Efficacy of a Bio-Absorbable Antibacterial Envelope to Prevent Cardiac Implantable Electronic Device Infections in High-Risk Subjects

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Efficacy of Bio-Absorbable Antibacterial Envelope. ***Introduction:*** **Cardiac implantable electronic device (CIED) infections are potentially preventable complications associated with high morbidity, mortality, and cost. A recently developed bio-absorbable antibacterial envelope (TYRX^{TM}-A) might prevent CIED infections in high-risk subjects. However, data regarding safety and efficacy have not been published.**

Methods and Results: **In a single-center retrospective cohort study, we compared the prevalence of CIED infections among subjects with ≥2 risk factors treated with the TYRX^{TM}-A envelope (N = 135), the nonabsorbable TYRX^{TM} envelope (N = 353), and controls who did not receive an envelope (N = 636). Infection was ascertained by individual chart review. The mean (95% confidence interval) number of risk factors was 3.08 (2.84–3.32) for TYRX^{TM}-A, 3.20 (3.07–3.34) for TYRX^{TM}, and 3.09 (2.99–3.20) for controls, P = 0.3. After a minimum 300 days follow-up, the prevalence of CIED infection was 0 (0%) for TYRX^{TM}-A, 1 (0.3%) for TYRX^{TM}, and 20 (3.1%) for controls (P = 1 for TYRX^{TM}-A vs. TYRX^{TM}, P = 0.03 for TYRX^{TM}-A vs. controls, and P = 0.002 for TYRX^{TM} vs. controls). In a propensity score-matched cohort of 316 recipients of either envelope and 316 controls, the prevalence of infection was 0 (0%) and 9 (2.8%), respectively, P = 0.004. When limited to 122 TYRX^{TM}-A recipients and 122 propensity-matched controls, the prevalence of CIED infections was 0 (0%) and 5 (4.1%), respectively, P = 0.024.**

Conclusions: **Among high-risk subjects, the TYRX^{TM}-A bio-absorbable envelope was associated with a very low prevalence of CIED related infections that was comparable to that seen with the nonabsorbable envelope.** *(J Cardiovasc Electrophysiol, Vol. 26, pp. 1111-1116, October 2015)*

antibacterial envelope, cardiac implantable electronic device, infection

Introduction

Cardiac implantable electronic device (CIED) infections have emerged as important complications of CIED procedures. CIED infections can be exceedingly difficult to treat, usually necessitating complete CIED system removal, and are associated with increased morbidity, mortality, and healthcare costs.[1-4] Perioperative strategies to prevent CIED infections are particularly important, since inoculation often occurs as a result of bacterial seeding of the operative site (incision, device pocket, capsule, and/or CIED components) at the time of device implantation.[5]

Among patients undergoing CIED procedures, the nonabsorbable version of the TYRX^{TM} antibacterial envelope has been associated with a low prevalence of CIED infections.[6-9] A new bio-absorbable version of the envelope is now commercially available, but its efficacy at preventing CIED infections is unknown. We hypothesized that the bio-absorbable TYRX^{TM}-A antibacterial envelope is associated with a low prevalence of CIED infections, similar to what has been observed with the nonabsorbable envelope. To test our hypothesis, we conducted a retrospective cohort study comparing the prevalence of CIED infections in subjects treated with the bio-absorbable envelope, the nonabsorbable envelope, and control subjects who underwent a CIED procedure but did not receive an envelope.

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Methods

Study Subjects

All patients age ≥18 years who had an antibacterial envelope implanted at Vanderbilt University Medical Center based on our institutional guidelines for use (see below) were included in the study. Nonabsorbable (TYRX™) envelope recipients underwent implantation between November 12, 2009 and June 20, 2014, whereas bio-absorbable (TYRX™-A) envelope recipients underwent implantation between October 11, 2012 and June 30, 2014. The control population included adult subjects with ≥2 risk factors for CIED infection who had a device implanted between June 24, 2005 and May 24, 2010 without an antibacterial envelope. Control subjects underwent their index CIED procedures prior to the widespread use of antibacterial envelopes at our institution. Controls were derived from the Vanderbilt University Medical Center Synthetic Derivative, a de-identified, time-shifted, and previously validated version of the electronic medical record.[10,11] The study protocol was approved by Vanderbilt University's institutional review board and found to be exempt from requiring individual informed consent.

