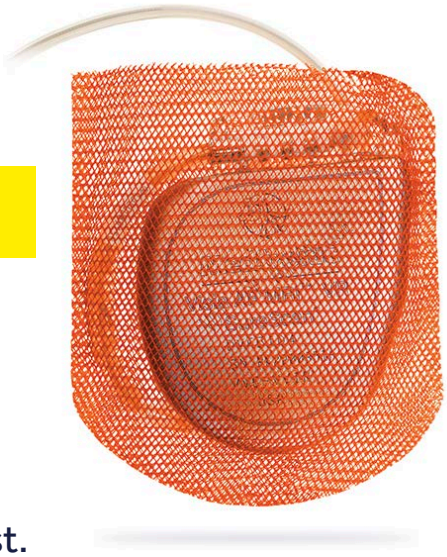
DEMONSTRATED CIED STABILIZATION, REDUCED INFECTION

TYRX™ Absorbable Antibacterial Envelope

Now available with up to 12 months shelf life.

Įmautė į kurią įdedamas elektrokardiostimuliatorius ar kardioverteris defibriliatorius implantacijos metu



Infections are a serious cardiac implantable electronic device (CIED) procedure-related complication, associated with significant morbidity, mortality, and cost.

1–4%
of CIED patients have been shown to develop infection[1,2]

>3x
mortality risk at 1 year[3]

$48K–83K
Range of average hospital cost to treat an infection[3-8]

$5K–36K
Range of average margin loss to treat an infection[3-11]

TYRX Envelope

- Demonstrated CIED stabilization and infection reduction[2,12-19]
- Locally delivered minocycline and rifampin sustained for 7 days[20]
- Polymer-controlled antibiotic elution[20]
- Multifilament knitted mesh fully absorbs in approximately 9 weeks[20,21]

pagaminta iš biorezorbuojamų polimerų, organizme besirezorbuojančių per 9 savaites, impregnuota antibiotikų deriniu.

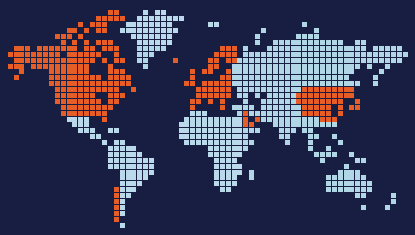
40%
reduction of major CIED infections.*[2]

61%
reduction of pocket infections[2]

SAFETY ENDPOINT MET
No increased risk of complications with use of TYRX through 12 months[2]

RISK OF CIED INFECTION
WITH THE TYRX ENVELOPE[1,14-19]

TYRX Envelope Significantly Reduces CIED Infections[1]



WRAP-IT STUDY
The largest randomized, controlled, global CIED trial[2]

- 6,983 patients at an increased risk for pocket infection†
- 25 countries
- 181 centers
- 776 implanters

*Primary endpoint included CIED infections requiring system extraction or revision, long-term antibiotic therapy with infection recurrence, or death within 12 months of the CIED procedure.
†Included patients for CIED revision, generator replacement, upgrade, or *de novo* CRT-D.

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INTERNATIONAL CONSENSUS DOCUMENT RECOMMENDS TYRX ENVELOPE TO REDUCE CIED INFECTION[22]

INCREASED RISK[2]
(Randomized, Controlled Trial Data)

- > 1.0% major CIED infection rate through 12 months
- 40% reduction of major CIED infection and 61% reduction of pocket infection with TYRX

HIGHEST RISK
(Real-world Data)

- 1–4% major CIED infection rate through 12 months[23]
- 70–100% reduction of major CIED infection with TYRX*[14-19]

TYRX Envelope is recommended for the WRAP-IT Study population AND for patients with high risk factors[22]

CIED Infection Risk

CRT-D	Increased†	Increased†	Highest
ICD	Low	Increased†	
Pacemaker/ CRT-P	Low	Increased†	

- **Initial Procedure**
- **Replacement**
- **Revision**
- **Upgrade**
- **Dialysis**
- **Immunosuppressive Agents**
- **Recent Infection**

Considerations for patient selection include use of TYRX to hold a CIED securely in order to provide a stable environment.
*Studies included the nonabsorbable antibacterial envelope. †Included in the WRAP-IT Study patient cohort.

