The World-Wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT): Long-Term Follow-Up

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Introduction: Cardiac implantable electronic device (CIED) infections are associated with substantial morbidity and mortality. A fully-absorbable multifilament mesh envelope (TYRX) was developed, which elutes minocycline and rifampin. In the largest global randomized trial of CIEDs to date, the WRAP-IT study, the primary objective was achieved with TYRX demonstrating a 40% reduction in major CIED infections, 61% reduction in pocket infections, and with no increased risk of complications through 12 months follow-up. We now sought to assess the longer-term effects of the envelope on infection reduction and on safety in these patients.

Methods: WRAP-IT was a worldwide multi-center trial in patients undergoing CIED replacement, upgrade, revision, or de novo CRT-D implant. All patients received standard-of-care infection prevention strategies and were then randomized 1:1 to receive the envelope or not. The primary endpoint was major CIED infection within 12 months of the procedure. The secondary endpoint was to confirm that the envelope does not increase CIED procedure- or system-related complication rates through 12-months post-procedure. We further characterized the envelope effect on infection and complications through the entire follow-up period. Data were analyzed with an as-treated approach using a Cox proportional hazards regression model and the observed hazard ratio for the effect of the envelope on the rate of CIED procedure- or system-related complications was compared to a non-inferiority margin of 1.33.

Result: A total of 6903 patients (mean age: 70.0±12.5 years, 28% female) underwent CIED generator replacement or revision, upgrade, or de novo CRT-D implant in 181 centers, in 25 countries, by 776 physicians. Device types included CRT-D (49%), CRT-P (4%), ICD (26%), and IPG (20%). At the initial procedure, 3396 patients received an envelope and 3507 did not receive an envelope. Mean follow-
up duration was 20.9±8.3 months. The effect of the envelope was sustained through 36 months of follow-up with a significant reduction in all CIED infections (HR: 0.70, CI: 0.5-0.98, p=0.036) and without increased risk of procedure- or system-related complications (non-inferiority test, p<0.001) (Figure). Implant site pain was less common in the envelope group (0.1% vs. 0.4%, p=0.0298). There were no significant group differences in the incidence of pocket erosion, lead damage, or pocket hematoma (all p>0.05). There were no reports of allergic reactions to the components of the envelope (mesh, polymer, or antibiotics).

**Conclusion:** In addition to standard-of-care infection prophylaxis, the TYRX envelope significantly reduced CIED infection by 40% through 12 months follow-up, and the beneficial effects of the envelope are sustained beyond the first year post-procedure. The envelope does not increase risk of complication and was associated with a reduced risk of implant site pain.