PERFECT-POCKET™ PROTECTION
STABILIZE CIED PLACEMENT
HELP PREVENT CIED INFECTION
With The TYRX™ Absorbable Antibacterial Envelope
WHY THE NEED FOR ENHANCED PROTECTION FOR YOUR CIED PROCEDURES?

Bacterial infection is one of the most common causes of Cardiac Implantable Electronic Device (CIED) complications, and it is on the rise

- Over a 15-year period, increase in incidence of infection was more than double the increase in implants (210% vs 96%).¹

- Increased rate of infection likely due to:¹
  - Older patients receiving devices
  - More patient comorbidities
  - Longer procedures
  - Changing mix of CIEDs
  - Increasing number of pulse generator replacements and upgrades
  - Revisions
  - More resistant *S. aureus* and coagulase (-) *Staphylococcus* species (e.g., *S. epidermidis*)

The TYRX™ Absorbable Antibacterial Envelope is NOT indicated for use in patients who have an allergy or history of allergies to tetracyclines, Rifampicin, or absorbable sutures. The TYRX Absorbable Antibacterial Envelope is also NOT indicated for use in patients with contaminated or infected wounds; or Systemic Lupus Erythematosus (SLE). The use of this product in patients with compromised hepatic and renal function, or in the presence of hepatotoxic or renal toxic medications, should be considered carefully, because Minocycline and Rifampicin can cause additional stress on the hepatic and renal systems. Patients who receive the TYRX Absorbable Antibacterial Envelope and who are also taking methoxyurane should be monitored carefully for signs of renal toxicity.
Current antibiotic prophylaxis falling short

- Cefazolin and vancomycin can have important clinical limitations when used as a single agent to prevent CIED Infection.2-7
- Coagulase (-) Staphylococcus species and S aureus are responsible for ~70% of CIED Infections and are increasingly resistant to methicillin.4,5,8-12

Migration, erosion, and Twiddler Syndrome

- CIED migration can occur with a frequency of 0.1% to 1.2%.13,14
- CIED erosion and lead dislodgement can occur as a result of migration.
- Although this complication has been expected to decrease along with weight and size of CIEDs, generator migration (1.2%) and lead dislodgement (5.87%) continue to occur at clinically significant rates in current series of CIED implantations that use modern generators.13,15

Twiddler Syndrome is a complication of CIED implantation with a frequency of 0.07% to 1.1%.16,17
Twiddler Syndrome is the intentional or unintentional twisting by the patient of the CIED within the pocket and may result in dislocation or fracture of the lead/electrode, creating diaphragmatic stimulation and loss of capture.18,19

"... CIED Infections continue to occur and can be life threatening."

Update on CIED Infections and their management: a scientific statement from the American Heart Association (AHA), endorsed by the Heart Rhythm Society (HRS).2

Coagulase (-) Staphylococcus & S aureus are responsible for ~70% of CIED Infections4,5,8-12
CONSEQUENCES OF CIED INFECTION ON PATIENTS AND THE HEALTHCARE SYSTEM

Infections typically cost the facility an average of ~$52,000,\textsuperscript{20} but may exceed well over $100,000.\textsuperscript{21}

CIED INFECTION AND LENGTH OF STAY

- The risk-adjusted average length of stay with infection was 15.5 to 24.3 days.\textsuperscript{21}

CIED INFECTION AND MORTALITY

- The risk-adjusted admission mortality with infection was 4.6% to 11.3%, depending on the CIED type (4.8- to 7.7-fold the mortality without infection).\textsuperscript{21}
- Nearly 50% of patients with CIED Infection did not survive beyond 3 years:\textsuperscript{22}
  - Patients with pacemaker (PM) infection had 54% mortality vs. 33% for those without pacemaker infection
  - Patients with Implantable Cardioverter-Defibrillator (ICD) infection had 48% mortality vs. 32% for those without ICD infection
  - Patients with Cardiac Resynchronization Therapy (CRT) infection had 51% mortality vs. 37% for those without CRT infection

TREATING CIED INFECTIONS IS COMPLEX AND EXPENSIVE.\textsuperscript{2,21}

CIED Infection rates affect Centers for Medicaid and Medicare Services (CMS) reimbursement.\textsuperscript{20}

- As of October 1, 2012, the CMS has reduced payments to hospitals when a patient undergoing a CIED procedure acquires an infection during their hospital stay.\textsuperscript{20}

HRS codes and physician reporting measures respond to rates of CIED Infection.\textsuperscript{23}

- As part of the HRS Performance Measurement Development Initiative, new physician-level performance measure coding-level specifications and code recommendations were developed and finalized in July 2012. Also included in HRS-9: Infection within 180 days of CIED Implantation, Replacement, or Revision. This proposal became active in 2015.\textsuperscript{23}
- This information is intended to ensure that Electrophysiologists (EPs) are accountable to their patients, and that EPs are ready to participate in the Physician Quality Reporting System (PQRS), which became mandatory in 2015. Under the PQRS, physician performance will be publicly reported and reimbursement will be linked to reporting on performance measures.\textsuperscript{23}

“The Economic Consequences, Including Healthcare Resource Utilization, of CIED Infections Are Substantial.” — The AHA Update on CIED Infections and Their Management\textsuperscript{2}
**RISK-ADJUSTED MORTALITY RATES**

<table>
<thead>
<tr>
<th>CIED TYPE</th>
<th>Without infection (%)</th>
<th>With infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>1.5</td>
<td>8.2</td>
</tr>
<tr>
<td>ICD</td>
<td>0.8</td>
<td>4.6</td>
</tr>
<tr>
<td>CRT-D</td>
<td>1.3</td>
<td>5.8</td>
</tr>
<tr>
<td>CRT-P</td>
<td>1.7</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Above: Risk-adjusted admission mortality for CIED procedures without (orange) and with (blue) infection.

