)	0.7	282 (4.9)	354 (6.2)	**0.003**

BMI = Body Mass Index, CKD = Chronic Kidney Disease, MRSA = Methicillin Resistant *Staphylococcus aureus*, MSSA = Methicillin Sensitive *Staphylococcus aureus*.

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

	High-Risk			Standard-Risk		
	Control	EOA	*P*-value	Control	EOA	*P*-value
Variable	3,628	3,628		2,073	2,073	
Age (Mean, range)	60 (27,89)	60 (23,89)	>0.9	61 (22,89)	61 (30,89)	0.5
Sex (*n*, %)			>0.9			0.4
Male	1,482 (41)	1,486 (41)		904 (44)	931 (45)	
Female	2,146 (59)	2,142 (59)		1,169 (56)	1,142 (55)	
Elixhauser Score (mean, sd)	3.8 (2.1)	4.0 (2.2)	**<0.001**	2.0 (1.5)	2.1 (1.6)	**0.020**
BMI > 35 (*n*, %)	1,954 (54)	1,933 (53)	0.6	0 (0)	0 (0)	–
Diabetes (*n*, %)	1,476 (41)	1,555 (43)	0.060	0 (0)	0 (0)	–
CKD (*n*, %)	326 (9.0)	357 (9.8)	0.2	0 (0)	0 (0)	–
Autoimmune (*n*, %)	705 (19)	675 (19)	0.4	0 (0)	0 (0)	–
Active Smoking (*n*, %)	450 (12)	451 (12)	>0.9	0 (0)	0 (0)	–
MRSA/MSSA colonization (*n*, %)	73 (2.0)	70 (1.9)	0.8	0 (0)	0 (0)	–
Other High Risk[a] (*n*, %)	323 (8.9)	355 (9.8)	0.2	0 (0)	0 (0)	–

BMI = Body Mass Index, CKD = Chronic Kidney Disease, MRSA = Methicillin Resistant *Staphylococcus aureus*, MSSA = Methicillin Sensitive *Staphylococcus aureus*.
[a] Other High Risk = Hepatitis C, Chronic Cystitis, Stasis Dermatitis, or History of Sepsis.

to correct for this violation and ensure validity of the model. There were no statistically significant interactions between covariates. All analyses utilized $P < 0.05$ as the significance threshold. Data analysis was performed using R Studio, Version 4.2.3 (PBC, Boston, MA).

3. Results

At 90 days, rates of PJI were not statistically significant between EOA or controls in any of the 3 cohort comparisons (Table 3) (any-risk: 0.7 vs 0.5%, $P = 0.12$; high-risk: 0.8 vs 0.7%, $P = 0.89$; standard-risk: 0.7 vs 0.3%, $P = 0.19$). There were also no significant differences in rates of superficial SSI (any-risk: 0.4 vs 0.3%, $P = 0.51$; high-risk: 0.4 vs 0.2%, $P = 0.26$; standard-risk: 0.4 vs <0.1%, $P = 0.11$) or *C. difficile* infection (any-risk: 0.2 vs 0.2%, $P = 0.54$; high-risk: <0.1 vs 0.1%, $P = 0.45$; standard-risk: 0.4 vs < 0.1%, $P = 0.11$). Compared to control patients, there were higher rates of wound complications in the EOA any-risk and high-risk cohorts (any-risk: 1.6 vs 1.1%, $P = 0.024$; high-risk: 1.6 vs 0.9%, $P = 0.012$). In all 3 cohorts, rates of extended LOS (any-risk: 8.3 vs 16%, $P < 0.001$; high-risk: 8.2 vs 18%, $P = 0.016$; standard-risk: 8.5 vs 12%, $P < 0.001$) and readmission (any-risk: 4.9 vs 6.6%, $P < 0.001$; high-risk: 5.7 vs 7%, $P = 0.016$; standard-risk: 3.5 vs 5.1%, $P = 0.009$) were lower in EOA vs controls. There were no significant differences in DVT, PE, MI, pneumonia, or sepsis at 90 days in any of the cohorts.