References

[1] Tarakji KG, Ellis CR, Defaye P, Kennergren C. Cardiac Implantable Electronic Device Infection in Patients at Risk. *Arrhythm Electrophysiol Rev*. May 2016;5(1):65-71.
[2] Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial Envelope to Prevent Cardiac Implantable Device Infection. *N Engl J Med*. May 16, 2019;380(20):1895-1905.
[3] Wilkoff BL, et al. Impact of CIED Infection: A Clinical and Economic Analysis of the Wrap-It Study. Presentation Su3088 at AHA Scientific Sessions 2019; Philadelphia, PA.
[4] Medicare Provider Analysis and Review (MEDPAR) File, FY 2012, on file with Medtronic, plc.
[5] Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med*. November 14, 2011;171(20):1821-1828.
[6] Shariff N, Eby E, Adelstein E, et al. Health and Economic Outcomes Associated with Use of an Antimicrobial Envelope as a Standard of Care for Cardiac Implantable Electronic Device Implantation. *J Cardiovasc Electrophysiol*. July 2015;26(7):783-789.
[7] 2012 Premier Healthcare Database. Data on file with Medtronic plc.
[8] Lopatto, et al. Antibacterial Envelope is Associated with Medical Cost Savings in Patients at High Risk for Cardiovascular Implantable Electronic Device Infection. Presented at ACC 2017; Washington, DC.
[9] Sohail MR, Eby EL, Ryan MP, Gunnarsson C, Wright LA, Greenspon AJ. Incidence, Treatment Intensity, and Incremental Annual Expenditures for Patients Experiencing a Cardiac Implantable Electronic Device Infection: Evidence From a Large US Payer Database 1-Year Post Implantation. *Circ Arrhythm Electrophysiol*. August 2016;9(8).
[10] Greenspon AJ, Eby EL, Petrilla AA, Sohail MR. Treatment patterns, costs, and mortality among Medicare beneficiaries with CIED infection. *Pacing Clin Electrophysiol*. May 2018;41(5):495-503.
[11] 2011-2015 large U.S. healthcare claims analysis. Data on file with Medtronic plc.
[12] Huntingdon Life Sciences Study TR-2011-054.
[13] Osoro M, Lorson W, Hirsh JB, Mahlow WJ. Use of an antimicrobial pouch/envelope in the treatment of Twiddler's syndrome. *Pacing Clin Electrophysiol*. February 2018;41(2):136-142.
[14] Bloom HL, Constantin L, Dan D, et al. Implantation success and infection in cardiovascular implantable electronic device procedures utilizing an antibacterial envelope. *Pacing Clin Electrophysiol*. February 2011;34(2):133-142.
[15] Mittal S, Shaw RE, Michel K, et al. Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AigisRx antibacterial envelope. *Heart Rhythm*. April 2014;11(4):595-601.
[16] Kolek MJ, Patel NJ, Clair WK, et al. Efficacy of a Bio-Absorbable Antibacterial Envelope to Prevent Cardiac Implantable Electronic Device Infections in High-Risk Subjects. *J Cardiovasc Electrophysiol*. October 2015;26(10):1111-1116.
[17] Shariff N, Eby E, Adelstein E, et al. Health and Economic Outcomes Associated with Use of an Antimicrobial Envelope as a Standard of Care for Cardiac Implantable Electronic Device Implantation. *J Cardiovasc Electrophysiol*. July 2015;26(7):783-789.
[18] Henrikson CA, Sohail MR, Acosta H, et al. Antibacterial Envelope Is Associated With Low Infection Rates After Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Therapy Device Replacement: Results of the Citadel and Centurion Studies. *JACC Clin Electrophysiol*. October 2017;3(10):1158-1167.
[19] Kolek MJ, Dresen WF, Wells QS, Ellis CR. Use of an antibacterial envelope is associated with reduced cardiac implantable electronic device infections in high-risk patients. *Pacing Clin Electrophysiol*. March 2013;36(3):354-361.
[20] Huntingdon Life Sciences Study TR-2013-001.
[21] Sinclair Labs Study D13599.
[22] Blomström-Lundqvist C, Traykov V, Erba PA, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace*. Published online November 8, 2019.
[23] Mansfield R. CIED Infection Rates. Medtronic data on file. April 2019.

Brief Statement
TYRX™ Absorbable Antibacterial Envelope

The TYRX™ Absorbable Antibacterial Envelope is intended to hold a pacemaker pulse generator or defibrillator securely in order to provide a stable environment when implanted in the body. The TYRX Absorbable Antibacterial Envelope contains the antimicrobial agents minocycline and rifampin, which have been shown to reduce infection in an *in vivo* model of bacterial challenge following surgical implantation of the generator or defibrillator. The TYRX Absorbable Antibacterial Envelope is NOT indicated for use in patients who have an allergy or history of allergies to tetracyclines, rifampin, 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 rifampin can cause additional stress on the hepatic and renal systems. Patients who receive the TYRX Absorbable Antibacterial Envelope and who are also taking methoxyflurane should be monitored carefully for signs of renal toxicity.

Caution: Federal (USA) law limits the device to sale by, or on the order of, a licensed practitioner. For full prescribing information, including warnings, cautions, and contraindications, see Instructions for Use.