After the TYRX™ envelopes became commercially available, we developed institutional guidelines for their use in patients undergoing a CIED procedure who had ≥2 of the following previously described risk factors for infection: diabetes mellitus (history of diabetes or use of glycemic control agents), chronic kidney disease (serum creatinine ≥1.5 mg/dL at the time of implantation), systemic anti-coagulation (heparin, warfarin, or a novel oral anticoagulant), chronic daily corticosteroid use, fever ≥100.5 °F or leukocytosis ≥11,000 WBC/μL 24 hours prior to implantation, prior documented CIED infection, ≥3 transvenous leads (3 lead cardiac resynchronization therapy [CRT] systems or ≥1 abandoned leads), pacemaker dependence, or early pocket reentry within 2 weeks of original implantation.

The control population was derived by conducting a multitiered search of the Vanderbilt University Medical Center Synthetic Derivative database. Subjects who had a CIED implanted prior to the routine use of the antibacterial envelope at our institution were selected by searching for the following Current Procedural Terminology codes: 33206, 33207, 33208, 33212, 33213, 33214, 33215, 33216, 33217, 33218, 33220, 33224, 33225, 33226, 33233, 33234, 33235, 33240, and 33249. The resulting patient records were queried for the presence of diabetes mellitus, chronic kidney disease, systemic anticoagulation, chronic corticosteroid use, fever, and leukocytosis, as defined above. The resulting records were manually reviewed for the remaining risk factors and for incident CIED infections.

Types of CIED Procedures

The index CIED procedure was defined for all subjects by chart review. This included control subjects where Current Procedural Terminology codes were used for initial screening but individual chart review was used to definitively determine procedure type. Procedure types included implantation of a single-chamber pacemaker, dual-chamber pacemaker, single-chamber implantable cardioverter-defibrillator (ICD), dual-chamber ICD, CRT pacemaker, CRT defibrillator, generator exchange, and device or lead revision. All of the CIED procedures considered as the index procedure for this study were performed at Vanderbilt University Medical Center by board-certified electrophysiologists in a dedicated electrophysiology laboratory or operating room. Patients specifically referred to Vanderbilt University Medical Center for management of a CIED infection related to a device implanted outside our facility were excluded from analysis. All subjects in the antibacterial envelope and control cohorts received perioperative antibiotics 0–15 minutes prior to skin incision. Outpatients received 1 g intravenous cefazolin, unless penicillin allergic, in which case 1 g intravenous vancomycin was used. Due to the high prevalence of antibiotic resistance at our institution, vancomycin was used as the first line agent for inpatients. Antibacterial envelopes were utilized by 9 out of 10 implanting electrophysiologists at our institution.

Ascertainment and Definition of Study Endpoints

CIED infection, the primary study endpoint, was defined as a local infection, or systemic infection (e.g., sepsis, bacteremia, or endocarditis), ascertained by individual chart review. When an infection was identified, charts were also reviewed to ascertain bacterial culture results, treatment, and outcome. Infected subjects were treated with complete CIED system explantation whenever feasible and/or systemic antibiotics. All subjects were followed for a minimum of 300 days after the index procedure.

Data Management and Statistical Analysis

All patient variables were ascertained retrospectively by chart review and entered into a secure REDCap database.[12] Group comparisons were made using nonparametric tests for continuous variables and Pearson chi-square test or Fisher's exact test for categorical variables, as appropriate. For the primary endpoint, CIED infection after a minimum of 300 days follow-up, Fisher's exact test was used to test the difference in prevalence between antibacterial envelope recipients and controls.

Given the large number of risk factors evaluated, the low number of CIED infections, and concerns about over-fitting, we were unable to use multivariable regression to adjust for individual CIED infection risk factors and other variables.[13] Rather, a propensity score for implantation of the antibacterial envelope, without regard for the primary study outcome, was calculated and used to create propensity-matched cohorts and outliers in each treatment group without an available match were excluded from further analysis.[14,15] The first propensity-matched cohort included recipients of either the bio-absorbable (TYRX™-A) or nonabsorbable (TYRX™) envelope and matching controls. The second propensity-matched cohort was limited to TYRX™-A recipients and matching controls. The variables used for propensity score matching included age, sex, type of device, diabetes mellitus, chronic kidney disease, systemic anticoagulation, chronic steroid use, ≥3 leads, pacemaker dependence, fever or leukocytosis at the time of implantation, generator change or device upgrade/revision, early pocket re-entry, previous CIED infection, and length of follow-up. In addition, we conducted a time to event analysis using Cox proportional-hazards regression that included the propensity score as a variable to adjust for confounders.

