

The World-Wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) to Reduce CIED Infection

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for the WRAP-IT Investigators

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The Scope of CIED* Infections

- An estimated 1.5 million patients receive a CIED worldwide every year¹
- 1-4% of procedures are associated with an infection²



*Cardiac Implantable Electronic Device (CIED)

1. Mond HG et al. *PACE* 2011;34:1013-27; 2. Tarakji KG et al. *Am Heart J.* 2016;180:12-21

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The Consequences of CIED Infection

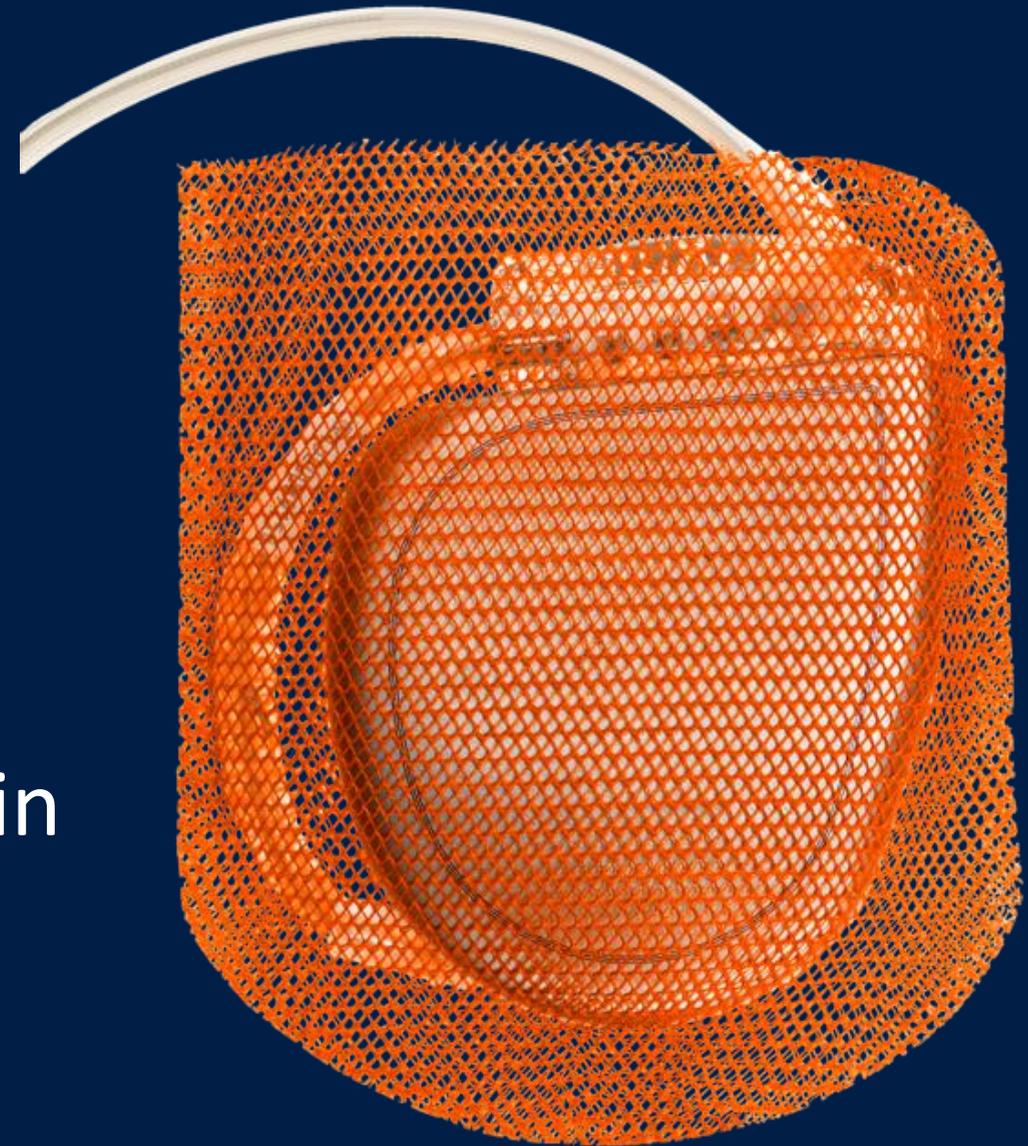
- Complete device and lead removal, prolonged antibiotic therapy¹
- Long hospital stay
- Short and long term mortality^{2,3}
- \$44,000 - \$83,000 average cost to treat⁴



Pre-operative antibiotics are the only intervention shown to reduce the risk of CIED infection⁵

The TYRX Absorbable Antibacterial Envelope

- A single-use device, stabilizes CIED
- Absorbable multifilament knitted mesh
- Polymer-controlled antibiotic elution
- Locally delivered minocycline and rifampin sustained for 7 days
- Fully absorbed in about 9 weeks