**SURVIVAL RATE FOR CIED PROCEDURES WITH AND WITHOUT INFECTIONS**

Above: Survival following 200,219 Medicare beneficiary admissions for CIED procedures (PM, ICD, CRT-D). Patients without an infection (orange) and patients with an infection (blue).

**COST TO TREAT CIED INFECTIONS BY IMPLANT VOLUME AND RATE OF INFECTION**

Above: As rate of CIED Infection and CIED implant volume increases, costs to treat CIED Infections rise. A lower rate of infection yields a lower CIED Infection treatment cost trajectory.
RISK FACTORS FOR CIED INFECTION AND FOR INFECTION-RELATED MORTALITY

Some patient procedures, medications, and characteristics significantly increase the risk of CIED-related infection (multivariate analysis).8,9,25-29

- CIED Infections are difficult and time-consuming to manage.2,30
  - Intervention typically results in the need to explant the CIED, deliver IV antibiotics, and reimplant a new device.2,30
  - Recommendations issued in January 2010 are the first evidence-based guidelines for CIED Infection prophylaxis issued by the AHA and the HRS.2

- The antibiotic combination of Minocycline and Rifampicin has significant in vitro activity against staphylococci.3,31-33

### ODDS RATIO FOR DEVELOPING A CIED INFECTION8,9,25-29

<table>
<thead>
<tr>
<th>PATIENT PROCEDURES</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Reintervention</td>
<td>15.04</td>
</tr>
<tr>
<td>CRT-D vs ICD/PM (heavier device)</td>
<td>7.57</td>
</tr>
<tr>
<td>&gt;2 Leads in Place (longer procedures)</td>
<td>5.41</td>
</tr>
<tr>
<td>Device Replacement/Revision</td>
<td>3.67</td>
</tr>
<tr>
<td>Temporary Pacing Wire</td>
<td>2.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT MEDICATIONS</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>13.90</td>
</tr>
<tr>
<td>Oral Anticoagulant</td>
<td>2.82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT CHARACTERISTICS</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis-Dependent</td>
<td>13.39</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>11.97</td>
</tr>
<tr>
<td>Fever &lt;24hr Prior to Implantation</td>
<td>5.83</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>5.46</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.50</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>2.57</td>
</tr>
<tr>
<td>Male Gender</td>
<td>2.23</td>
</tr>
</tbody>
</table>

### HAZARD RATIO FOR MORTALITY WITH A CIED INFECTION34,35

<table>
<thead>
<tr>
<th>PATIENT MEDICATIONS</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>1.97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT CHARACTERISTICS</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Embolization</td>
<td>7.11</td>
</tr>
<tr>
<td>Abnormal Right Ventricle Function</td>
<td>3.59</td>
</tr>
<tr>
<td>Abnormal Renal Function</td>
<td>2.98</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2.01</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>1.94</td>
</tr>
</tbody>
</table>

Some patient medications and patient characteristics significantly increase the risk of death once an infection is present.34,35
The Tyrx™ Absorbable Antibacterial Envelope

Innovative technology provides clinicians, patients, and hospitals with a novel solution that may help to confidently improve patient outcomes and reduce the cost of treating infections in high-risk patients.\textsuperscript{20,36}

Proven stabilization in holding CIEDs, such as pacemakers and ICDs, securely in place to provide a stable environment when implanted in the body.\textsuperscript{37-41}
- Reduces chance of device migration, erosion, or Twiddler Syndrome.\textsuperscript{37,38}

Synergistic combination of Minocycline and Rifampicin shown to reduce infection associated with other medical devices in multiple, randomized controlled trials.\textsuperscript{42-46}
- Minocycline and Rifampicin elute locally into the tissue pocket enabling MIC tissue concentration levels to be reached within 2 hours of implantation, which are maintained for a minimum of 7 days: locally delivered, adjunctive antibacterial protection.\textsuperscript{47,48}

The only antibacterial device available for CIED implants that is fully absorbable.
- Fully absorbs into the body in ~9 weeks.\textsuperscript{37}
- Requires no adjustment to standard surgical techniques during replacement or revision procedure.
- After absorption, no foreign body nidus for infection.

Novel, large-pore mesh knitted from bioabsorbable multifilaments coated with a bioabsorbable polyarylate polymer that breaks down into naturally occurring components Generally Regarded As Safe (GRAS) over ~9 weeks. The composition of the mesh filament is similar to bioabsorbable suture.\textsuperscript{47}

Fully absorbable technology uniquely designed for Perfect-Pocket™ Protection

Proven stabilization in holding CIEDs, such as pacemakers and ICDs, securely in place to provide a stable environment when implanted in the body.\textsuperscript{37-41}
- Reduces chance of device migration, erosion, or Twiddler Syndrome.\textsuperscript{37,38}

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More antibacterial coverage when added to single-agent therapies

The amount of drug dose contained in the TYRX Absorbable Antibacterial Envelope is < 10% of the recommended daily oral dose of Minocycline and Rifampicin.\(^{3}\)

Cefazolin and vancomycin are infrequently used in combination.
- Substantial overlap (both have activity against gram (+) organisms).\(^{3}\)
- Neither has a strong profile against gram (-) organisms.

