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BRIEF REPORT

Role of asymptomatic bacteriuria on early periprosthetic joint infection after hip hemiarthroplasty. BARIFER randomized clinical trial

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Abstract

Purpose To evaluate preoperative asymptomatic bacteriuria (ASB) treatment to reduce early-periprosthetic joint infections (early-PJIs) after hip hemiarthroplasty (HHA) for fracture.

Methods Open-label, multicenter RCT comparing fosfomycin-trometamol versus no intervention with a parallel follow-up cohort without ASB. Primary outcome: early-PJI after HHA.

Results Five hundred ninety-four patients enrolled (mean age 84.3); 152(25%) with ASB (77 treated with fosfomycin-trometamol/75 controls) and 442(75%) without. Despite the study closed without the intended sample size, ASB was not predictive of early-PJI (OR: 1.06 [95%CI: 0.33–3.38]), and its treatment did not modify early-PJI incidence (OR: 1.03 [95%CI: 0.15–7.10]).

Conclusions Neither preoperative ASB nor its treatment appears to be risk factors of early-PJI after HHA. ClinicalTrials.gov Identifier: Eudra CT 2016-001108-47

Keywords Asymptomatic bacteriuria · Fosfomycin-trometamol · Early-periprosthetic joint infection · Hip hemiarthroplasty

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Introduction

Early-periprosthetic joint infection (early-PJI) after joint replacement is a challenging complication. Rates of early-PJI are higher in HHA patients than in total hip arthroplasty (THA) and range between 1.3 and 9% [1–5].

Bacterial colonization of the genitourinary tract as an infection cause of hip prostheses due to a hematogenous seeding or skin contamination by continuity has been suggested. This asymptomatic colonization is called asymptomatic bacteriuria (ASB), and its prevalence reaches 30–50% in older women in long-term care facilities [6]. Published studies demonstrated that preoperative ASB treatment in elective total hip and knee arthroplasties has no impact in early-PJI rates [7–11]. However, its impact on HHAs is controversial. A single-center study concluded that treating ASB in geriatric patients with a femur fracture decreases the risk of PJIs [12].

We evaluate preoperative ASB treatment's impact on the cumulative incidence of early-PJI in patients undergoing HHA for a hip fracture. We hypothesized that preoperative ASB treatment in these populations could decrease the incidence of early-PJI caused by Gram-negative bacilli (GNB).

Patients and methods

BARIFER was a phase IV, multicenter, randomized, open-label, and parallel-group clinical trial conducted at 11 sites in Spain designed to evaluate the impact of treating ASB on the incidence of early-PJI in HHA.

All patients provided informed consent. Protocol approval was obtained from an independent ethics committee at each site. The trial (EudraCT 2016-001108-47) was performed under the principles of the Declaration of Helsinki. Adherence to the Consolidated Standards of Reporting Trials [13] (CONSORT) is supported by the completed checklist provided as Supplementary material.

Patients ≥18 years requiring HHA for fracture were recruited. Exclusion criteria include any concomitant infection requiring antibiotics and hip fractures treated with screws or THA.

Urine analysis was performed before HHA surgery. ASB referred to a urine culture growing $\geq 10^5$ colony-forming units/mL of a bacterial species in a patient lacking symptoms of a urinary tract infection (UTI). Standard procedures identified all microorganisms isolated. Antimicrobial susceptibility was performed by microdilution (Vitek bioMérieux, France). The MIC values of fosfomycin were interpreted according to EUCAST criteria 2012 (version 2.0) guidelines (www.eucast.org).

Participants with ASB were randomly assigned in a 1:1 ratio, centralized, and stratified by center, to receive 3 g of fosfomycin-trometamol (oral route) vs. no treatment, between 24 and 6h before surgery. A parallel follow-up cohort of HHA candidates without ASB was established.

Preoperative antibiotic prophylaxis was decided according to each center protocol (Supplementary Table 1). All patients were followed for three months after HHA or until early-PJIs or death was diagnosed, whichever occurred first.