Kaplan-Meier survivorship free of PJI for any-risk, high-risk, and standard-risk patients is depicted in Figures 1–3, respectively. Cox regression analysis, controlling for Elixhauser Comorbidity Index, did not find a significant difference in PJI-free survivorship at 90 days, 1 year, or 2 years with administration of EOA prophylaxis in any of the cohorts (Table 4). Contrarily, at all-time points, increasing ECI significantly increased the hazard of PJI in the any-risk cohorts (90 days: HR:1.20, CI:1.08–1.32, $P < 0.001$); 1-year: HR:1.19, CI:1.04–1.37, $P = 0.010$, 2-year: HR:1.20, CI:1.08–1.32, $P < 0.001$). At 2 years, ECI was also significant for the low-risk cohorts (HR:1.23, 95% CI:1.03–1.47, $P = 0.023$).

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

Complication	Any-Risk			High-Risk			Standard-Risk		
	Control *N* = 5,701 *n* (%)	EOA *N* = 5,701 *n* (%)	*P*-Value[1]	Control *N* = 5,701 *n* (%)	EOA *N* = 5,701 *n* (%)	*P*-Value[1]	Control *N* = 2,073 *n* (%)	EOA *N* = 2,073 *n* (%)	*P*-Value[1]
PJI	28 (0.5)	42 (0.7)	0.12	26 (0.7)	28 (0.8)	0.89	7 (0.3)	14 (0.7)	0.19
Superficial SSI	16 (0.3)	21 (0.4)	0.51	7 (0.2)	13 (0.4)	0.26	2 (<0.1)	8 (0.4)	0.11
CDI	14 (0.2)	10 (0.2)	0.54	5 (0.1)	2 (<0.1)	0.45	2 (<0.1)	8 (0.4)	0.11
Wound Complication	63 (1.1)	92 (1.6)	**0.024**	34 (0.9)	59 (1.6)	**0.012**	19 (0.9)	33 (1.6)	0.071
DVT	157 (2.8)	129 (2.3)	0.10	92 (2.5)	88 (2.4)	0.82	54 (2.6)	41 (2.0)	0.21
PE	55 (1.0)	51 (0.9)	0.77	34 (0.9)	35 (1.0)	>0.9	22 (1.1)	16 (0.8)	0.40
MI	14 (0.2)	16 (0.3)	0.86	15 (0.4)	10 (0.3)	0.42	4 (0.2)	6 (0.3)	0.75
Pneumonia	50 (0.9)	61 (1.1)	0.34	41 (1.1)	47 (1.3)	0.60	17 (0.8)	14 (0.7)	0.72
Sepsis	39 (0.7)	44 (0.8)	0.66	28 (0.8)	30 (0.8)	0.90	1 (0.2)	1 (0.2)	>0.9
Extended LOS	930 (16)	476 (8.3)	**<0.001**	646 (18)	299 (8.2)	**<0.001**	249 (12)	177 (8.5)	**<0.001**
Readmission	379 (6.6)	277 (4.9)	**<0.001**	255 (7.0)	205 (5.7)	**0.018**	106 (5.1)	72 (3.5)	**0.009**

PJI = Periprosthetic Joint Infection, SSI = Surgical Site Infection, CDI = *Clostridioides difficile* infection, DVT = Deep Vein Thrombosis, PE = Pulmonary Embolism, MI = Myocardial Infarction, LOS = Length of Stay.

