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TYRX pocket- the perfect pocket?

Approximately 1.5 million cardiac implantable electronic devices (CIEDs) are inserted worldwide annually.[1] In this month's DASON newsletter, we review a recent randomized controlled trial that evaluated the safety and efficacy of the TYRX Absorbable Antibacterial Envelope in preventing CIED infections (WRAP-IT trial).[2]

Trends in CIED infections

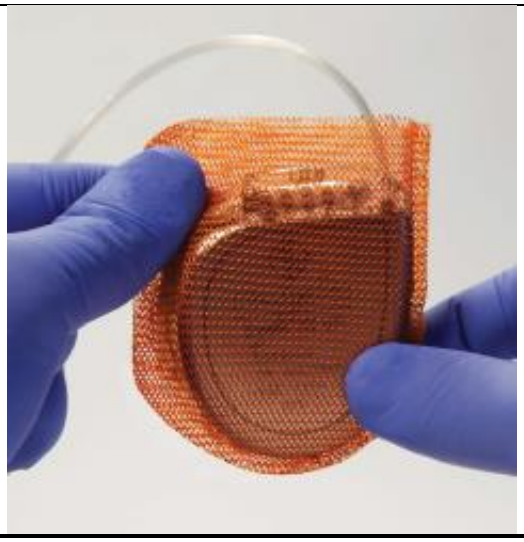
CIED infections are devastating complications with potentially fatal outcomes and are associated with prolonged hospitalization and high financial costs.[3] Even with optimal surgical techniques and use of effective peri-operative antibiotics, the total 'infection burden' associated with CIED implantations continues to rise. This rising burden is primarily due to an exponential increase in the volume of CIED procedures, many times involving elderly patients with complex comorbidities.[3, 4] The only prior randomized controlled trial that was proven to reduce CIED infections related to the use of peri-operative antibiotics.[5]

Thus, the findings of the WRAP-IT trial are important as there is a clear need for novel infection prevention strategies to prevent CIED infections.

TYRX envelope/pocket

The TYRX envelope is an absorbable single-use mesh envelope placed around a CIED at the time of its insertion. The composition of the mesh filament is similar to a bioabsorbable suture.[6] This mesh material is fully absorbed in approximately 9 weeks.[6] The mesh elutes minocycline and rifampin into local tissue for a minimum of 1 week, which in turn may reduce the local bacterial burden introduced at the time of insertion and subsequent biofilm formation after insertion.[6] Minocycline and rifampin were selected because of their activity against Staphylococcus aureus and coagulase-negative Staphylococcus species- the causative pathogens in approximately 70% of CIED infections.[4, 7]

Figure 1: TYRX Absorbable Antibacterial Envelope. From Medtronic, TYRX Clinician Brochure 2016.



WRAP-IT Trial

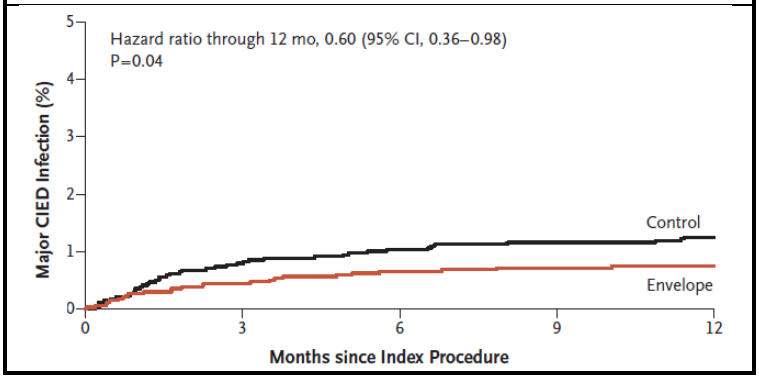
The WRAP-IT trial was an international, multi-center, manufacturer-sponsored, prospective, non-blinded randomized controlled trial involving 6893 adults who were randomized in a 1:1 ratio to receive the TYRX envelope or standard therapy. Patients who were receiving an initial cardiac resynchronization therapy defibrillator (CRT-D) implant, undergoing a CIED generator replacement or pocket revision were enrolled in this trial. Immunosuppressed patients, patients with an active infection, patients with a prior CIED infection in the preceding year or receiving renal replacement therapy were excluded. All patients received standard-of-care infection prevention strategies. The mean duration of follow up was 20.7 months. Approximately 60 patients in each group were lost to follow up.