WRAP-IT Study Aim

To evaluate the safety and effectiveness of the TYRX envelope in reducing CIED infections in addition to standard infection prevention strategies

WRAP-IT Study Design

- Prospective, randomized, controlled, multicenter, global trial
- Randomized 1:1 to TYRX Envelope vs Control (no TYRX)
- Independent Clinical Events Committee
 - Electrophysiologists & Infectious Disease specialists
- Independent Data Monitoring Committee
- Independent validation of results
 - The Cleveland Clinic Coordinating Center for Clinical Research

WRAP-IT Study Patients

Included

- CIED generator replacement, system upgrade, or revision
- Initial CRT-D

Excluded

- Hemodialysis or peritoneal dialysis
- Immunosuppressive agents (chronic oral or ≥ 20 mg of prednisone)
- Recent CIED infection (<12 months)

WRAP-IT Study Primary Objective

Rate of Major CIED Infections through 12-months post-procedure

- TYRX Envelope vs Control
- Intention-to-treat analysis
- Cox regression stratified by device class
 - Low-power and high-power devices

WRAP-IT Study Definitions of CIED Infection, Major Infection

CIED infections were defined as:

- 1) Superficial cellulitis with wound dehiscence, erosion, or purulent drainage
- 2) Deep incisional or generator pocket infection
- 3) Persistent bacteremia
- 4) Endocarditis

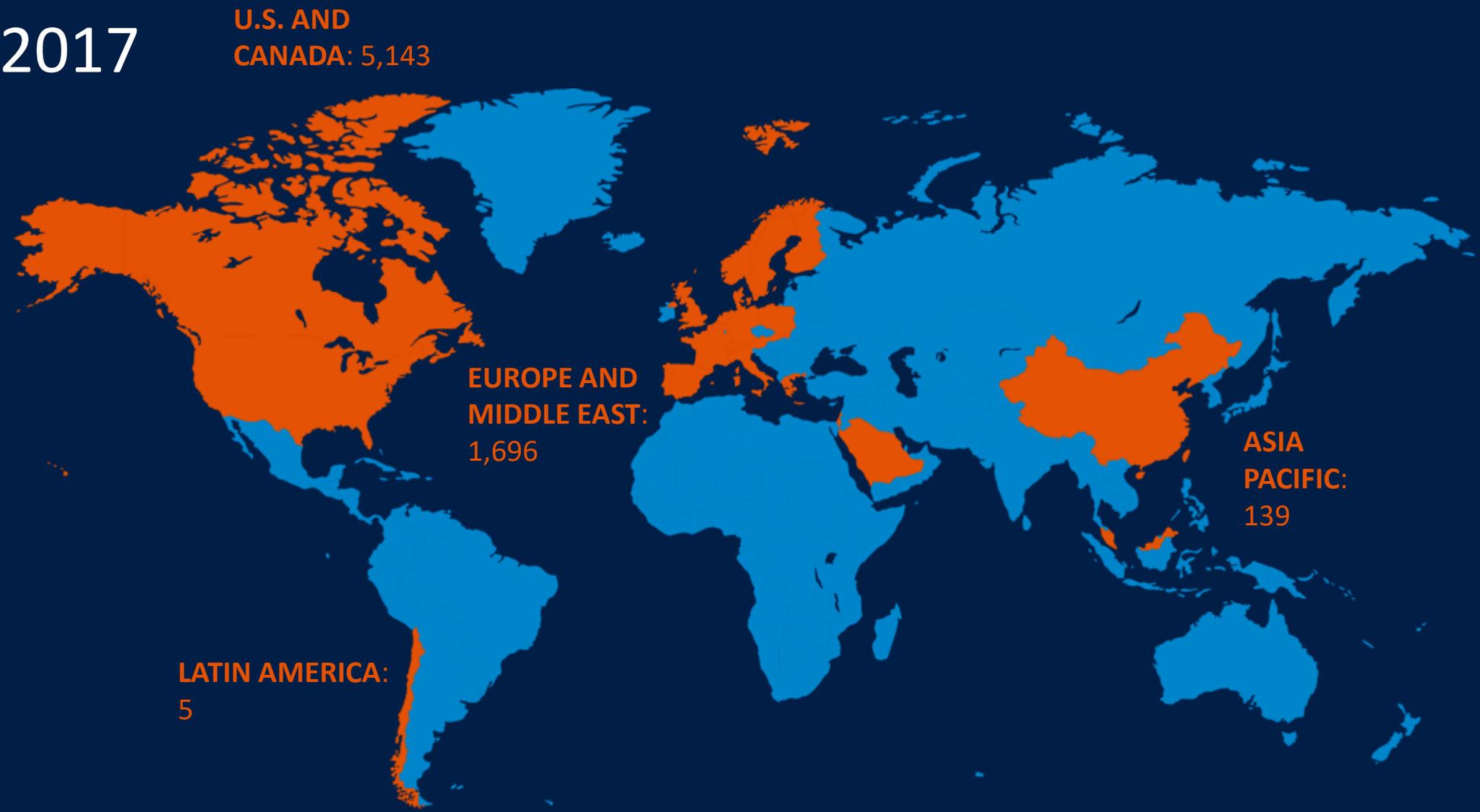
Major CIED Infections were defined as CIED infections resulting in one or more of the following:

- CIED system removal
- Any invasive procedure (e.g. pocket opened) without system removal
- Extended antibiotic therapy if the patient was not a candidate for system removal
- Death

Note: All other CIED infections including superficial incisional surgical site infections that met the CDC criteria, independent of the time from surgery, were defined as minor CIED infections unless they met the major CIED infection criteria.

WRAP-IT Study Patient Enrollment

- January 2015-July 2017
- 6,983 patients randomized
- 25 countries
- 181 centers
- 776 implanting physicians



Balanced Baseline Characteristics Between Groups

Characteristic	Envelope (N = 3495)	Control (N = 3488)
Age, (years) [Mean ± SD]	70.0 ± 12.6	70.1 ± 12.4
Female (%)	997 (28.6%)	976 (28.0%)
BMI (kg/m ²) [Mean ± SD]	29.1 ± 6.1	29.2 ± 6.3
Diabetes	1080 (31.0%)	1085 (31.2%)
Renal dysfunction	585 (16.8%)	554 (15.9%)
Baseline Medications		
Antiplatelets	2007 (57.5%)	1972 (56.6%)
Anticoagulants	1377 (39.5%)	1390 (39.9%)
Antibiotics	36 (1.0%)	37 (1.1%)
Immunosuppressive*	48 (1.4%)	85 (2.4%)
Insulin	348 (10.0%)	375 (10.8%)
Oral antidiabetic	615 (17.6%)	620 (17.8%)

*No significant differences between groups except for the use of immunosuppressive agents (p=0.001); standardized difference does not suggest imbalance

Balanced Procedure Characteristics Between Groups

Characteristic	Envelope (N = 3495)	Control (N = 3488)
Infection Management Strategy*		
Peri-procedure antibiotic	3402 (98.6%)	3413 (98.7%)
Post-procedure antibiotic	987 (28.6%)	1058 (30.6%)
Pocket wash	2539 (73.6%)	2610 (75.5%)
CIED Low Power†		
Pacemaker	723 (20.7%)	709 (20.3%)
CRT-P	133 (3.8%)	157 (4.5%)
CIED High Power†		
ICD	964 (27.6%)	909 (26.1%)
CRT-D	1675 (47.9%)	1713 (49.1%)
Procedure attempted, no CIED	2 (0.1%)	3 (0.1%)
No procedure attempted	44 (1.3%)	31 (0.9%)

Very low
cross-over rate
(0.7% Control;
2.3% Envelope)