PJIs occurring within 3 months after HHA were considered early-PJIs [14]. Patients were diagnosed with a PJI following diagnostic criteria established by the Infectious Diseases Society of America [15]. In the case of early-PJI, a new visit was completed in which the microorganism causing the infection was recorded.

The primary outcome was cumulative incidence of early-PJI after preoperative ASB treatment. Secondary analyses included global incidence of ASB and early-PJI, risk factors for early-PJI, and fosfomycin treatment safety.

Statistical analysis

Categorical variables were presented as numbers and percentages, and quantitative variables as a median and interquartile range or a mean and standard deviation, as appropriate. Comparative analyses were performed using X^2 or Fisher's test for categorical variables and Student's t test or Mann–Whitney U test for continuous variables. The level of significance was set to $p < 0.05$. Predictors of early-PJI were determined by univariate analysis. The Kaplan-Meier method was used to describe cumulative probability early-PJI stratified by study group.

The EAST program calculated the sample size. We assumed a prevalence of ASB up to 20% in men and 50% in women, an incidence of 9% of early-PJI, and an expected 50% reduction with fosfomycin treatment with a test power of 90% and alpha error of 0.05. We needed 1394 patients (697 in each treatment group). An interim analysis was planned to stop the study if it would not be possible to test the hypothesis. Analyses were performed with the STATA 15.1 software (StataCorp, TX, USA) in the intention-to-treat (ITT) population.

Results

A total of 594 patients were included from September 2016 to November 2018. Overall, 420 (71.0%) were women, and the mean age was 84.3 years. ASB was diagnosed in 152 (25%) patients, 77 treated with fosfomycin and 75 untreated controls. Figure 1 shows the flow chart of patients' distribution.

Patients with ASB versus the non-ASB group mainly were women, with a higher Charlson comorbidity index score and more commonly with urinary incontinence (Table 1). Supplementary Table 2 shows causative isolates of ASB. As expected, 82% were GNB (Mostly *Escherichia coli* and *Klebsiella* spp.), of which 89%