Gentamicin has variable activity against coagulase (-) Staphylococcus, MSSA, and MRSA, and may be effective in some infections, but not in others.\(^{3}\)

Topical Ionic Silver does not cover coagulase (-) Staphylococcus and has no data to support coverage in M catarrhalis or Corynebacterium jeikeium.\(^{3}\)

<table>
<thead>
<tr>
<th>PATHOGENS RESPONSIBLE FOR CIED INFECTIONS</th>
<th>SINGLE-AGENT THERAPY (^{3})</th>
<th>TYRX (^{TM} 3,31-33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefazolin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Coagulase (-) Staphylococcus (e.g., S epidermidis)</td>
<td>VA</td>
<td>VA</td>
</tr>
<tr>
<td>Methicillin-sensitive S aureus (MSSA)</td>
<td>VA</td>
<td>VA</td>
</tr>
<tr>
<td>Methicillin-resistant S aureus (MRSA)</td>
<td>VA</td>
<td>VA</td>
</tr>
<tr>
<td>E coli</td>
<td>VA</td>
<td>VA</td>
</tr>
<tr>
<td>H influenzae</td>
<td>VA</td>
<td>VA</td>
</tr>
<tr>
<td>M catarrhalis</td>
<td>VA</td>
<td>VA</td>
</tr>
<tr>
<td>Corynebacterium jeikeium</td>
<td>VA</td>
<td>VA</td>
</tr>
</tbody>
</table>

VA = Variable Activity

Time sequence simulation demonstrating elution and absorption of TYRX Absorbable Antibacterial Envelope from implantation to ~9 weeks.
**CLINICAL SUPPORT SUMMARY**

**STUDIES DEMONSTRATING BENEFITS OF TYRX™ ANTIBACTERIAL ENVELOPES**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>COMMAND Study Completed 2011</th>
<th>Valley Health Study Completed 2014</th>
<th>Vanderbilt (Absorbable &amp; Non-Absorbable) Completed 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Multicenter Retrospective Cohort Study</td>
<td>Retrospective Dual Cohort Study</td>
<td>Retrospective Matched Cohort Study</td>
</tr>
<tr>
<td>Centers</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient Enrollment</td>
<td>624 TYRX*</td>
<td>275 TYRX 965 Controls</td>
<td>488 TYRX 638 Controls</td>
</tr>
<tr>
<td>% of CIED Infection</td>
<td>1.05% TYRX (COMMAND Study) 2.60% NO TYRX (Krahn Study, 2011)**</td>
<td>1.1% TYRX 3.6% Control</td>
<td>0% TYRX Absorbable 0.3% TYRX Non-Absorbable 3.1% Control</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>1.9 ± 2.4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Conclusions</td>
<td>&gt; 99% of implantations were successful; 60% to 70% fewer infections than in some previous studies</td>
<td>79% - 100% fewer CIED Infections in medium- and high-risk patient groups that received the TYRX Antibacterial Envelope</td>
<td>90% to 100% reduction in CIED Infection in patients who received either the TYRX Absorbable or Non-Absorbable Antibacterial Envelope</td>
</tr>
</tbody>
</table>

*All subjects in this study received the TYRX Envelope.

**Comparator study**
# TYRX™ ABSORBABLE AND NON-ABSORBABLE ANTIBACTERIAL ENVELOPE
## CLINICAL STUDIES REFERENCE GUIDE

<table>
<thead>
<tr>
<th>STUDY</th>
<th>UPMC Study Completed 2015</th>
<th>Citadel &amp; Centurion Studies Completed 2015</th>
<th>WRAP-IT Study (Began Jan. 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Single-Center Retrospective Cohort Study</td>
<td>Multicenter Prospective Cohort Study</td>
<td>Prospective, Randomized, Single-Blind, Multicenter Post-Market, Interventional Clinical Study</td>
</tr>
<tr>
<td><strong>Centers</strong></td>
<td>1</td>
<td>55</td>
<td>~225</td>
</tr>
<tr>
<td><strong>Patient Enrollment</strong></td>
<td>365 TYRX 1,111 Controls</td>
<td>1,129 TYRX*</td>
<td>~7,764 total</td>
</tr>
<tr>
<td><strong>% of CIED Infection</strong></td>
<td>0% TYRX 1.9% Control</td>
<td>0.44% TYRX (Citadel &amp; Centurion Studies) 2.20% NO TYRX (Gould Study, 2008)**</td>
<td>TBD</td>
</tr>
<tr>
<td><strong>Follow up (months)</strong></td>
<td>12</td>
<td>12</td>
<td>12-36</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>Prevented ~6.2 infections or ~$340,000 in treatment costs; significantly fewer infections and suggests lower costs to healthcare system</td>
<td>73% to 90% fewer CIED Infections in patients who received the TYRX Antibacterial Envelope</td>
<td>TBD</td>
</tr>
</tbody>
</table>

*All subjects in this study received the TYRX Envelope.