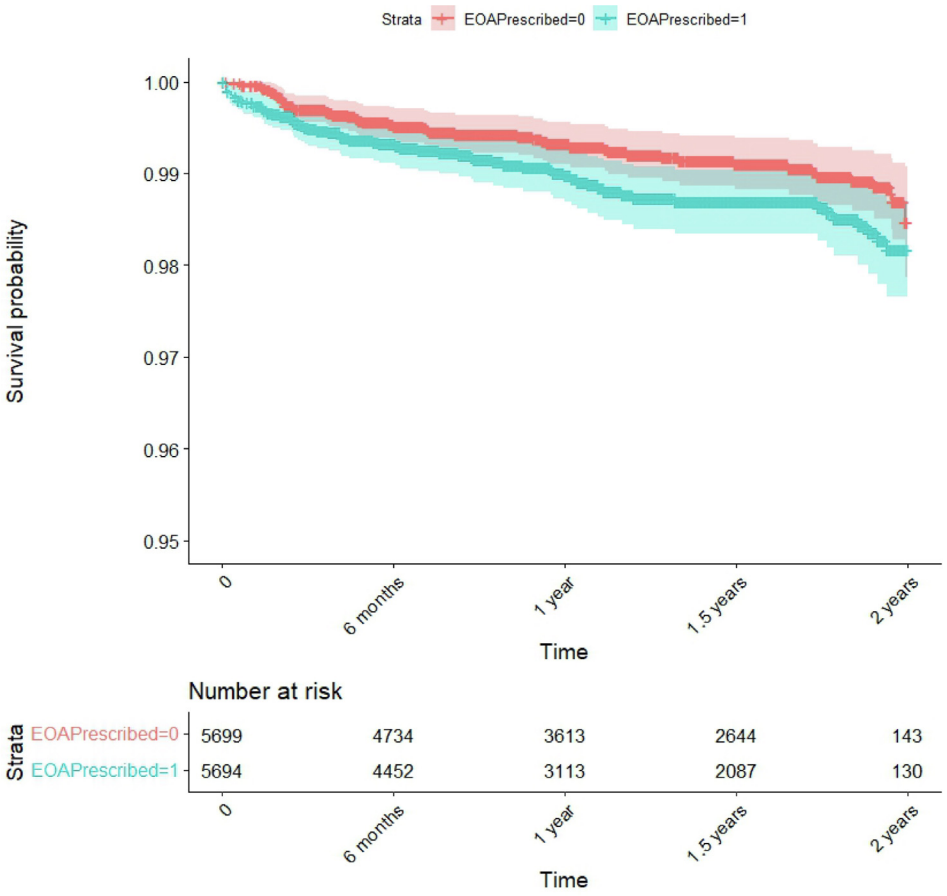

Figure 1. 2-Year PJI-free survival curve – any-risk cohorts.

Breakdown of antibiotics prescribed for EOA prophylaxis is included in Figure 4. The most commonly used antibiotic was cephalexin (36.5%) followed by cefadroxil (29%). Clindamycin was the least commonly used antibiotic included (5.4%).

4. Discussion

In this large database study, we found no significant reduction in PJI-free survivorship with use of EOA prophylaxis following TKA. This relationship was found at 90-days, 1 year, and 2 years postoperatively. Reassuringly, we also did not find any significant increases in rates of 90-day CDI following administration of EOA, though there was a trend towards significance in standard risk patients. These results warrant further discussion.

Despite generally favorable outcomes after primary TKA, PJI has been associated with decreased morbidity and increased reoperation, costs, and mortality [6,23]. Contemporary data continues to demonstrate rates of PJI after TKA to be 1.3% and 1.6% at 12 and 24 months, respectively [5]. Because PJI rates have remained relatively stable despite optimization efforts, an increased burden of PJI is expected due to increasing incidence and prevalence of TKA, necessitating further methods of risk reduction [24,25]. The use of EOA prophylaxis to reduce PJI rates after TJA has gained traction in recent years after the publication of data demonstrating significant reductions in PJI rates among high-risk individuals receiving EOA prophylaxis [11,12]. Inabathula et al. found that high-risk patients not receiving EOA prophylaxis had a 4 times higher risk of developing PJI after primary TKA at 90 days compared to similar patients who received postoperative EOA prophylaxis [11]. The same group then followed up this pilot study with a larger sample size and 1 year follow-up for both TKA and THA, again demonstrating a reduction in PJI in high-risk patients with EOA [12]. Other institutions have subsequently published their experience with some series reporting similar findings [10], and others finding no difference [14]. Given the discrepant data and that this practice is predicated on relatively small, single institution data, further clarification is needed as to the role this practice plays in contemporary arthroplasty.