Statistical analysis, including propensity score matching, was performed using SPSS for Mac (v22, IBM Corporation, Armonk, NY, USA).

TABLE 1
Clinical Characteristics for the Entire Study Cohort

	Bio-absorbable Envelope Recipients (N = 135)	Nonabsorbable Envelope Recipients (N = 353)	Controls (N = 636)	P-Value*
Age, years, median (95% CI)	67 (63.5–70.5)	69 (67–71)	70 (68–71)	0.059
Women	43 (31.9%)	111 (31.4%)	236 (37.1%)	0.153
Serum creatinine, median, mg/dL (95% CI)	1.28 (1.15–1.39)	1.23 (1.15–1.29)	1.31 (1.27–1.36)	0.124
Chronic kidney disease	43 (31.9%)	121 (34.3%)	296 (46.5%)	< 0.001
Diabetes mellitus	55 (40.7%)	148 (41.9%)	344 (54.1%)	< 0.001
Systemic anticoagulation	77 (57%)	204 (57.8%)	433 (68.1%)	0.001
Chronic corticosteroids	9 (6.7%)	28 (7.9%)	92 (14.5%)	0.001
Prior CIED infection	4 (3%)	27 (7.6%)	25 (3.9%)	0.019
Pacemaker dependent	48 (35.6%)	109 (30.9%)	198 (31.1%)	0.569
Fever/leukocytosis	14 (10.4%)	56 (15.9%)	178 (28%)	< 0.001
Generator change/upgrade	90 (66.7%)	180 (51%)	215 (33.8%)	< 0.001
3 or more leads	68 (50.4%)	208 (58.9%)	168 (26.4%)	< 0.001
Early pocket reentry	8 (5.9%)	50 (14.2%)	18 (2.8%)	< 0.001

CI = confidence interval; CIED = cardiac implantable electronic device. *P-values from the Kruskal–Wallis test for continuous variables and Pearson chi-square for discrete variables.

Role of the Manufacturer of the TYRX™-A and TYRX™ Antibacterial Envelopes

Medtronic Inc., the manufacturer of the TYRX™-A and TYRX™ antibacterial envelopes, did not play a role in the conception, planning, funding, conduct, or analysis of this investigator-initiated study. The authors independently made the decision to submit the study results for publication. A version of the manuscript was provided to Medtronic Inc. prior to final submission for publication to ensure appropriate use of terms and protection of intellectual property.

Results

The study cohort included 1,124 subjects with at least 2 CIED infection risk factors who underwent a CIED procedure. Of these, 135 received the TYRX™-A, 353 received the original TYRX™ envelope, and 636 did not receive an antibacterial envelope. Baseline patient characteristics including CIED infection risk factors are presented in Table 1. The mean (95% confidence interval [CI]) number of risk factors was similar among the 3 groups: 3.08 (2.84–3.32) for TYRX™-A, 3.20 (3.07–3.34) for TYRX™, and 3.09 (2.99–3.20) for controls, P = 0.3. The median (bootstrap 95% CI) length of follow-up differed significantly between TYRX™-A recipients, TYRX™ recipients, and controls: 421 (393–442) days, 649 (557–757) days, and 1,082 (972–1,176) days, respectively, P<0.001.

To address the significant differences in individual risk factors and length of follow-up between TYRX™-A recipients, TYRX™ recipients, and controls, we performed propensity score matching. For the 1st propensity matched cohort, we matched antibacterial envelope recipients (TYRX™-A or TYRX™) with controls. This resulted in a well-matched cohort of 632 subjects (Table 2). We also matched recipients of the absorbable TYRX™-A with controls, resulting in a well-matched cohort of 244 subjects (Table 3).