99.7% implant
procedure
success rate
with TYRX‡

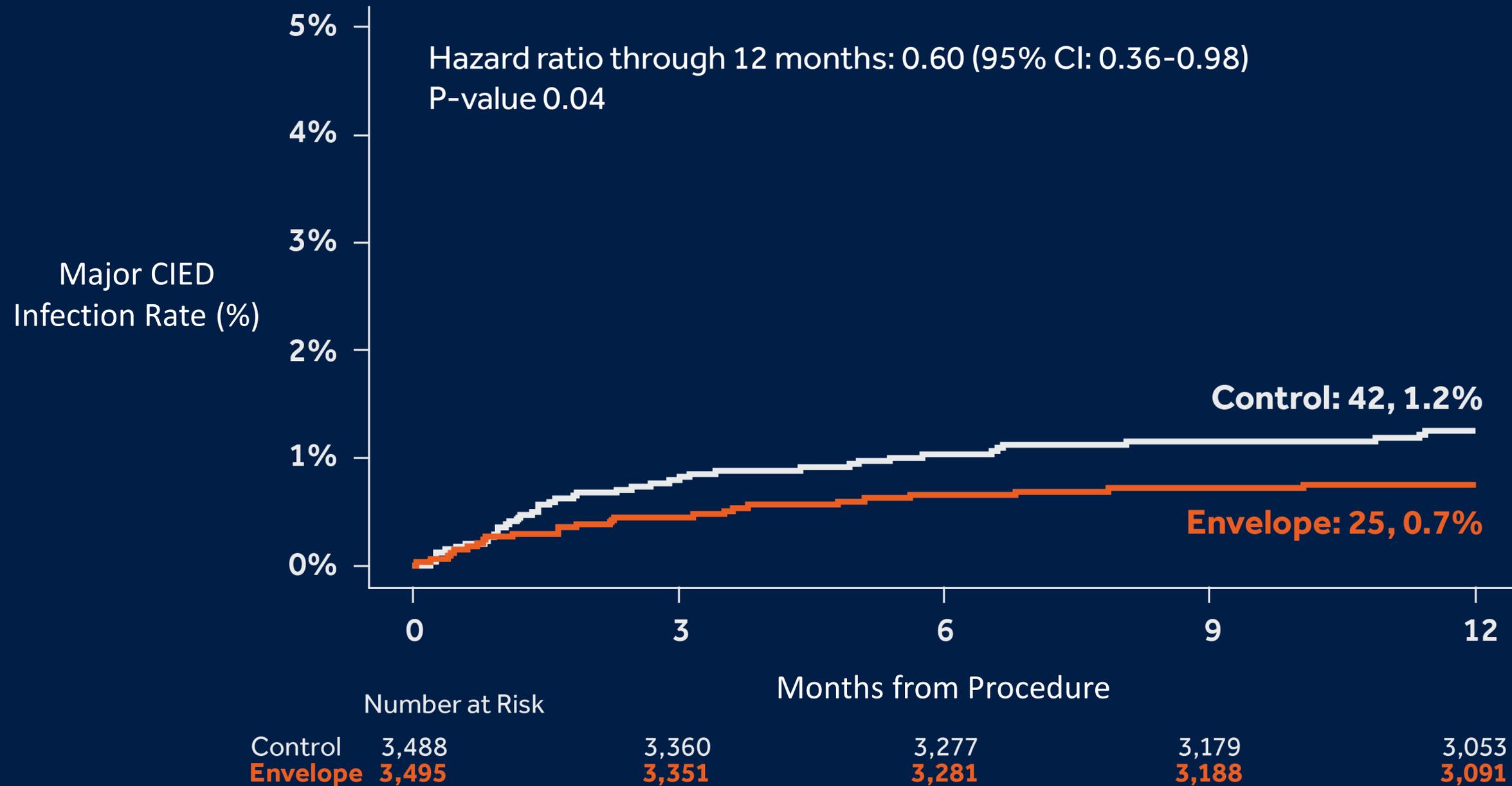
*Counts and percentages reflect subjects with procedure attempts.

†Device type planned at randomization

‡Envelope group patients with successful CIED procedure and TYRX implant attempt by 646 implanters

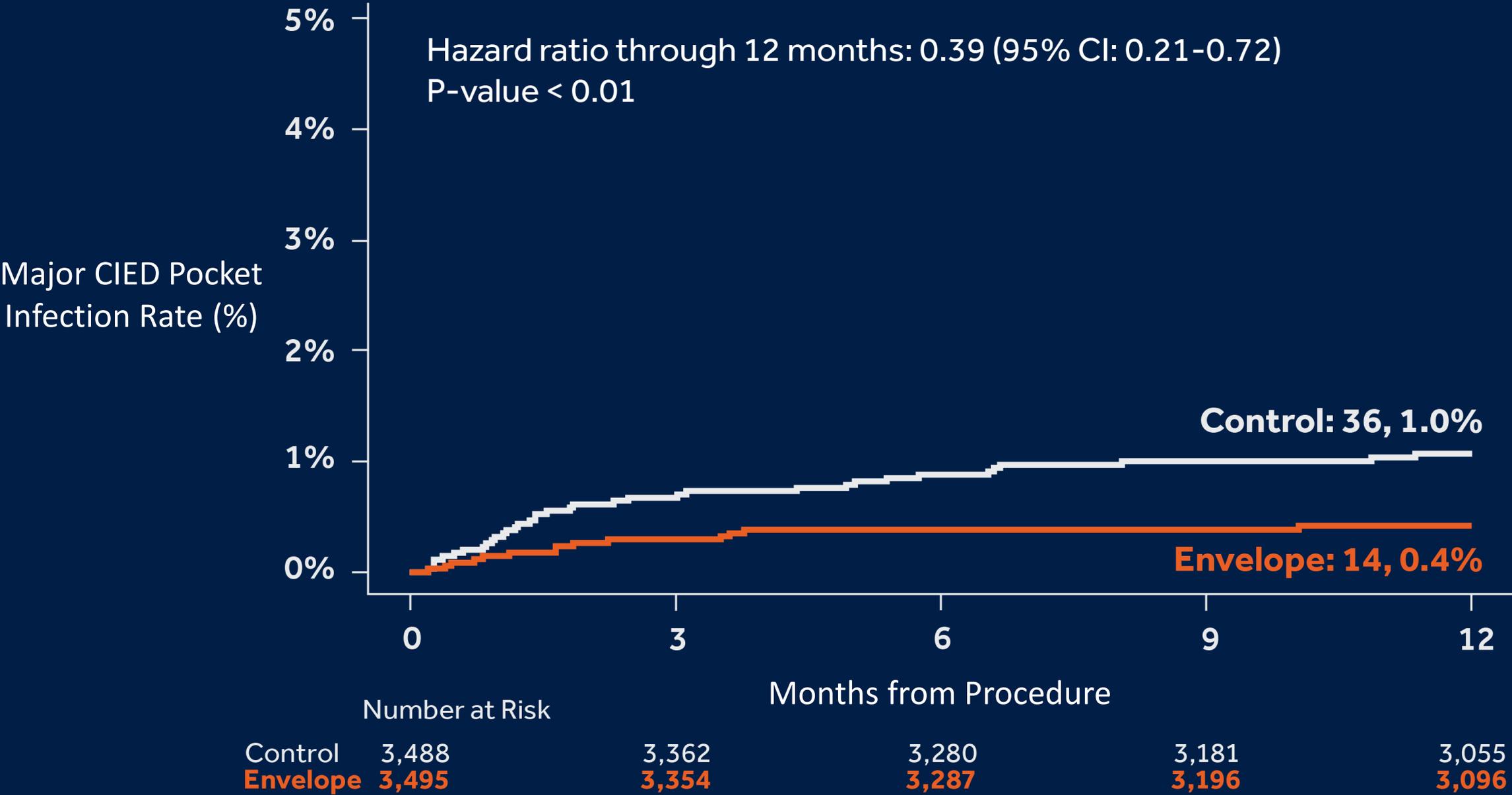
WRAP-IT Study Primary Endpoint: Major CIED Infection