In this study, we did not note a statistically or clinically significant reduction in PJI at 90 days, 1-year, or 2 years in all patients or in risk-stratified cohorts receiving EOA prophylaxis. This contrasts with some available literature but agrees with the experience published by Flynn et al. [10–12,14]. Although our overall rates of PJI are comparable to those reported in

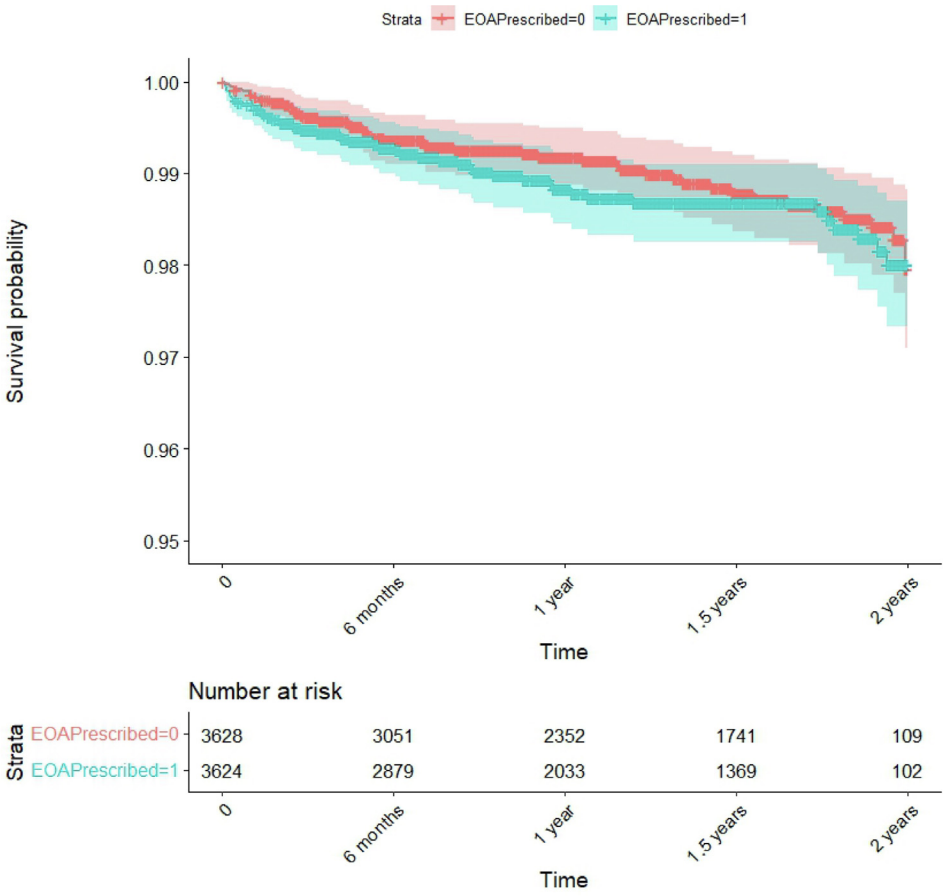

Figure 2. 2-Year PJI-free survival curve – high-risk cohorts.

prior studies and higher in the high-risk cohort as anticipated, rates of PJI in high-risk individuals not receiving EOA (0.7% at 90-days and 1 year) were substantially lower than those reported in some prior, single institutional studies – 2.1% at 90 days and 4.2% at 1 year, though Flynn et al reported lower rates of 1.7% at 90 days and 1.9% at 1 year [5,14,26]. The reason for this finding is unclear and unexpected given use of similar criteria for determining high-risk status among patients, such as diabetes, autoimmune disease, BMI > 35, and CKD. The heterogeneity in reported PJI risk factors may reflect a myriad of important variables including severity, duration, or level of disease control, which plays a crucial role in determining infection risk and may vary across studies. The low PJI rates found in our study may be indicative of recent advances in multimodal infection control protocols and preoperative medical optimization or be a product of poor sensitivity for PJI capture using an insurance claims database. However, prior analysis of claims data codes has indicated that a high degree of accuracy can be expected for the identification of infection [27,28].

