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

Khaldoun G. Tarakji, MD, MPH
Cleveland Clinic, Cleveland, OH
@khaldoorrentarakji

Khaldoun G. Tarakji M.D., M.P.H., Suneet Mittal M.D., Charles Kennergren M.D., Ph.D., Ralph Corey M.D., Jeanne E. Poole M.D., Edward Schloss M.D., Jose Gallastegui M.D., Robert A. Pickett M.D., Rudolph Evonich M.D., François Philippon M.D., Janet M. McComb M.D., Steven F. Roark M.D., Denise Sorrentino M.D., Darius Sholevar M.D., Edmond Cronin M.B. B.Ch. B.A.O., Brett Berman M.D., David Riggio M.D., Mauro Biffi M.D., Hafiza Khan M.D., Marc T. Silver M.D., Jack Collier M.D., Zayd Eldadah M.D. Ph.D., David Justin Wright M.D., Jeff D. Lande Ph.D., Daniel R. Lexcen Ph.D., Alan Cheng M.D., and Bruce L. Wilkoff M.D., for the WRAP-IT Investigators

Sunday, March 17th, 2019 | #WRAPITstudy | #ACC19
The Scope of CIED* Infections

• An estimated 1.5 million patients receive a CIED worldwide every year\(^1\)

• 1-4% of procedures are associated with an infection\(^2\)

*Cardiac Implantable Electronic Device (CIED)
The Consequences of CIED Infection

• Complete device and lead removal, prolonged antibiotic therapy\(^1\)

• Long hospital stay

• Short and long term mortality\(^2,3\)

• $44,000 - $83,000 average cost to treat\(^4\)

Pre-operative antibiotics are the only intervention shown to reduce the risk of CIED infection\(^5\)

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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
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 ≥20mg 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

Nominal P-value less than 0.0488 for the primary objective was considered significant to adjust for an interim analysis.
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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Envelope (N = 3495)</th>
<th>Control (N = 3488)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years) [Mean ± SD]</td>
<td>70.0 ± 12.6</td>
<td>70.1 ± 12.4</td>
</tr>
<tr>
<td>Female (%)</td>
<td>997 (28.6%)</td>
<td>976 (28.0%)</td>
</tr>
<tr>
<td>BMI (kg/m²) [Mean ± SD]</td>
<td>29.1 ± 6.1</td>
<td>29.2 ± 6.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1080 (31.0%)</td>
<td>1085 (31.2%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>585 (16.8%)</td>
<td>554 (15.9%)</td>
</tr>
<tr>
<td>Baseline Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>2007 (57.5%)</td>
<td>1972 (56.6%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>1377 (39.5%)</td>
<td>1390 (39.9%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>36 (1.0%)</td>
<td>37 (1.1%)</td>
</tr>
<tr>
<td>Immunosuppressive*</td>
<td>48 (1.4%)</td>
<td>85 (2.4%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>348 (10.0%)</td>
<td>375 (10.8%)</td>
</tr>
<tr>
<td>Oral antidiabetic</td>
<td>615 (17.6%)</td>
<td>620 (17.8%)</td>
</tr>
</tbody>
</table>

*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

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

*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

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

99.7% implant procedure success rate with TYRX‡
40% Reduction in Major CIED Infections with TYRX through 12 Months

WRAP-IT Study Primary Endpoint: Major CIED Infection

Hazard ratio through 12 months: 0.60 (95% CI: 0.36-0.98)
P-value 0.04

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Envelope</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3,488</td>
<td>3,495</td>
</tr>
<tr>
<td>3</td>
<td>3,360</td>
<td>3,351</td>
</tr>
<tr>
<td>6</td>
<td>3,277</td>
<td>3,281</td>
</tr>
<tr>
<td>9</td>
<td>3,179</td>
<td>3,188</td>
</tr>
<tr>
<td>12</td>
<td>3,053</td>
<td>3,091</td>
</tr>
</tbody>
</table>
WRAP-IT Study: Major CIED Pocket Infections

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

Hazard ratio through 12 months: 0.39 (95% CI: 0.21-0.72)
P-value < 0.01

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

Hazard ratio through 12 months: 0.87 (95% CI: 0.72-1.06)
P-value (non-inferiority test): < 0.001

Complication Rate (%)

Control: 236, 6.9%
Envelope: 201, 6.0%

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

- Hazard ratio through all follow-up: 0.63 (95% CI: 0.40-0.98)
- P-value: 0.04

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Envelope:Control Hazard Ratio</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>6,983</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>3,016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>3,959</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,973</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>1,754</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[25,29)</td>
<td>2,099</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[25,32)</td>
<td>1,210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 32</td>
<td>1,882</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>2,234</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4,758</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
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<td></td>
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<tr>
<td>No</td>
<td>4,045</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>2,927</td>
<td></td>
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</tbody>
</table>

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
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
## WRAP-IT Study Committees

### Steering Committee
- Bruce Wilkoff, MD (Chair)
  *Cleveland Clinic*
- Ralph Corey, MD
  *Duke Clinical Research Institute*
- Charles Kennergren, MD
  *Sahlgrenska University Hospital*
- Suneet Mittal, MD
  *Valley Health System*
- Jeanne Poole, MD
  *University of Washington*
- Khaldoun Tarakji, MD MPH
  *Cleveland Clinic*

### Clinical Events
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- Antonio Curnis, MD
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  *Jefferson University*
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- Charles Swerdlow, MD
  *UCLA*

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- Helen Boucher, MD
  *Tufts Medical Center*
- Anne Curtis, MD
  *Buffalo General Medical Center*
- Thomas Heywood, MD
  *Scripps Clinic*
- Kerry Lee, PhD
  *Duke Clinical Research Institute*
Antibacterial Envelope to Prevent Infections of Cardiac Implantable Devices

Khaledoun G. Tarakji, M.D., M.P.H., Suneet Mittal, M.D.,
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WRAP-IT Investigators*