40% Reduction in Major CIED Infections with TYRX through 12 Months



WRAP-IT Study: Major CIED Pocket Infections

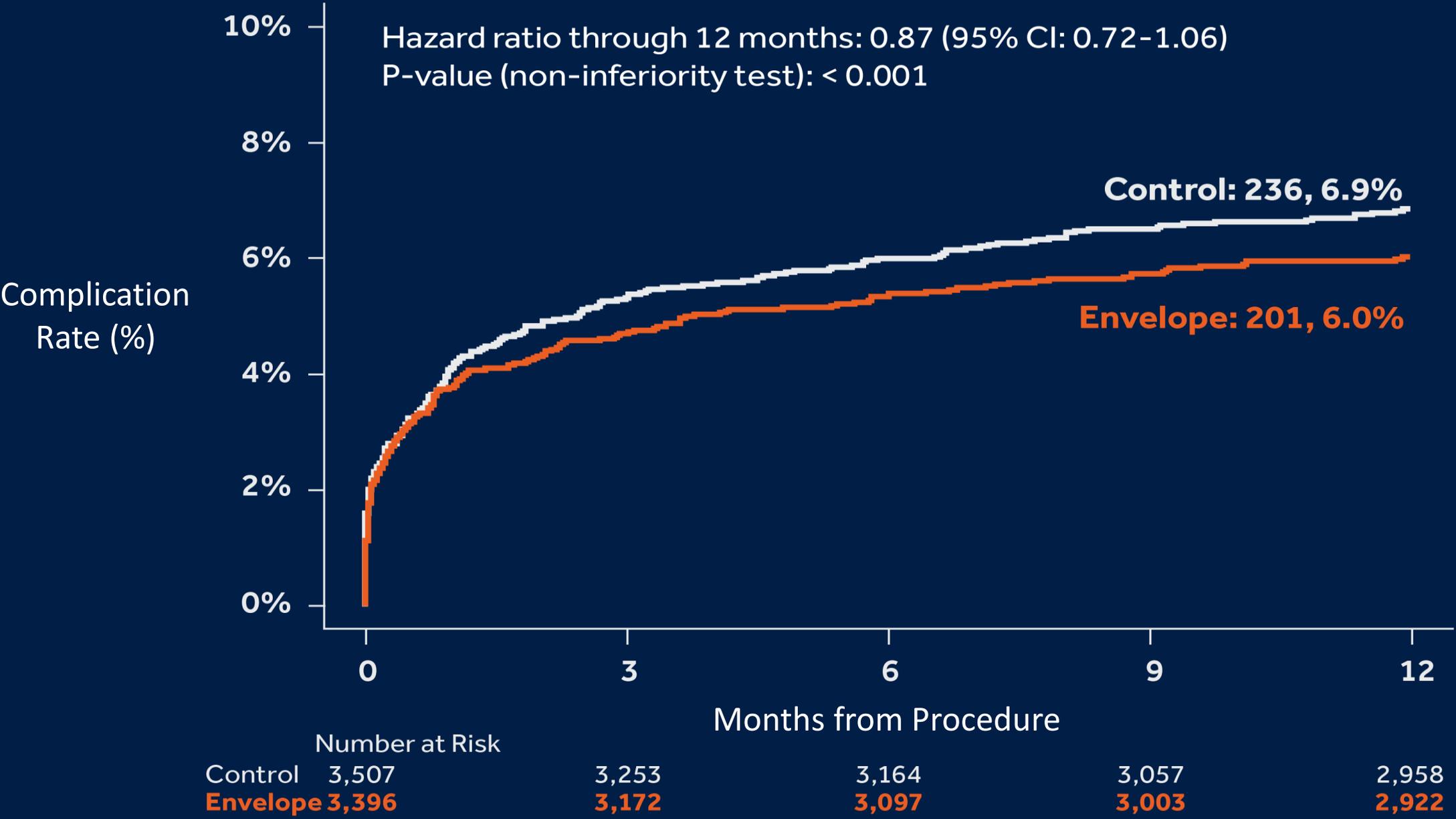
61% Reduction in Major CIED Pocket Infections with TYRX through 12 Months