For the entire study cohort, the prevalence of CIED infection was significantly lower among antibacterial envelope recipients than in controls: 0 (0%) for TYRX™-A, 1 (0.3%) for TYRX™, and 20 (3.1%) for controls (P = 0.001 for global comparison, P = 1 for TYRX™-A vs. TYRX™, P = 0.034 for TYRX™-A vs. controls, P = 0.002 for TYRX™ vs. controls, and P< 0.001 for any antibacterial envelope vs. controls, Table 4). In a propensity score-matched cohort of 316 envelope recipients (either TYRX™-A or TYRX™) and 316 controls, the prevalence of infection was 0 (0%) and 9 (2.8%), respectively, P = 0.004. When limited to 122 TYRX™-A recipients and 122 propensity-matched controls, the prevalence of CIED infections was 0 (0%) and 5 (4.1%), respectively, P = 0.024.

We also conducted Cox proportional-hazards regression analysis and constructed Kaplan–Meier curves for CIED-free survival in antibacterial envelope recipients and controls. After adjusting for propensity score, the hazard ratio (95% CI) for CIED infection for antibacterial envelope recipients, compared with controls, was 0.05 (0.006–0.397), P = 0.005 (Fig. 1).

In an exploratory analysis, we analyzed the risk of CIED infection after early pocket reentry (within 2 weeks). In our total cohort of 1,124 patients, 76 had early pocket reentry (18 of 636 [2.8%] controls, 50 of 353 [14.2%] of nonabsorbable envelope recipients, and 8 of 135 [5.9%] of bio-absorbable envelope recipients). None of the subjects who had early pocket reentry suffered a CIED infection.

Time to presentation, culture results, and outcomes of the 21 subjects who suffered a CIED infection are presented in Table 5. Sixteen patients (76.2%) had positive blood cultures. Sixteen were treated with complete CIED system extraction. Three patients (14.3%) died within 6 months of CIED infection presentation.

Discussion

We found that in high-risk subjects with at least 2 CIED infection risk factors, the use of a new bio-absorbable antibacterial envelope (TYRX™-A) was associated with a very low prevalence of CIED infections. The prevalence of CIED infections observed with the bio-absorbable TYRX™-A envelope was similar to the prevalence observed with the older nonabsorbable envelope and was considerably lower than in control subjects who harbored a similar number of risk factors but were not treated with an antibacterial envelope. Our findings are clinically important because they provide evidence for the efficacy of the new bio-absorbable TYRX™-

TABLE 2
Clinical Characteristics for Antibacterial Envelope (TYRX™-A or TYRX™) Recipients and Propensity Score-Matched Controls

	Antibacterial Envelope Recipients (N = 316)	Controls (N = 316)	P-Value*
Absorbable envelope	76 (24.1%)	0	–
Age, years, median (95% CI)	70 (68–71)	70 (68–72)	0.925
Women	101 (32%)	116 (36.7%)	0.209
Serum creatinine, median, mg/dL (95% CI)	1.36 (1.26–1.44)	1.28 (1.21–1.34)	0.250
Chronic kidney disease	136 (43%)	133 (42.1%)	0.809
Diabetes mellitus	150 (47.5%)	143 (45.3%)	0.577
Systemic anticoagulation	204 (64.6%)	202 (63.9%)	0.868
Chronic corticosteroids	32 (10.1%)	40 (12.7%)	0.317
Prior CIED infection	19 (6%)	16 (5.1%)	0.602
Pacemaker dependent	103 (32.6%)	91 (28.8%)	0.301
Fever/leukocytosis	63 (19.9%)	71 (22.5%)	0.436
Generator change/upgrade	151 (47.8%)	144 (45.6%)	0.577
3 or more leads	150 (47.5%)	133 (42.1%)	0.174
Early pocket reentry	15 (4.7%)	17 (5.4%)	0.717
Length of follow-up, days, median (95% CI)	569 (524–640)	559 (435–768)	0.073

CI = confidence interval; CIED = cardiac implantable electronic device. *P-values from Mann–Whitney U-test for continuous variables and Pearson chi-square or Fisher's exact test, as appropriate, for discrete variables.