**Comparator study
Rate of Infection in high-risk patients implanted with the TYRX Antibacterial Envelope is significantly lower than in certain historical control cohorts

**DESIGN**
A cooperative, multicenter, retrospective cohort study was performed to monitor a CIED antimicrobial device. Procedures following an explantation for a prior CIED Infection or for off-label indication were excluded from analyses.

**METHODS**
Patients enrolled in the COMMAND Study were at high-risk for CIED Infection, compared to the typical US electrophysiology practice. All subjects in the study received the TYRX Antibacterial Envelope.

- Objectives were defined as:
  - Successful CIED implantation.
  - Measurement of CIED Infection rate in patients undergoing CIED procedures with the TYRX Antibacterial Envelope.

- 642 patients enrolled at 10 US academic, community, and VA Medical Centers.

- 624 patients met criteria for analyses.

**RESULTS**
- >99% of implantations were successful.
- There were low rates of CIED Infection following COMMAND Study procedures:
  - 0.00% for initial implant procedures.
  - 0.48% for all procedures.
  - 0.71% for all replacement/revision procedures.

**CONCLUSIONS**
- After an average follow-up of 1.9 ± 2.4 months, the COMMAND Study demonstrated that there were fewer infections in the study cohort that received the TYRX Antibacterial Envelope, than in certain historical control cohorts that did not receive the Envelope.

- In the highest-risk subset, ICD/CRT replacements/revisions, the CIED Infection rate in the COMMAND Study was lower than the rate in published series of similar cohorts of patients implanted without the TYRX Antibacterial Envelope; the study demonstrated 60% to 70% fewer infections than in some previous studies.

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**LOW RATE OF CIED INFECTION**

<table>
<thead>
<tr>
<th></th>
<th>PM</th>
<th>ICD/CRT</th>
<th>All CIED Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Procedure</td>
<td>0/84</td>
<td>0/117</td>
<td>0/201</td>
</tr>
<tr>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Replacement/Revision</td>
<td>0/137</td>
<td>3/286</td>
<td>3/423</td>
</tr>
<tr>
<td>Procedure</td>
<td>0.00%</td>
<td>1.05%</td>
<td>0.71%</td>
</tr>
<tr>
<td>All Procedures</td>
<td>0/221</td>
<td>3/403</td>
<td>3/624</td>
</tr>
<tr>
<td>0.00%</td>
<td>0.74%</td>
<td>0.48%</td>
<td></td>
</tr>
</tbody>
</table>

*Study performed utilizing the TYRX™ Non-Absorbable Antibacterial Envelope.*
Patients in the COMMAND Study had high rates of successful CIED Implantation across all CIED devices.

Patients in the COMMAND Study implanted with the TYRX Envelope experienced low rates of infection in procedures for ICD/CRT replacement/revision compared to certain historical control cohorts who did not receive the TYRX Envelope.
High-risk patients implanted with the TYRX Antibacterial Envelope are significantly less likely to develop CIED Infection than comparatively low-risk cohorts.\textsuperscript{54}

**RESULTS**
- Compared to patients who did not receive a TYRX Envelope, those who did receive the Envelope were more likely to have risk factors associated with an increased risk of an infection: early pocket re-exploration, male gender, diabetes, device upgrade, congestive heart failure (CHF), hypertension, GFR < 60ml/min. All these variables have been associated with CIED Infection.\textsuperscript{54}
- The 6-month infection rate was significantly lower in patients who received an Envelope, compared to propensity score matched patients who did not (1.1\% vs. 3.6\%, \( p = 0.048 \)).\textsuperscript{54}

**CONCLUSIONS**
- The Envelope reduced infections by 79\% and 100\% in the medium- and high-risk groups, respectively.\textsuperscript{54}
- There were ~70\% fewer infections in patients who received the TYRX Antibacterial Envelope, compared to those who did not, across all device types.\textsuperscript{54}

### 6-MONTH CIED INFECTION RATE: STRATIFIED BY DEVICE AND PROCEDURE TYPE(\%)\textsuperscript{54}

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Device</th>
<th>DeNovo</th>
<th>Generator</th>
<th>Upgrade</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D</td>
<td>4.0%</td>
<td>3.1%</td>
<td>3.9%</td>
<td>33.0%</td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>1.5%</td>
<td>1.7%</td>
<td>18.2%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>0.8%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>CRT-P</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
</tr>
</tbody>
</table>

Device groups with highest infection rates were CRT-D and ICD. Procedure types with highest infection rates were Upgrade and early pocket re-exploration groups (Other).

*Study performed utilizing the TYRX™ Non-Absorbable Antibacterial Envelope.*
Above: A composite risk score was created by weight, adjusting for the seven risk factors. 3 groups emerged—low-risk (score 0-7; 1% infection), medium-risk (score 8-14; 3.4% infection), and high-risk (score ≥ 15; 11.1% infection).