74.6% of initial major CIED infections were pocket infections

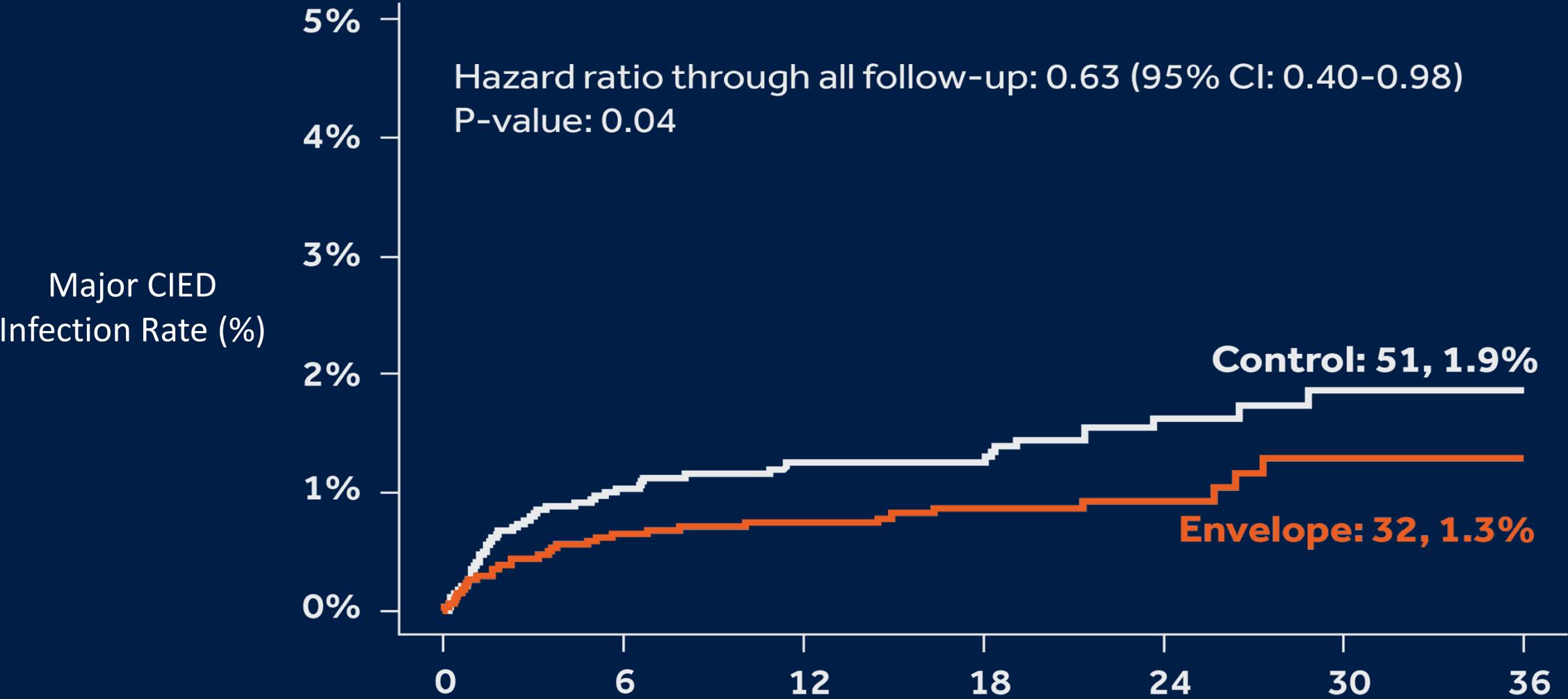
WRAP-IT Study Secondary Endpoint: Safety Objective

No Increased Risk of Complications with TYRX through 12 Months



Prespecified secondary analysis for non-inferiority, as treated. When excluding the primary endpoint major infections, the 12-month Kaplan-Meier complication event rates were 5.7% Envelope vs. 5.9% Control.