Despite its potential benefits, there are concerns regarding the safety of increased use of extended antibiotics after joint arthroplasty including greater risk of antibiotic resistance and *C. difficile* infection (CDI) [12]. CDI is a rare complication after TKA, occurring at an estimated incidence of 0.1% in primary TKA and THA [29]; however, antibiotic exposure even in limited doses has been shown association with risk of CDI [30,31]. Patients with multiple comorbidities are known to be at higher risk for hospital-acquired CDI; therefore, the addition of an extended course of antibiotics may further compound this risk [32]. Development of antimicrobial resistance is also a major concern given the potential for selective pressure that may alter the epidemiology of subsequent PJI [33,34]. Nevertheless, existing studies have shown no substantially increased incidences of either CDI or antimicrobial resistance after EOA prophylaxis [12,14,35]. While we were unable to assess for antibiotic resistance profiles following EOA prophylaxis, we did not note significantly increased rates of CDI following administration of EOA prophylaxis in the any-risk and high-risk cohorts, supporting its overall safety profile. However, while not significant there was a trend toward increased CDI in standard risk individuals who received EOA with a 90-day incidence of 0.4% (P = 0.057). Given the lack of evidence supporting utilization of EOA outside of high-risk patients, this trend suggests that the prescribing of EOA prophylaxis in patients not at high risk for infection may not be entirely benign. More long-term safety data is needed, especially if EOA prophylaxis is extended to greater populations of patients.