At Left: The survival functions show that those with a TYRX Envelope were less likely to develop an infection (1.1% infection rate) compared to those without a TYRX Envelope (3.6% infection rate) over a 6-month period.
CLINICAL SUPPORT
VANDERBILT HEART AND VASCULAR INSTITUTE
STUDY WITH THE TYRX™ ABSORBABLE AND
NON-ABSORBABLE ANTIBACTERIAL ENVELOPES

High-risk patients with TYRX Antibacterial Envelopes experienced fewer
CIED-related Infections versus patients without these Envelopes.\textsuperscript{55,56}

**DESIGN**
A retrospective, matched-cohort study was performed to compare the incidence of CIED Infection in patients receiving a CIED with or without the TYRX Absorbable Antibacterial Envelope or the TYRX Non-Absorbable Antibacterial Envelope.\textsuperscript{55,56}

**METHODS**
Surgical procedures, medications, and patient characteristics significantly increase the risk of CIED-related Infection.\textsuperscript{55,56}

- The following risk factors were used to identify patients at high-risk for CIED Infection: generator change or device/lead revision; early pocket re-entry < 72 hours; renal insufficiency (serum creatinine ≥ 1.5mg/dL); diabetes mellitus; systemic anticoagulation with heparin, warfarin or novel oral anticoagulants; chronic corticosteroid use; the presence of ≥ 3 leads (cardiac resynchronization or abandoned leads); prior CIED Infection; fever (≥ 100.5° F) or leukocytosis (≥ 11,000 WBCs/µL) at time of implantation; and pacemaker dependence.\textsuperscript{55,56}

- Patients with ≥ 2 risk factors received either the TYRX Absorbable Antibacterial Envelope, the TYRX Non-Absorbable Antibacterial Envelope, or no TYRX Envelope in the control group.\textsuperscript{55,56}

A total of 488 TYRX Absorbable and Non-Absorbable Antibacterial Envelopes were implanted from November 1, 2009 to June 30, 2014.\textsuperscript{55,56}

- The incidence of CIED Infection in 488 TYRX Envelope recipients (135 receiving the Absorbable Envelope, 353 receiving the Non-Absorbable Envelope) was compared to 638 controls.\textsuperscript{55,56}

- While the incidence of individual risk factors differed between the groups, the mean (standard deviation) number of risk factors was equivalent among the groups: 3.1 (1.4) for the Absorbable Envelope, 3.2 (1.3) for the Non-Absorbable Envelope, and 3.1 (1.3) for the control group, p = 0.30.\textsuperscript{55,56}
RESULTS
After a minimum of 90 days post-implantation, the incidence of CIED Infection was significantly lower in the groups that received either the TYRX Absorbable or TYRX Non-Absorbable Envelope, compared to the control group\textsuperscript{55,56}:

- 0 (0%) infection in the TYRX Absorbable Antibacterial Envelope group ($p = 1$)
- 1 (0.3%) infection in the TYRX Non-Absorbable Antibacterial Envelope group ($p = 0.03$)
- 20 (3.1%) infections in the control group ($p = 0.002$)

The results were adjusted using Propensity Score Matching (PSM) to control for risk factors as a confounding factor.

- All TYRX Envelope recipients vs. control:
  In a PSM cohort of 334 TYRX Antibacterial Envelope recipients (either Absorbable or Non-Absorbable) and 334 controls, the incidence of CIED Infection was 0 (0%) and 11 (3.3%) respectively, $p = 0.001$\textsuperscript{55,56}
- TYRX Absorbable Envelope recipients vs. control:
  In a PSM cohort of 125 TYRX Absorbable Envelope recipients and 125 controls, the incidence of CIED Infection was 0 (0%) and 6 (4.8%) respectively, $p = 0.03$\textsuperscript{56}

CONCLUSIONS
There was a 90% to 100% reduction in CIED Infection in high-risk patients who received either the TYRX Absorbable Antibacterial Envelope or the TYRX Non-Absorbable Antibacterial Envelope compared to those who did not. Using PSM to control for risk factors, there was a 100% reduction in CIED Infection\textsuperscript{55,56}.

<table>
<thead>
<tr>
<th>CIED Infection Rate (%)</th>
<th>0%</th>
<th>0.3%</th>
<th>3.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbable</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Non Absorbable</td>
<td>0%</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
CLINICAL SUPPORT
UPMC STUDY WITH THE TYRX ANTIBACTERIAL ENVELOPE*

Use of the TYRX Antibacterial Envelope as Standard of Care for CIED patients is associated with significantly lower rates of CIED Infection and lower costs to the healthcare system.57

DESIGN
The goal of this single-center, retrospective cohort study from University of Pittsburgh Medical Center (UPMC) was to evaluate the clinical and economic impact of using the TYRX Antibacterial Envelope as Standard of Care (SoC).57
SoC use-calculations included an average cost to treat an infection, the infection rate percentage from the No-TYRX group (patients who were not implanted with the TYRX Antibacterial Envelope), and the acquisition cost of the TYRX Envelopes. The TYRX Antibacterial Envelope cost was $795.00 per unit for PMs and $895.00 per unit for ICDs.57

METHODS
Every patient undergoing a CIED implantation in the electrophysiology (EP) laboratory was included in this study (n = 1,476). In the 2 years prior to the study, the infection rate in this EP laboratory was between 1% and 2% of procedures. In this study, some implanters (surgeons who implanted the device) used the TYRX Antibacterial Envelope in every patient as a SoC, termed “Yes-TYRX” group (n = 365), whereas other implanters did not use it at all, termed “No-TYRX” group (n = 1,111).57

RESULTS
- 1.7% CIED Infection rate without the TYRX Envelope at 6 months (19 infections, p = 0.06)57
- 1.9% CIED Infection rate without the TYRX Envelope at 12 months (20 infections, p = 0.023)57
- 0% CIED Infection rate with the TYRX Envelope at 6 and 12 months (0 infections, p = 0.006)57
- The average hospital stay was 13 days for treatment of an infection57
- 15.7% mortality in patients with a CIED Infection at 6 months compared to 4.5% mortality in patients without a CIED Infection at 6 months (p = 0.021)57
- 21.1% mortality in patients with a CIED Infection at 12 months compared to 6.4% mortality in patients without a CIED Infection at 12 months (p = 0.011)†

...SoC WAS ASSOCIATED WITH A SIGNIFICANTLY LOWER RATE OF CIED INFECTIONS.