WRAP-IT Study Secondary Endpoint: Major CIED Infections All Follow-up Effect Sustained with TYRX through Follow-up

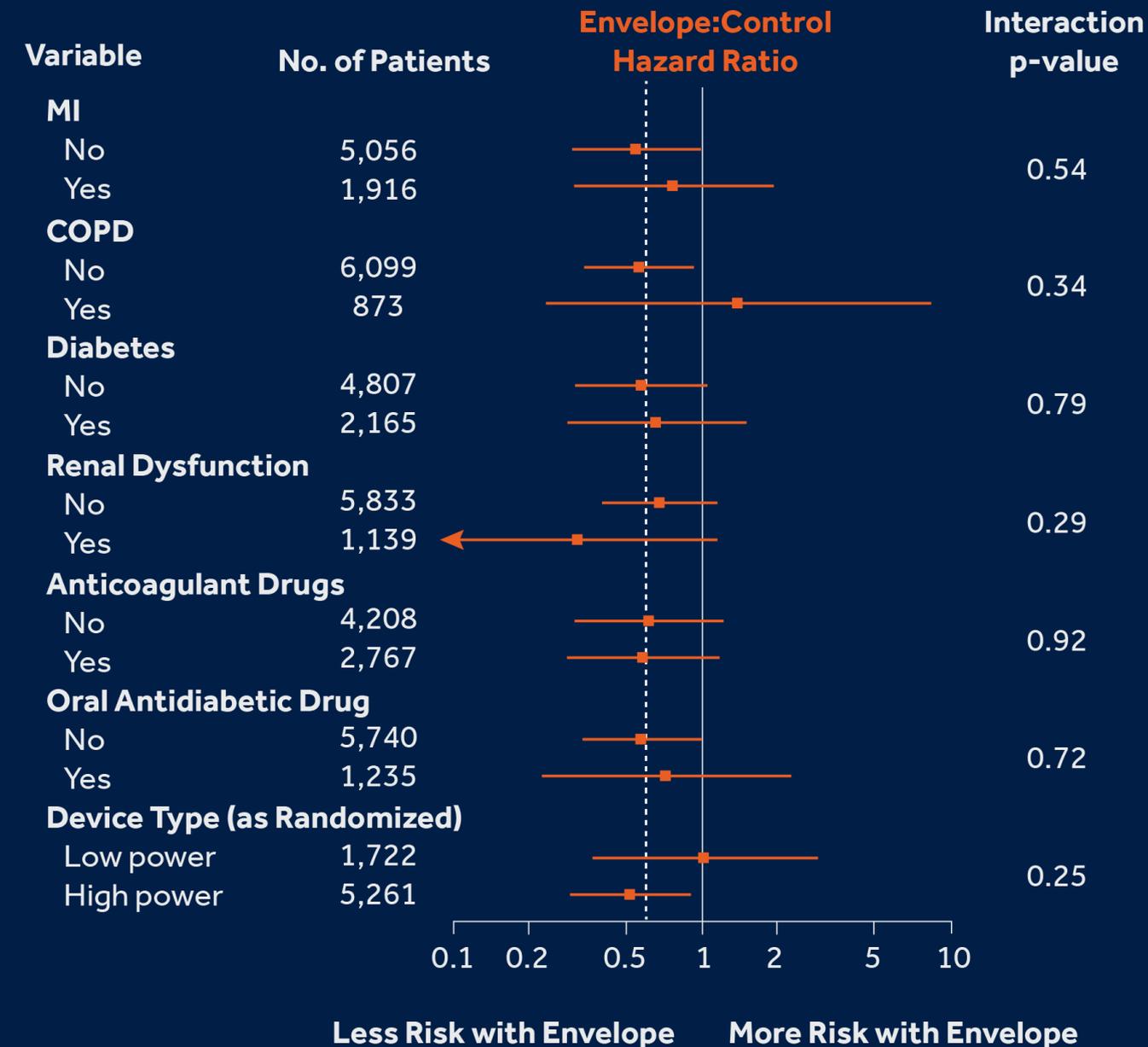
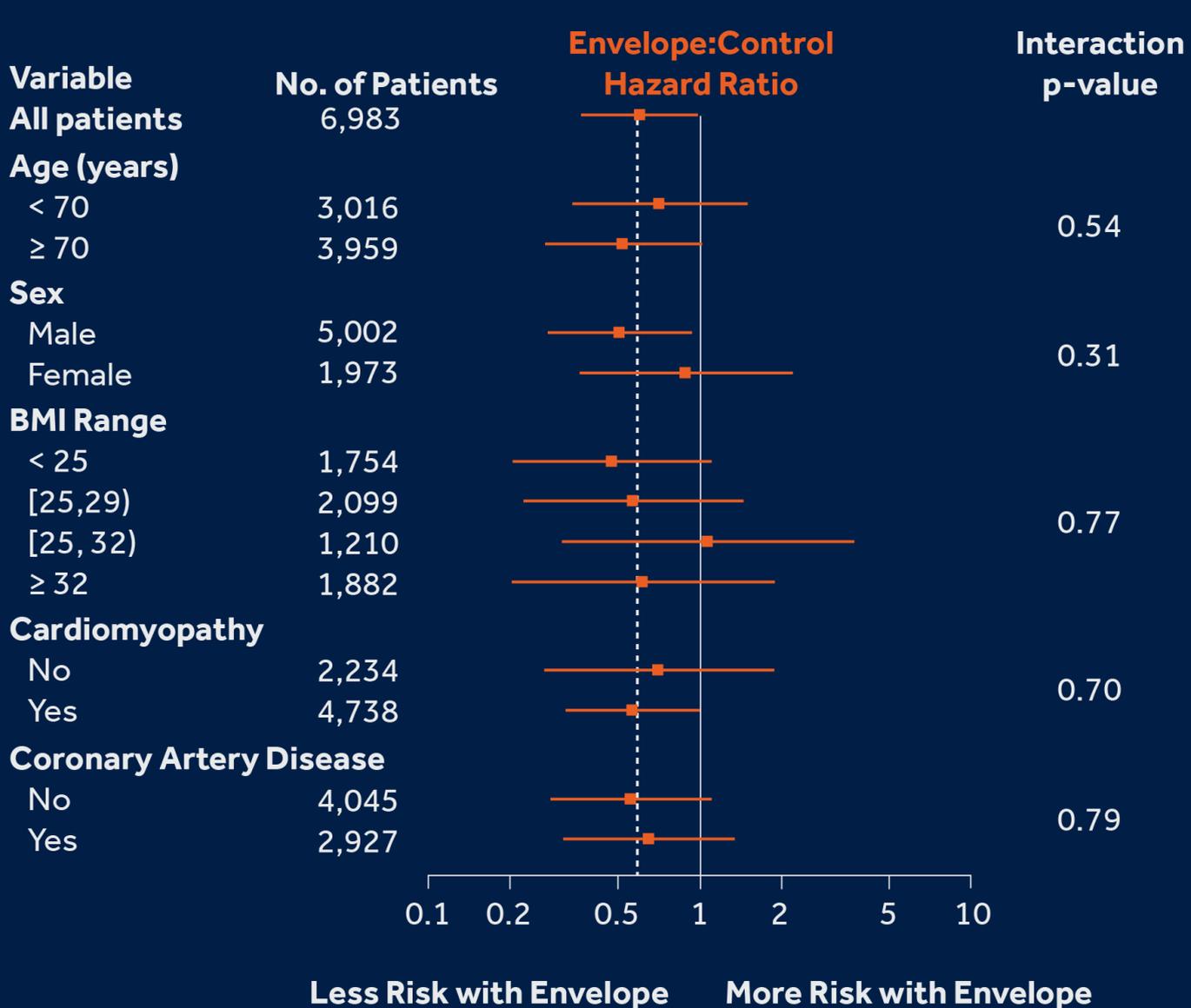


	Number at Risk						
	0	6	12	18	24	30	36
Control	3,488	3,277	3,053	2,193	1,408	571	130
Envelope	3,495	3,281	3,091	2,178	1,395	581	121

P-value shown was not adjusted for multiple comparisons. After the prespecified adjustment for multiple comparison was done, the adjusted p-value was not significant. Patients were followed for an average of 20.7±8.5 months.

WRAP-IT Study Subgroup Analysis

Reduction in Major CIED Infections Consistent Across Sub-groups



The subgroup analysis was conducted to test for interaction among various baseline variables for the primary end point through 12 months.

WRAP-IT Study Limitations

- One manufacturer's devices, non-sequential patients
- Commercial availability of TYRX Envelope allowed for possible selection bias
- Immunosuppressive use at baseline was not balanced between cohorts

WRAP-IT Study Conclusions

In patients undergoing CIED generator replacement, system upgrade, or revision or initial CRT-D implantation

- The rate of major CIED infections was 1.2% at 1 year
- The TYRX envelope significantly reduced major CIED infections by 40%, without increasing complications
- Major pocket infections were reduced by 61%

This study provides comprehensive data on CIED infection and strong evidence for the use of the TYRX envelope for infection prevention in this patient population

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ORIGINAL ARTICLE

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