The results and their interpretation

The primary outcome was major CIED infection within 12 months after CIED procedure. A major infection was defined as infections resulting in CIED removal or treatment with long course antibiotics with infection recurrence following antibiotic therapy completion or the need for a subsequent invasive CIED procedure (such as pocket revision), or death.

Using an intention-to-treat analysis, study authors found a 40% lower incidence of major CIED infections in the envelope group than the control group (12-month Kaplan-Meier estimated event rate 0.7% and 1.2% respectively; hazard ratio, 0.60; 95% CI, 0.35-0.98; p=0.04). This difference was largely driven by a reduction in pocket infections (0.4% in the envelope group compared to 1.0% in the control group). However, more patients receiving the envelopes developed endocarditis or persistent bacteremia infections but this difference was not statistically significant (hazard ratio 1.57; 95% CI 0.61-4.05; p value not significant).

Figure 2: Kaplan-Meier curves for the first major CIED infection through 12 months. From Tarakji et al, NEJM 2019.



Staphylococci were the causative pathogen in 64% of initial infection events. A major weakness of the trial was the lack of antibiotic susceptibility data in the patients in the trial who developed infections. Thus, we do not know if the patients who received envelopes became infected with organisms that were resistant to minocycline and/or rifampin.

A post-hoc analysis revealed that the sub-group of patients who received an envelope and an initial CRT-D implant were more than twice as likely to develop major CIED infections as those in the control group (1.3% in the intervention group compared to 0.5% in the control group; hazard ratio 2.55). Secondary endpoints (complications and death) did not raise any safety concerns.

The number needed to treat to prevent one infection was approximately 200 patients. Thus, using an estimated price of $1000 per envelope, the cost of preventing one infection would be approximately $200,000.

Other limitations of the trial were the low rate of CIED infection in the trial (1.2% compared to 2% expected rate of infection in the control arm), which meant the trial was close to being underpowered. More importantly, if 1 additional patient in the intervention group had developed the primary outcome, the trial would have lost its statistical significance (i.e. for a p-value of <0.05),

Additionally, as the median time from CIED implantation to development of infection was reported in a recent study to be 2.3 years, longer-term outcomes on the safety and efficacy of TYRX envelopes in preventing CIED infections could not be evaluated.[4] Finally, the impact of selective pressure on antibiotic resistance was not assessed in this trial.

Recommendations

1. At present, we do not recommend the use of the TYRX device for the following reasons:
    a. The benefit derived from a small reduction in pocket infections may be off-set by the trend towards increased serious infections (endocarditis or bacteremia).
    b. The disproportionate cost-benefit ratio of a small absolute risk reduction (0.5%) translates into approximately 200 patients to treat and a cost of approximately $200,000 to prevent 1 CIED infection.
    c. The potential of this device to induce antibiotic resistance to minocycline and/or rifampin was not assessed.

2. The concept is valid and promising and expansion of this concept to include other antibiotics or agents (such as antiseptic agents) is an area for future research.
3. Extrapolating from studies on antibiotic-impregnated central venous catheters, subgroups where this device may be most beneficial in are patients with compromised skin integrity (such as burn patients) or when the risk of CIED infections remains higher than average despite implementing bundled standard procedures.[8, 9] In these sub-groups, this device could be considered to reduce pocket infections, however with the trend towards increased serious infections (endocarditis or bacteremia), this is unlikely to resolve the underlying issue of CIED infections.
4. We strongly recommend that CIED infection prevention strategies should continue to concentrate on operating theatres or catheterization suites meeting operating theatre guidelines and administration of peri-operative intravenous antibiotics, according to the existing standards of the American Heart Association.[10] Anecdotally, CIED insertions are often performed in catheterization suites that traditionally have not adhered to strict sterility practices as in an operating room. The DICON position statement on January 21 2013 highlights standard-of-care infection prevention standards recommended by DICON in suites and laboratories where CIEDs are inserted.[11]

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