* Study performed utilizing the TYRX™ Non-Absorbable Antibacterial Envelope.
† The 12-month mortality rates were not published in the paper, but the senior author provided permission for our use.
Assuming that Yes-TYRX patients experience the same infection rate as actually observed among No-TYRX patients, SoC use of the TYRX Envelope:

- Prevented an estimated 6.2 infections⁵⁷
- Avoided treatment costs of ~$340,000, which was comparable to the actual cost of the TYRX Envelopes at $320,000⁵⁷
- Treatment costs of ~$340,000 include an estimated $54,926 ± $11,374 per patient, and do not include costs to the healthcare delivery organization (ambulatory care, home care), patient (physician fees, non-covered service fees, co-pays, lost wages/earning potential, travel, lodging, sustenance), and patient family (lost wages, travel, lodging, sustenance).⁵⁷

### CONCLUSIONS

- Use of the TYRX Antibacterial Envelope as SoC was associated with a significantly lower rate of CIED Infections.⁵⁷
- CIED Infections result in significant patient and healthcare system burden, high costs, long length of stays, and higher mortality rates.⁵⁷

### FINANCIAL IMPLICATIONS OF USE OF TYRX ENVELOPE AS A SoC

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>INFECTION RATE (N)</th>
<th>INFECTION CARE COST**</th>
<th>DIFFERENTIAL COST***</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>365</td>
<td>1.71% (6.20)</td>
<td>$342,854</td>
<td>$23,863</td>
</tr>
<tr>
<td>Preoperative Risk Score &lt; 3</td>
<td>179</td>
<td>1.03% (1.85)</td>
<td>$101,708</td>
<td>-$54,729</td>
</tr>
<tr>
<td>Preoperative Risk Score ≥ 3</td>
<td>186</td>
<td>2.45% (4.55)</td>
<td>$250,115</td>
<td>$87,560</td>
</tr>
<tr>
<td>Early Reintervention</td>
<td>12</td>
<td>6.67% (0.80)</td>
<td>$43,941</td>
<td>$33,453</td>
</tr>
</tbody>
</table>

Hypothetical projection assumes that Yes-TYRX patients experience the same infection rate as actually observed among No-TYRX patients.

---

**Infection Care Cost = Number Infected multiplied by the Cost of Infection**

***Differential Cost = Infection Care Cost minus Cost of TYRX Envelope as a SoC"
**CLINICAL SUPPORT**

**CITADEL & CENTURION STUDIES WITH THE TYRX ANTIBACTERIAL ENVELOPE**

Significantly reduced rate of CIED Infection among high-risk patients using the TYRX Non-Absorbable Antibacterial Envelope at 12-month clinical follow-up\(^58\)

**DESIGN**

Prospective cohort studies were designed to define the major CIED Infection and CIED mechanical complication rates in high-risk ICD or CRT patients receiving the TYRX Non-Absorbable Antibacterial Envelope during upgrade or replacement procedures. The studies compared these rates to those of a published control of ICD/CRT replacement patients who did not receive the TYRX Antibacterial Envelope.\(^58,59\)

At Right: The combined Citadel & Centurion cohort after 12 months of follow up demonstrates 80% less infection (0.44% vs. 2.2%) than the comparator study cohort.

\*Citadel & Centurion Studies performed utilizing the TYRX™ Non-Absorbable Antibacterial Envelope.
METHODS
A total of 1,262 patients were entered into the database of participants in two studies at 55 U.S. study sites: the Citadel Single and Dual Chamber (ICD) Study (n = 459) & the Centurion Cardiac Resynchronization Therapy Defibrillator (CRT-D) and Cardiac Resynchronization Therapy Pacemaker (CRT-P) Study (n = 670). 133 patients were excluded from analysis because they had ineligible informed consent (n = 44), an ineligible procedure (n = 18), or an ineligible device (n = 71). The remaining 1,129 patients comprised the prospective database.58

An analysis of the primary efficacy endpoints at 12-month follow-up was performed utilizing an historical comparator study cohort comprised of 451 ICD/CRT implant replacement patients having a mean follow-up of 355 days at 12 Canadian study sites.58

RESULTS
- 12-month follow-up of the 1,129 combined Citadel (ICD+TYRX) & Centurion (CRT+TYRX) patient group identified 5 major infections (0.44%), the primary efficacy endpoint of the study.58
- 12-month follow-up results for the combined 1,129 patient cohort demonstrated 80% fewer major CIED Infections (0.44% vs. 2.2%; p = 0.0023) than the comparator study cohort.58,59
- 12-month follow-up results from the 459-patient Citadel cohort demonstrated 90% fewer major CIED Infections (0.22% vs. 2.2%; p = 0.0052) vs. the comparator study cohort.58,59
- 12-month follow-up results from the 670-patient Centurion cohort demonstrated 73% fewer major CIED Infections (0.6% vs. 2.2%; p = 0.0177) vs. the comparator study cohort.58,59