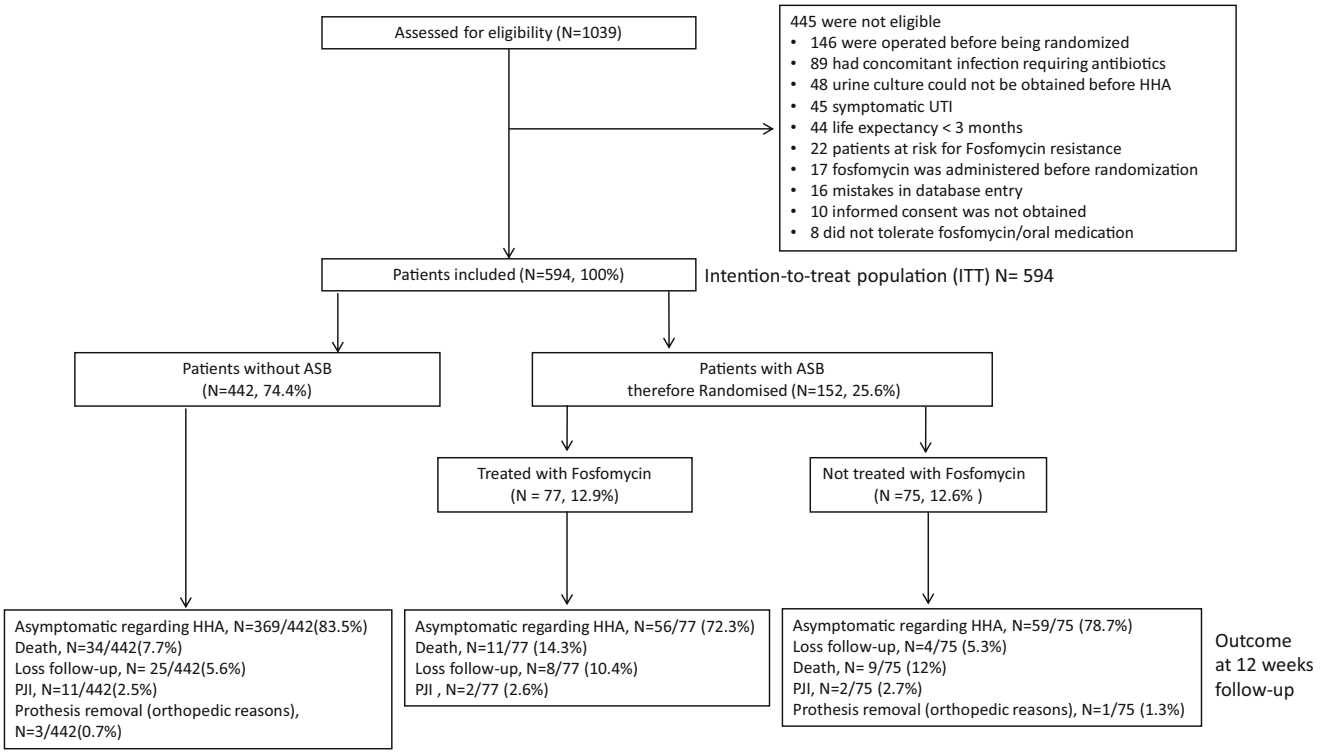

Fig. 1 Overall flow chart and outcome of patients included in BARIFER clinical trial (ITT analyses), N= 594. Abbrebiations: ITT, intention to treat; UTI, urinary tract infection; ASB, asymptomatic bacteriuria; PJI, periprosthetic joint infection. Twenty-two patients with ASB were considered at risk for Fosfomycin resistance as they were under chronic antibiotic prophylaxis with Fosfomycin-trometamol for recurrent cystitis. Therefore, they were not randomized

Table 1 Baseline demographics and clinical characteristics of patients (ITT analysis)

Characteristics	Patients with ASB (n = 152, 100%)	Patients without ASB (n = 442, 100%)	Total (n = 594,100 %)	p value	OR (95% CI)
Age, mean (SD)	84.5 (7.9)	84.2 (8.5)	84.3 (8.34)	0.7725	1.003 (0.981; 1.026)
Median (Q1–Q3), years	86.0 (81.7; 89.6)	86.0 (80.6;89.7)	86.0 (80.7; 89.7)		
Female sex	124 (81.6%)	296 (67.0%)	420 (70.7%)	0.0008	2.18 (1.39; 3.44)
Comorbid conditions					
BMI mean (SD)	24.4 (4.5)	24.3 (3.5)	24.4 (3.8)	0.8319	1.01 (0.95; 1.07)
Median (Q1–Q3), kg/m^2	24.8 (21.5;26.6)	24.2 (21.6;26.6)	24.2 (21.6;26.6)		
Obesity (BMI ≥ 30 kg/m^2)	9 (8.3%)	14 (5.3%)	23 (6.2%)	0.2886	1.46 (0.73; 2.95)
Cardiac failure	19 (12.6%)	45 (10.2%)	64 (10.8%)	0.4124	1.27 (0.72; 2.25)
Peripheral vasculopathy	15 (9.9%)	41 (9.3%)	56 (9.4%)	0.8114	1.27 (0.58; 2.01)
Diabetes	45 (29.8%)	106 (24.0%)	151 (25.4%)	0.1573	1.35 (0.89; 2.03)
Dementia	50 (33.1%)	118 (26.7%)	168 (28.3%)	0.1317	1.36 (0.91; 2.03)
Chronic bronchopathy	19 (12.6%)	49 (11.1%)	68 (11.5%)	0.6184	1.15 (0.66; 2.03)
Cirrhosis	6 (3.97%)	6 (1.4%)	12 (2.0%)	0.0600	3.01 (0.95; 9.47)
Chronic renal failure	28 (18.4%)	67 (15.1%)	95 (16.0%)	0.3446	1.26 (0.78; 2.05)
Charlson index score*					
Mean (SD)	6.1 (2.2)	5.6 (1.9)	5.8 (2.0)	0.0146	1.12 (1.02; 1.22)
Median (Q1–Q3)	6.0 (5.0; 7.0)	5.0 (4.0; 7.0)	6.0 (4.0; 7.0)		
Urinary incontinence	52 (34.4%)	78 (17.7%)	130 (22.0%)	<0.0001	2.44 (1.61; 3.70)
Rheumatoid arthritis	1 (0.7%)	8 (1.8%)	9 (1.5%)	0.3395	0.36 (0,04;2.92)
Immunosuppressors**	7 (4.6%)	25 (5.6%)	32 (5.4%)	0.6121	0.81 (0.34;1.90)
Malignancy	11 (7.2%)	32 (7.2%)	43 (7.2%)	0.9990	1.00 (0.491; 2.04)
Anticoagulant treatment	40 (26.5%)	101 (22.8%)	141 (23.8%)	0.3649	1.22 (0.80; 1.86)
Antiplatelet treatment	44 (29.1%)	130 (29.4%)	174 (29.3%)	0.9493	0.36 (0.04; 2.92)