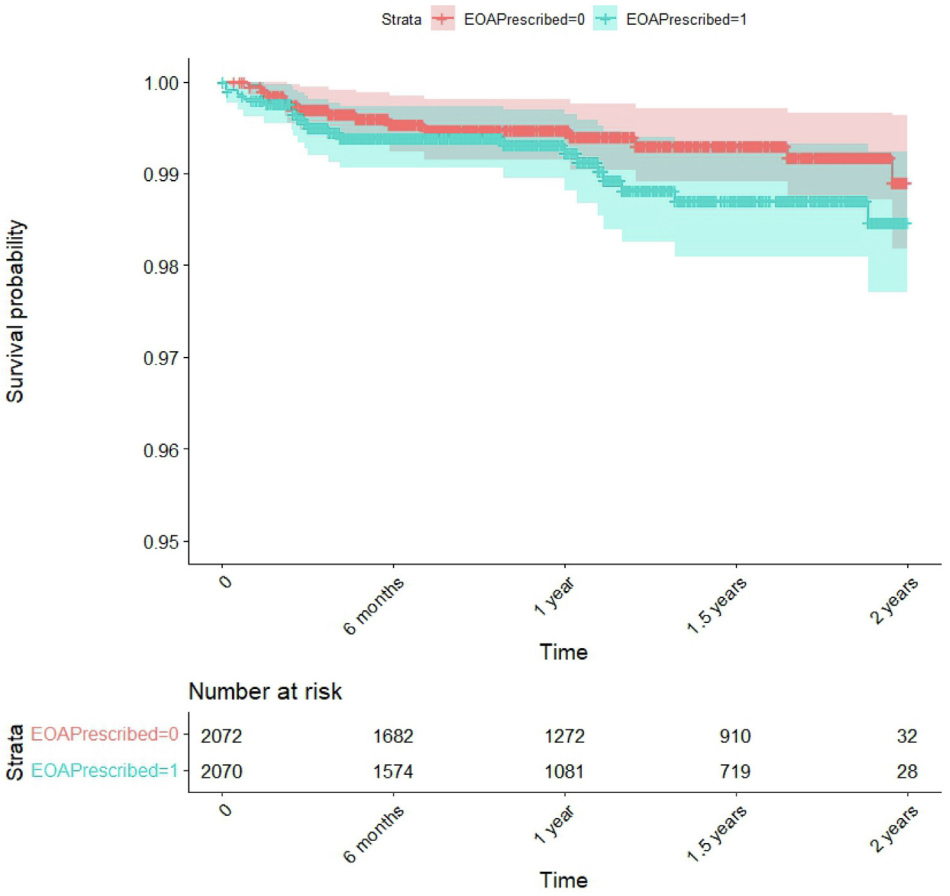

Figure 3. 2-Year PJI-free survival curve – standard-risk cohorts.

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

	90 Days			*1 Year*			*2-Year*		
Characteristic	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	1.65	0.90–3.04	0.11	1.50	0.97–2.32	0.071	1.42	0.98–2.05	0.065
ECI	1.20	1.08–1.32	**<0.001**	1.19	1.04–1.37	**0.010**	1.20	1.08–1.32	**<0.001**
High-Risk									
EOA Prescribed	1.37	0.69–2.70	0.4	1.36	0.83–2.24	0.2	1.14	0.76–1.73	0.5
ECI	0.99	0.83–1.17	>0.9	1.06	0.95–1.18	0.3	1.09	1.00–1.19	0.058
Standard-Risk									
EOA Prescribed	1.51	0.53–4.26	0.4	1.43	0.63–3.21	0.4	1.51	0.76–2.98	0.2
ECI	1.03	0.73–1.45	0.9	1.09	0.86–1.38	0.5	1.23	1.03–1.47	**0.023**

[a] Hazard Ratio.
[b] Confidence Interval.

There were also several unanticipated findings observed in our study. First, significantly higher rates of noninfectious wound complications were observed in the cohorts receiving EOA at 90 days. Given that cohorts were closely matched on factors most often related to wound healing, patients receiving EOA should theoretically be at the same or lower risk of wound complications given that wound dehiscence is often closely linked to infection [36,37]. In the absence of plausible mechanisms for these observations, residual confounding and comorbidity imbalance between the cohorts may be responsible for this finding.

There are multiple strengths to this study. We included the largest sample size to date from a nationally representative database, increasing the power and generalizability of this study. Additionally, we controlled for a large number of potentially confounding factors not accounted for in previous studies, including anemia, malnutrition, cardiovascular disease,