CONCLUSIONS
The Citadel & Centurion Studies demonstrated that after implantation of a TYRX Non-Absorbable Antibacterial Envelope in patients at high-risk for CIED Infection, there were significantly fewer major infections at 12 months compared to the published comparator study cohort. There was a 73% to 90% infection rate reduction vs. the comparator study cohort, and the overall rate of mechanical complications was low.58,59

THERE WAS A 73% - 90% REDUCTION IN INFECTION RATE AT 12-MONTHS FOLLOW-UP VS. THE COMPARATOR STUDY COHORT
The World-wide Randomized Antibiotic Envelope Infection Prevention Clinical Study (WRAP-IT) is the first large-scale study of its kind to evaluate an antibacterial envelope in CIED patients at risk for infection.

BACKGROUND
The WRAP-IT Study is an ongoing CIED complication replacement study targeted at the 2 most common complications related to CIED implants: infection and lead system events. Medtronic will utilize the TYRX Absorbable Antibacterial Envelope as well as the Medtronic proprietary Lead Monitoring Algorithms in an attempt to drive down the rate of these complications, which could potentially result in better patient outcomes and substantial cost savings to the healthcare system.

PURPOSE
- Evaluate the ability of the TYRX Absorbable Antibacterial Envelope to help reduce major CIED Infections through 12 months post-implantation
- Accumulate post-market safety information, such as generator migration, related to the CIED implant procedure or system from other geographical regions
- Prospectively characterize the performance of Medtronic’s lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead

DESIGN
The WRAP-IT Study is a prospective, randomized, single-blind, multicenter, post-market, interventional clinical study

- Up to 225 investigational sites projected worldwide (including the United States, Canada, Europe, Middle East, Greater China, New Zealand, Latin America, Singapore, Malaysia, India)
- Up to 7,764 subjects projected for enrollment
- Medtronic-only generators (including upgrades, replacements, revisions)

The anticipated study duration is approximately 36 months. Subjects will be followed for a minimum of 12 months, and may be followed for the full 36 months, depending on their date of enrollment.

The study will also prospectively evaluate the performance of Medtronic lead monitoring algorithms—such as Lead Integrity Alert (LIA) and Lead Noise Alert (LNA) software—to identify lead system issues in defibrillator patients.
METHODOLOGY

- Subjects undergoing CIED generator replacement, upgrade, revision, or the implant of a de novo CRT-D system will be randomized to either receive or not receive the TYRX Absorbable Antibacterial Envelope.

- Randomization will be 1:1 and stratified by study site and device type: high power (ICD and CRT-D) vs. low power (Implantable Pulse Generator [IPG] and CRT-P) devices.

- The rate of major infection in CIED patients at 12 months following a procedure, and the consequent healthcare costs, will be compared between patients receiving a TYRX Absorbable Antibacterial Envelope at implantation and those not receiving the Envelope.

OBJECTIVES

Primary Objective:
To compare the rate of major CIED Infections through 12 months post-procedure between the TYRX Absorbable Antibacterial Envelope group and the control group (no TYRX Absorbable Antibacterial Envelope).

Secondary Objectives:
- Confirm that the TYRX Absorbable Antibacterial Envelope does not increase the CIED procedure-related or system-related mechanical complication rate through 12 months post-procedure.
- Compare the major CIED Infection rate during the entire follow-up between the TYRX Absorbable Antibacterial Envelope group and the control group.
- Compare the rate of major and minor CIED Infections through 12 months post-procedure between the TYRX Absorbable Antibacterial Envelope group and the control group.

Post-Market CE Mark Objective:
Characterize the rate of all system and/or procedure-related adverse events which include, but are not limited to, CIED Infections, CIED migrations, or adverse events related to the TYRX Envelope.
CLINICAL SUPPORT
WRAP-IT STUDY WITH THE TYRX™ ABSORBABLE ANTIBACTERIAL ENVELOPE

PRIMARY ENDPOINT
Major CIED Infections:
TYRX Absorbable Antibacterial Envelope vs. Control CIED
Infections are 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
- Treatment with antibiotic therapy if the subject is not a candidate for system removal and infection recurrence after completion of antibiotic therapy, or evidence of deep infection with wound dehiscence, erosion, or purulent drainage
- Death due to CIED Infection

INCLUSION CRITERIA
- Subject is willing to sign and date the study Patient Informed Consent
- Subject is at least 18 years of age and meets age requirements per local law
- Subject is scheduled for at least one of the following:
  - Has an existing CIED (any manufacturer) and is undergoing IPG (including CRT-P), ICD, or CRT-D replacement or upgrade with a new Medtronic generator (Note: subjects planning to have leads added, or extracted and added for upgrade can be enrolled.)
  - Will undergo a de novo or a Medtronic CRT-D system implant per approved indications
  - Has an existing study-eligible Medtronic CIED in which the pocket was not accessed within the last 365 days, and is undergoing pocket or lead revision
- Subject is willing to provide the contact information for the physician who provides follow-up care for his/her CIED
- Subject is willing and able to comply with scheduled follow-up and study-related activities