TABLE 3
Clinical Characteristics for TYRX™-A Absorbable Envelope Recipients and Propensity Score-Matched Controls

	TYRX™-A Recipients (N = 122)	Controls (N = 122)	P-Value*
Age, years, median (95% CI)	68 (65–71)	69 (66–72.5)	0.454
Women	39 (32%)	47 (38.5%)	0.284
Serum creatinine, median, mg/dL (95% CI)	1.30 (1.19–1.45)	1.19 (1.11–1.31)	0.434
Chronic kidney disease	43 (35.2%)	45 (36.9%)	0.790
Diabetes mellitus	52 (42.6%)	59 (48.4%)	0.368
Systemic anticoagulation	75 (61.5%)	67 (54.9%)	0.299
Chronic corticosteroids	9 (7.4%)	14 (11.5%)	0.273
Prior CIED infection	4 (3.3%)	2 (1.6%)	0.408
Pacemaker dependent	42 (34.4%)	41 (33.6%)	0.893
Fever/leukocytosis	13 (10.7%)	18 (14.8%)	0.336
Generator change/upgrade	77 (63.1%)	77 (63.1%)	1
3 or more leads	58 (47.5%)	54 (44.3%)	0.607
Early pocket reentry	7 (5.7%)	5 (4.1%)	0.554
Length of follow-up, days, median (95% CI)	412 (371.5–432)	230 (149–326)	0.001

CI = confidence interval; CIED = cardiac implantable electronic device. *P-values from Mann–Whitney U-test for continuous variables and Pearson chi-square or Fisher's exact test, as appropriate, for discrete variables.

TABLE 4
Frequency of Cardiac Implantable Electronic Device Infections Among Antibacterial Envelope Recipients and Controls in the Entire Study Cohort and in the Propensity Score-Matched Cohorts

	TYRX™-A	TYRX™	Controls	P-Value*
Entire study cohort (N = 1,124)	0	1 (0.3%)	20 (3.1%)	0.001
Propensity-matched cohort 1 (N = 632)	0	0	9 (2.8%)	0.004
Propensity-matched cohort 2 (N = 244)	0	–	5 (4.1%)	0.024

*P-values from Fisher's exact test. Propensity-matched cohort 1 includes TYRX™-A and TYRX™ recipients and matching controls. Propensity-matched cohort 2 includes TYRX™-A recipients and matching controls.

A antibacterial envelope for preventing CIED infections in selected high-risk patients. Due to the high morbidity, mortality, and costs associated with CIED infections, prevention of these complications is critically important. Additionally, increased accountability for preventable device related complications mean U.S. hospitals may shoulder the burden of payment for costly extraction, CIED re-implantation, and treatment of CIED infection.

Most CIED infections are thought to occur as a result of bacterial seeding at the time of implantation.[5] Accordingly, strategies to reduce the incidence of CIED infections have focused on keeping the implantation site sterile in the perioperative period and include intraoperative intravenous cefazolin,[16] skin preparation with chlorhexidine-alcohol,[17] intraoperative antibacterial wash solutions, and perioperative oral antibiotics.[18] Despite these therapies, the incidence of CIED infections remains unacceptably high at 1–3%,[1-3,19-23] and additional strategies to reduce the rate of infections are needed. The TYRX™-A antibacterial envelope might emerge as a first line prophylactic therapy for patients at