Unless otherwise specified, data represent no. (%) of patients

ITT, intention to treat analysis; *ASB*, asymptomatic bacteriuria; *OR*, odds ratio; *CI*, confidence interval; *SD*, standard deviation; *BMI*, body mass index

*Charlson index score is adjusted by age

**Immunosuppressors includes steroids, classic immunosuppressors (i.e., methotrexate, azathioprine, mycophenolate), biological drugs, and chemotherapy

Table 2 Baseline characteristics of Treated and Untreated Patients with ASB

Characteristic	Patients, no. (%)		Total (*N*=152, 100%)
	Untreated ASB (*N*= 75, 100%)	ASB treated with fosfomycin (*N*=77, 100%)	
Age, mean (SD), years	84.2 (8.6)	84.6 (7.2)	84.5 (7.9)
Median (Q1–Q3), years	85.9 (81.6;89.9)	86.15 (81.7;89.4)	85.96 (81.7;89.6)
Female sex	59 (78.7%)	65 (84.4%)	124 (81.6%)
Comorbid conditions			
BMI[a] mean (SD), years	24.6 (4.7)	24.2 (4.1)	24.4 (4.46)
Median (Q1–Q3), years	24.9 (21.6;26.7)	23.5 (21.5;26.6)	24.8 (21.5;26.6)
Cardiac failure	11 (14.9%)	8 (10.4%)	19 (12.6%)
Peripheral vasculopathy	8 (10.8%)	7 (9.1%)	15 (9.9%)
Cerebral vasculopathy	14 (18.9%)	13 (16.9%)	27 (17.9%)
Dementia	22 (29.7%)	28 (36.4%)	50 (33.1%)
Chronic bronchopathy	12 (16.2%)	7 (9.1%)	19 (12.6%)
Cirrhosis	3 (4.0%)	3 (3.1%)	6 (4.0%)
Diabetes	24 (32.4%)	21 (27.3%)	45 (29.8%)
Chronic renal failure	14 (18.7%)	14 (18.2%)	28 (18.4%)
Malignancy	6 (8.7%)	5 (6.5%)	11 (7.3%)
Immunosuppressors**	7 (9.3%)	1 (1.3%)	8 (5.3%)
Anticoagulant treatment	20 (27.0%)	20 (26.0%)	40 (26.5%)
Antiplatelet treatment	23 (31.1%)	21 (27.3%)	44 (29.1%)
Rheumatoid arthritis	1 (1.3%)	0 (0%)	1 (0.7%)
Urinary incontinence	27 (36.5%)	25 (32.5%)	52 (34.4%)
Charlson index score*			
Mean (SD)	6.19 (2.3)	6.0 (2.2)	6.1 (2.2)
Median (Q1–Q3)	6.0 (5.0;8.0)	6.0 (4.0;7.0)	6.0 (5.0;7.0)
Days from admission to HHA*			
Mean (SD)	4.3 (6.9)	3.7 (2.2)	4.0 (5.1)
Median (Q1–Q3)	3.0 (2.0;5.0)	3.0 (2.0;5.0)	3.0 (2.0;5.0)
Duration of HHA surgery			
Mean (SD), min	94.9 (27.2)	93.26 (23.4)	94.1 (25.4)
Median (Q1–Q3), min	90.0 (75.0;120.0)	90.0 (80.0;5.0)	90.0 (75.0;115.0)
Duration of HHA surgery > 75th percentile	17 (28.3%)	12 (21.0%)	29 (24.8%)
Antibiotic cemented HHA	67 (89.3%)	66 (89.2%)	133 (89.3%)
HHA dislocation	4 (5.3%)	4 (5.2%)	8 5 (26%)
Postoperative UTI	6 (8%)	7 (9.1%)	13 (8.5%)
Postoperative infection other than UTI	4 (5.3%)	3 (3.9%)	7 (4.6%)
Patients transferred to a convalescence center	28 (40%)	35 (50%)	53 (37.9%)