Note: All other CIED Infections including superficial incisional Surgical Site Infections (SSIs) which meet the Center for Disease Control and Prevention (CDC) criteria, independent of the time from surgery, are defined as minor CIED Infections unless they meet the major CIED Infection criteria.
EXCLUSION CRITERIA

- Known allergy to Minocycline or Rifampicin or their derivatives, or any other known contraindications to implantation of the TYRX Absorbable Antibacterial Envelope
- Current therapy with chronic oral immunosuppressive agents or ≥ 20mg/day of Prednisone or equivalent
- Hemodialysis or peritoneal dialysis
- Prior cardiac transplantation or existing Ventricular Assist Device (VAD)
- Require long-term vascular access for any reason
- Prior history of a CIED Infection, other prosthetic device infection, or endovascular infection, including endocarditis, in the past 12 months
- Physical, clinical, or laboratory signs or symptoms consistent with an active infection (including but not limited to pneumonia, urinary tract, cellulitis, or bacteremia)
- Systemic Lupus Erythematosus (SLE), because Minocycline has been reported to aggravate this condition
- Female patient who is pregnant (women of childbearing potential are required to have a negative pregnancy test within 7 days prior to device procedure)
- Participation in another study that may confound the results of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic Study Manager.

...THE TYRX ABSORBABLE ANTIBACTERIAL ENVELOPE, AS WELL AS THE MEDTRONIC PROPRIETARY LEAD MONITORING ALGORITHMS, COULD REDUCE COMPLICATIONS, RESULTING IN BETTER PATIENT OUTCOMES AND COST SAVINGS.
“CIED-related Infections have contributed significantly to patient mortality and healthcare costs as they have risen rapidly over the last decade. As a result, there has been a concerted effort and focus within the cardiac community to find ways to reduce these infections. The findings of our study clearly showed that patients whose CIED implantation included the use of the TYRX Antibacterial Envelope experienced a significantly lower rate of infection, compared to a matched cohort of patients who underwent implantation without the antibacterial device. We expect similar, lower rates of infection with the use of the TYRX Absorbable Envelope and this is currently under study.”

Christopher R. Ellis, MD, FACC
Vanderbilt Heart and Vascular Institute, Nashville, TN

“I have been using the TYRX Antibacterial Envelope for preventing infection for 5 years now. I find it to be easy to implant. It requires very minimal expansion of the pocket and incision to accommodate, adding a significant benefit to my patients. I’m more confident knowing that I’m doing everything possible to help reduce infection in my CIED patients. I’m especially glad that the absorbable version is now available, because I feel more comfortable placing it in those patients I have with sub-pectoral devices.”

Heather Bloom, MD, FACC
Emory University and Atlanta VA Medical Center, Atlanta, GA

“I started using the Non-Absorbable TYRX Antibacterial Envelope several years ago and found it to be very effective at stabilizing the cardiac device, while reducing the Surgical Site Infection (SSI) rate at my facility. I now employ the second generation, fully absorbable version, which gives me the same advantages as the non-absorbable, but now with the benefit of having it fully absorb after ~9 weeks. With the PQRS incorporated in 2015, and the transparency that comes with that, I am more confident that I am doing all I can to prevent SSIs in my patients.”

Charles Kinder, MD
MacNeal Hospital, Berwyn, IL

“In a recent study, we found that CIED Infections occurred commonly in ICD and CRT-D patients, especially when there was an upgrade procedure or need for early pocket re-exploration. Once the TYRX Antibacterial Envelope became available and used in high-risk patients, the 6-month CIED Infection rate at our institution decreased substantially. We developed a novel scoring index that can risk-stratify patients; high-risk patients seemed to particularly benefit from use of the envelope to reduce CIED Infections.”

Suneet Mittal, MD, FACC, FHRS
Valley Health System of NY and NJ
THE TYRX™ ABSORBABLE ANTIBACTERIAL ENVELOPE: THE ONLY ANTIBACTERIAL DEVICE AVAILABLE FOR CIED STABILIZATION AND INFECTION PREVENTION THAT IS FULLY ABSORBABLE.  

- Specifically designed to aid in the stabilization of CIED placement.
- Synergistic combination of Minocycline & Rifampicin has been shown to reduce medical device infections.  
- Minocycline & Rifampicin elute locally into the tissue pocket enabling MIC tissue concentration levels to be reached within 2 hours of implantation, which are maintained for a minimum of 7 days: locally delivered, adjunctive antibacterial protection.
- Fully absorbs into the body in ~9 weeks.
- Associated with 70% to 100% fewer infections compared to patients without it.

Available in a variety of sizes to accommodate your choice of CIEDs

TYRX™ Absorbable Antibacterial Envelope (Medium)
Size: 6.3 cm x 6.9 cm
Product # CMRM6122EU (Single Unit)

TYRX™ Absorbable Antibacterial Envelope (Large)
Size: 7.6 cm x 8.5 cm
Product # CMRM6133EU (Single Unit)

Storage: Store between 2°-25°C (36° to 77°F). Each TYRX polymer-coated envelope is placed in a Tyvek® folder insert, which is packaged inside a single-barrier foil pouch.

Brief Statement: See Instructions For Use for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events.

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