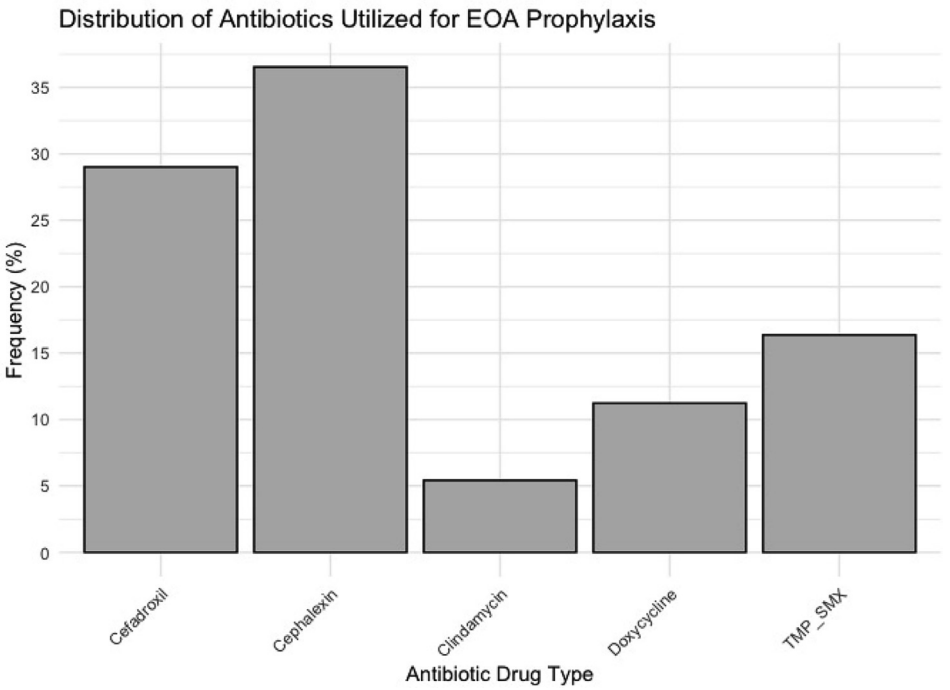

Figure 4. Distribution of antibiotics given for EOA prophylaxis by drug type.

alcohol use disorder, and depression, all of which are known risk factors for PJI [12]. Utilization of a matched cohort design allowed the comparison of EOA prophylaxis in patients of similar risk. We also conducted survivorship analysis to two years after index surgery, which to our knowledge, is the longest studied follow-up period after EOA prophylaxis following primary TKA.

Despite its strengths, there are notable limitations to consider when interpreting the results of this study. Utilization of a retrospective database hindered access to clinically important information related to comorbidities and outcomes and is ultimately reliant on the sensitivity of insurance claims reporting. For instance, disease severity could not be quantified using clinical and laboratory data with this study design. Consequently, the cohorts receiving EOA prophylaxis may have been at intrinsically higher risk of PJI from greater disease severity, preventing the true effects of EOA prophylaxis on PJI rates from being measured. Moreover, decreased sensitivity in detecting PJI may have underestimated the efficacy of EOA using this dataset, although the PJI rates in the study closely match contemporary PJI rates at our own as well as other institutions. Additionally, despite matching on a comprehensive number of comorbidities, other relevant confounders may not have been included. Patient compliance with EOA prophylaxis could not be verified as EOA status was determined only via prescription fills. There was significant loss to follow-up in all cohorts, particularly after 1 year postoperatively (Figures 1–3). However, we censored patients at last known follow-up, and our statistical methodology appropriately handles this cohort attrition. Further informative censoring was observed to occur only with increased comorbidity index, this was addressed via use of a time-transformed variable and EOA status did not impact observed follow-up patterns. Nevertheless, even if there was greater loss to follow-up in the EOA cohorts this would likely have led to underestimation rather than overestimation of PJI rates of this group.

In summary, no significant reduction in hazards of PJI-free survivorship at 90-days, 1-year or 2-years with administration of EOA prophylaxis was observed after primary TKA. This data adds to the currently observed discrepancy in reported findings on this topic and highlights the need for continued research efforts on this important topic. At present, further research in the form of randomized controlled trials is warranted to confirm the efficacy of EOA prophylaxis with low contemporary infection rates and delineate what populations might benefit the most from 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 and most optimally reserved for patients at the highest risk of infection.

CRediT authorship contribution statement

Andrew A. Fuqua: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jacob A. Worden:** Writing – original draft, Conceptualization. **Ayomide M. Ayeni:**

Writing – review & editing, Data curation, Conceptualization. **Kyle E. Bundschuh:** Writing – review & editing, Conceptualization. **Ajay Premkumar:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Jacob M. Wilson:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Variables entered in propensity score match

Age	HTN
Sex	Paralysis
CHF	Neurological Disorders
Arrythmia	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

HTN = Hypertension, CHF = Congestive Heart Failure, PVD = Peripheral Vascular Disease, CKD = Chronic Kidney Disease, HLD = Hyperlipidemia, PUD = Peptic Ulcer Disease, HIV = Human Immunodeficiency Virus, AIDS = Acquired Immunodeficiency Syndrome, MRSA = Methicillin Resistant *Staphylococcus aureus*, MSSA = Methicillin Sensitive *Staphylococcus aureus*, CAD = Coronary Artery Disease, MI = Myocardial Infarction.

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