Unless otherwise specified, data represent no. (%) of patients

ASB, asymptomatic bacteriuria; *BMI*, body mass index; *ASA*, American society of anaesthesiologists; *HHA*, hip hemiarthroplasty; *UTI*, urinary tract infection; *PJI*, periprosthetic joint infection

[a] Data available for 109 patients (58 untreated ASB and 51 treated ASB)

*Charlson index score is adjusted by age

**Immunosuppressors includes steroids, classic immunosuppressors (i.e., methotrexate, azathioprine, mycophenolate), biological drugs, and chemotherapy

were susceptible to fosfomycin. Table 2 compares baseline characteristics of treated and untreated patients with ASB.

HHA implants were 65.46% cemented with antibiotics (64% with single-antibiotic and 36% with dual-antibiotic Vancogenx®).

Table 3 Overall outcomes (ITT analysis)

Outcome	ASB patients		Non-ASB patients 442 (100%)	Total 594 (100%)
	Not treated with fosfomycin 75 (100%)	Treated with fosfomycin 77 (100%)		
No HHA infection after 12 weeks	59 (78.7%)	56 (72.7%)	369 (83.5%)	484 (81.7%)
Death within 12 weeks	9 (12%)	11 (14.3%)	34 (7.7%)	54 (9%)
Early-PJI	2 (2.7%)	2 (2.6%)	11 (2.5%)	15 (2.5%)
Loss of follow-up	4 (5.3%)	8 (10.4%)	25 (5.6%)	36 (6.1)
Prostheses removed due to orthopedic reasons	1 (1.3%)	0 (0%)	3 (0.7%)	4 (0.7%)

ITT, intention to treat; *ASB*, asymptomatic bacteriuria; *HHA*, hip hemiarthroplasty; *PJI*, periprosthetic joint infection

Overall, 558(93.9%) patients (140 with ASB and 418 without) completed three months of follow-up (Table 3). Early-PJI rate was 2.5% (15 of 594 patients). Of these 15 patients, 4 (2.7%) showed previous ASB, but only two received fosfomycin (Table 3). Our trial showed that treating preoperative ASB does not modify the incidence of early-PJI (OR: 1.03 [95%CI: 0.15–7.10], p= 0.9787). Of note, all early-PJI occurred within 60 days after HHA (Fig. 2). Table 4 shows the etiology of the 15 early-PJIs. We observed a lack of correspondence between ASB and early-PJI causing microorganisms. Univariate analysis of risk factors for early-PJI is presented in Table 5. Preoperative ASB was not a predictor of early-PJI (OR: 1.06 [95%CI: 0.33–3.38], p= 0.9228).

AEs related to fosfomycin occurred in 4 patients, all of them of mild intensity. Three patients suffered from nausea, and one reported dizziness (Supplementary Table 3).