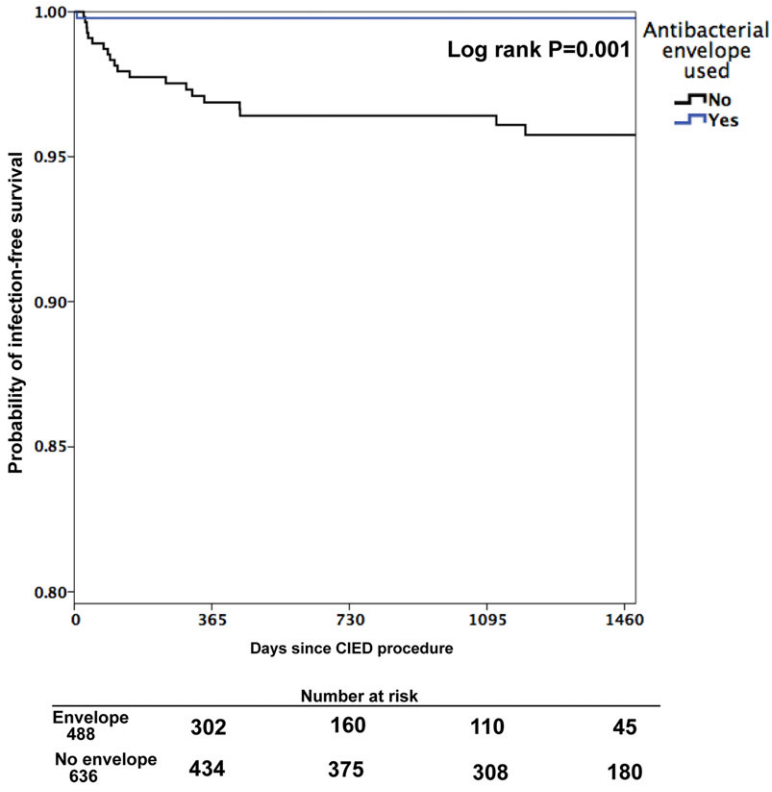

Figure 1. *Probability of cardiac implantable electronic device infection-free survival among subjects with ≥2 risk factors for infection who did (blue curve) and did not (black curve) receive an antibacterial envelope. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce*

TABLE 5

Clinical Presentation, Treatment, and Outcomes of Subjects Who Had a Cardiac Implantable Electronic Device Infection

Days Until Infection, Median (95% CI)	**107 (48–297)**
Time until infection, n (%)	
< 6 months	13 (61.9%)
6–12 months	4 (19%)
>12 months	4 (19%)
Infection type, n (%)	
Pocket only	6 (28.6%)
Systemic	15 (71.4%)
Blood culture results, n (%)	
CoNS	4 (19%)
MSSA	3 (14.3%)
MRSA	3 (14.3%)
Enterococcus	3 (14.3%)
Streptococcus	2 (9.5%)
Pseudomonas	1 (4.8%)
Negative	5 (23.8%)
CIED system extraction, n (%)	16 (76.2%)
Died within 6 months of infection, n (%)	3 (14.3%)

CIED = cardiac implantable electronic device; CoNS = coagulase-negative Staphylococcus; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

high risk for CIED infections. Although efficacy data from randomized prospective studies of the antibacterial envelope are not yet available, several studies have found that the use of the nonabsorbable envelope is associated with a low prevalence of CIED infection.[6-8] A recent retrospective study found that the routine use of the nonabsorbable envelope was not only associated with a significant reduction of CIED infections but was also cost-effective.[9] In addition to confirming these findings, our study provides the first clinical efficacy data on infection rates comparing subjects treated with the TYRX^{TM}-A bio-absorbable antibacterial envelope, the nonabsorbable antibacterial envelope, and matched high-risk control subjects who were not treated with an envelope.

Several important limitations should be considered when interpreting the results of our study. As with all retrospective, nonrandomized studies, our study is prone to selection bias and unmeasured confounders. There were potentially important differences in the prevalence of CIED risk factors between antibacterial envelope recipients and controls. Potential reasons for this observation include differences in how cases and controls were selected and how data were extracted, the use of historical controls, selection bias, or other, unknown reasons. In addition, the follow-up period was significantly shorter for antibacterial envelope recipients, particularly those treated with the TYRX^{TM}-A, than for controls. Because of concerns about over-fitting a model with the low number of events (n = 21) in our cohort, we were unable to adjust for length of follow-up, individual risk factors, and other variables with multivariable regression. Because of the low number of events, we were unable to stratify for individual CIED infection risk factors or determine their relative impact on the primary outcome. We sought to overcome many of these limitations by utilizing propensity score matching. We found that our primary results were similar in the propensity-matched cohorts and in the entire, unmatched cohort. However, it should be noted that the use of propensity score matching could introduce bias and result in over- or under-estimation of the treatment effect.

Conclusions

Among high-risk subjects with at least 2 established risk factors for infection, the use of the TYRX^{TM}-A

bio-absorbable envelope was associated with a very low prevalence (0%) of CIED related infections that was comparable to that seen with the nonabsorbable envelope. Randomized clinical trial data are needed to support more wide spread use of the antibacterial envelope.

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