Table 4 Etiology, relationship with ASB, and outcome of early-PJI infections

Patients	Patients without ASB	Patients with ASB		Etiology of early-PJI	Etiology of ASB
		Treated with fosfomycin	Not treated with fosfomycin		
1	x			MSSA	
2		x		*S. epidermidis*	*E. coli*
3	x			*MSSA*	
4			x	*C. striatum*	*K. pneumoniae*
5	x			*E. coli* ESBL *producer*	
6	x			*E. coli ESBL producer*	
7	x			*MRSA.*	
8	x			*K. pneumoniae*	
9		x		*MRSA*	*E. coli ESBL producer*
10	x			*E. coli ESBL producer**	
11	x			*S. epidermidis*	
12			x	*S. epidermidis* *Bacillus* spp. *S. haemolyticus*	*E. coli*
13	x			Negative culture[≠]	
14	X			Negative culture[≠]	
15	x			*E. faecalis*	

HHA, hip hemiarthroplasty; *ASB*, asymptomatic bacteriuria; *PJI*, prosthetic joint infection; *MSSA*, methicillin susceptible *S. aureus*; *MRSA*, methicillin resistant *S. aureus*; *ESBL* producer, extended spectrum beta-lactamase producer

*This patient was diagnosed with a postoperative UTI caused by *E. coli ESBL* producer

[≠] Although purulence was observed at surgical debridement in those 2 cases, both under broad-spectrum antibiotic treatment at that time, cultures were negative

Table 5 Univariate analysis of risk factors for early-PJI (ITT analysis)

Risk factor	Patients, no. (%) *N*=594		Univariable analysis	
	No HHA infection *N*= 579, 100%	HHA infection *N* =15, 100%	*p* value	OR (95%CI)
Age, mean (SD), years	84.3 (8.4)	85.1 (5.0)	0.7163	1.01 (0.95;1:08)
Age, median (Q1–Q3), years	85.96 (80.7;89.7)	86.0 (81.1;88.9)		
Female sex	409 (70.6%)	11 (73.3%)	0.8210	1.14 (0.36;3.64)
Comorbid conditions				
Preoperative ASB	148 (25.6%)	4 (26.7%)	0.9228	1.06 (0.33;3.38)
BMI mean (SD)	24.3 (3.8)	25.6 (2.5)	0.2712	
Median (Q1–Q3), kg/m^2	24.2 (21.7;26.5)	25.9 (22.9;27.3)		
Obesity (BMI ≥ 30 kg/m^2)	22 (6.1%)	1 (9.1%)	0.5103	1.00 (1.00;1.00)
Ischemic heart disease	48 (8.3%)	1 (6.7%)	0.8205	0.79 (0.10;6.13)
Dementia	161 (27.1%)	7 (46.7%)	0.1197	2.27 (0.81; 6.35)
Cirrhosis	11 (1.9%)	1 (6.7%)	0.2270	3.68 (0.44;30.51)
Diabetes	147 (25.4%)	4 (26.7%)	0.9138	1.07 (0.33;3:40)
Charlson index score*				
Mean (SD)	5.7 (2.0)	6.4 (2.9)	0.2198	1.15 (0.92;1.44)
Median (Q1–Q3)	6.00 (4,0; 7.0)	6.0 (4.0; 7.0)		
Immunosuppressors**	32 (5.5%)	0 (0%)	0.3492	1.00 (1.00; 1.00)
Malignancy	40 (6.9%)	3 (20%)	0.0682	3.37 (0.91;12.43)
Anticoagulant treatment	136 (23.5 %)	5 (33.3%)	0.3659	1.63 (0.55;4.84)
Antiplatelet treatment	171 (29.5%)	3 (20%)	0.4258	0.60 (0.17;2.14)
Days since admission to HHA				
Mean (SD)	4.26 (4.8)	4.7 (2.9)	0.7412	1.01 (0.93;1.10)
Median (Q1–Q3)	3.00 (2.0; 5.0)	4.00 (3.0; 6.0)		
Days since admission to HHA > 75th percentile	113 (19.5%)	5 (33.3%)	0.1957	2.06 (0.69;6.14)
Duration of HHA surgery				
Mean (SD), min	93.97 (25.57)	100.0 (17.3)	0.6863	1.01 (0.96;1.06)
Median (Q1–Q3), min	90 (75.0; 115.0)	90 (90.0; 120.0)		
Duration of HHA surgery > 75th percentile	28 (24.6%)	1 (33.3%)	0.7302	1.54 (0.13;17.58)
Antibiotic cemented HHA	372 /568 (65.6%)	9 /15 (60%)	0.7351	0.83 (0.29;2.38)
HHA dislocation	13 (2.2%)	1 (6.7%)	0.2901	3.11 (0.38;25.45)
Any postoperative infection	36 (6.2%)	4 (26.7%)	0.0052	5.48 (1.66;18.08)

Unless otherwise specified, data represent no. (%) of patients

PJI, prosthetic joint infection; *ITT*, intention to treat analysis; *HHA*, hip hemiarthroplasty; *BMI*, body mass index; *ASB*, asymptomatic bacteriuria; *OR*, odds ratio; *CI*, confidence interval; *SD*, standard deviation.

*Charlson index score is adjusted by age

**Immunosuppressors includes steroids, classic immunosuppressors (i.e., methotrexate, azathioprine, mycophenolate), biological drugs, and chemotherapy

N/N with data available when appropriate

Discussion

Identifying potentially modifiable preoperative risk factors of PJIs is of great interest. Experts traditionally recommended treating ASB before THA [16–19], although the latest published studies contradict this recommendation [7, 8, 10, 11]. There are only two previous randomized controlled trials addressing this in THA and HHA [7, 8]. Our findings suggest that preoperative ASB treatment does not impact on the reduction of early-PJI after HHA. BARIFER is the first randomized trial that only enrolled this subgroup of patients.

ASB prevalence in our cohort was 25% higher than in THA candidates [7, 8, 16] and consistent with data reported for HHA [20]. Female sex, adjusted Charlson index, and urinary incontinence are significantly more prevalent in the ASB group as previously reported [7].

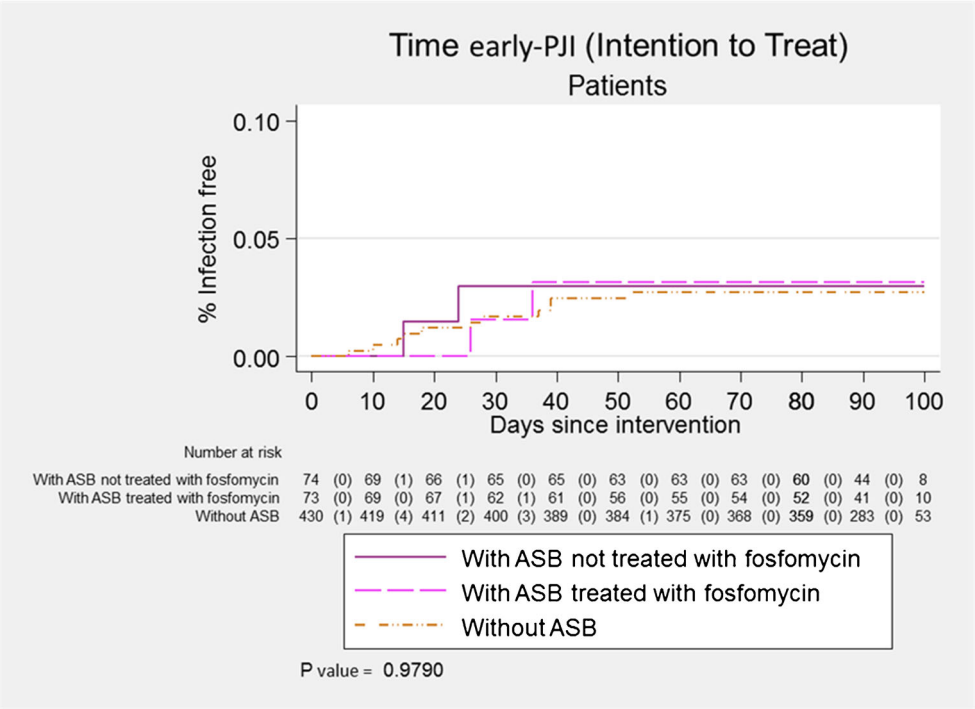

Fig. 2 Distribution of the time to early-PJI according to study group. Early-PJI, early periprosthetic joint infection

In our trial, almost 90% of the identified GNB causing ASB were susceptible to fosfomycin as previously published [21, 22]. The efficacy of a single dose of fosfomycin-trometamol for uncomplicated lower UTI maybe be comparable to standard regimens with fluoroquinolones or trimethoprim/sulfamethoxazole [23] and easier to administer. On this basis, it was chosen as preoperative treatment. Fosfomycin has a good tolerability with a low incidence of adverse events (AEs), mainly mild and transient gastrointestinal symptoms [23]. This coincides with our study as only four patients experienced associated nausea or dizziness.

Only four patients with ASB showed an early-PJI which represents an incidence of 2.7%. Although this is lower than expected [4, 7, 8], it is consistent with the latest data collected in the VINCat registry (surveillance database of nosocomial infections in Catalonia) [5]. When investigating risk factors for early-PJI, our study focuses on preoperative ASB. Among our series, ASB is not a risk factor for early-PJI unlike other published data stating that, although the risk of PJI is not influenced by ASB treatment, there seems to be an increased risk of PJI in this population [7]. It should also be noted that in no case, the microorganism causing ASB was the same as the one causing early-PJI and this has also been described by other authors [7, 24]. Our experience shows that ASB treatment does not modify the incidence of early-PJI. Although we observed a delay from HHA surgery to onset of infection of about 10 days higher in patients treated with fosfomycin, the exceptionally low number of events prevents us from reaching any conclusion. Consequently, since we could not demonstrate a potential benefit in treating preoperative ASB, we do not recommend systematic urinalysis screening and treatment.

Besides, the percentage of antibiotic-loaded cement used is also significant. Published studies show that it reduces the rate of PJIs in HHA with no associated increase in complications [25–27]. This approach could justify a global reduction of early-PJ rates compared to our previous incidence between 2011 and 2013 [4].

Finally, global mortality in our study is high (9%) and can be explained by the population's age and comorbidity, particularly among those with ASB, as evidenced by the high Charlson comorbidity index values [1, 28].

The main limitation of our study is the small sample size. The difficulty of obtaining the informed consent signed and all study requirements at least 6 h before surgery made our inclusion rate slow. We did an interim analysis that showed that it would not be possible to test the hypothesis so we decided to end the study. It is also possible that we overestimate ASB and early-PJI after HHA incidences since our calculations were based on our previous experience [4] and data published regarding ASB prevalence in the elderly [29]. ASB and early-PJI after HHA incidences were lower than expected so the study might be underpowered to confirm the hypothesis. The study's main strengths are its randomized design and recruiting geriatric patients (often underrepresented in clinical trials) all of them undergoing HHA.

In conclusion, our results suggest that ASB appears not to be an independent risk factor for early-PJ, and its treatment did

not reduce the incidence of early-PJI after HHA. Therefore, we cannot recommend routine screening and treatment of preoperative ASB in HHA surgery.

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Author contribution Dr Rodriguez-Pardo and Dr Pigrau contributed to its conception, clinical trial design, protocol, data collection, patient recruitment, data analysis, and writing the paper with the assistance of a medical writer. Dr Corona and Dr Almirante contributed to its conception, clinical trial design, and reviewing and editing the manuscript. All the other authors participated in patient recruitment, data collection, and reviewing and editing the manuscript. All authors approved the submitted versions, had full access to the data (under confidentiality agreements), and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

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Declarations

Competing interests The authors declare no competing interests.

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