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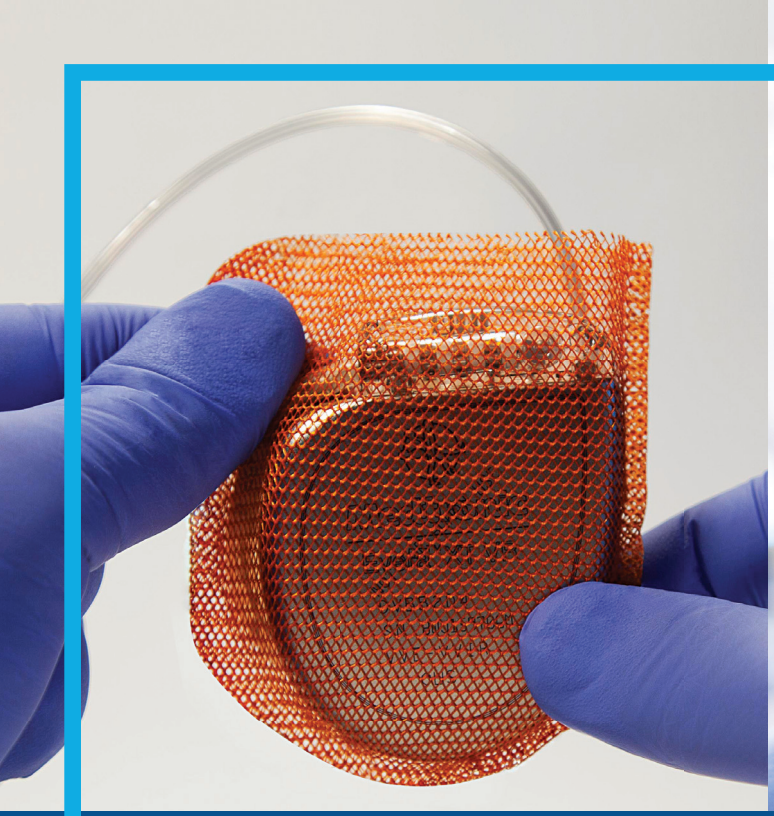

PERFECT-POCKET™ PROTECTION

STABILIZE CIED **PLACEMENT**
HELP **PREVENT** CIED **INFECTION**

With The TYRX™ Absorbable Antibacterial Envelope

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Further, Together

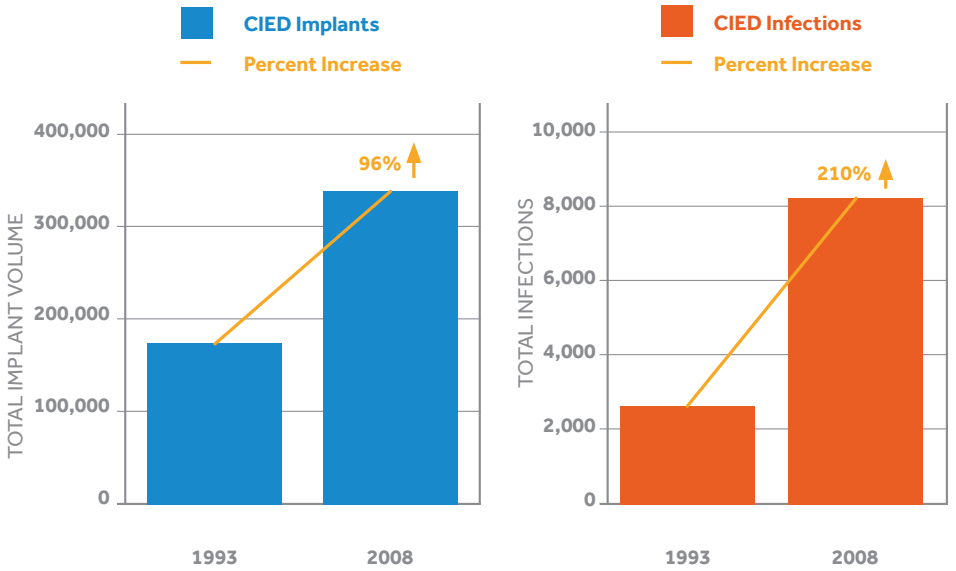
WHY THE NEED FOR ENHANCED PROTECTION FOR YOUR CIED PROCEDURES?

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*)

CHANGE IN CIED IMPLANTS AND INFECTIONS BETWEEN 1993-2008[1]



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

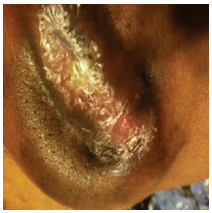
Update on CIED Infections and their management: a scientific statement from the American Heart Association (AHA), endorsed by the Heart Rhythm Society (HRS).[2]

Current antibiotic prophylaxis falling short

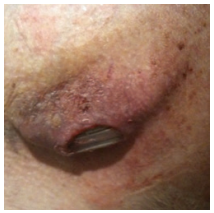
- Cefazolin and vancomycin can have important clinical limitations when used as a single agent to prevent CIED Infection.[2-7]
- Coagulase (-) *Staphylococcus* species and *S aureus* are responsible for ~70% of CIED Infections and are increasingly resistant to methicillin.[4,5,8-12]

Migration, erosion, and Twiddler Syndrome

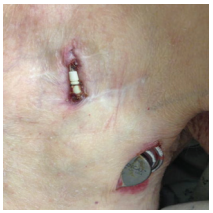
- CIED migration can occur with a frequency of 0.1% to 1.2%.[13,14]
- CIED erosion and lead dislodgement can occur as a result of migration.
- Although this complication has been expected to decrease along with weight and size of CIEDs, generator migration (1.2%) and lead dislodgement (5.87%) continue 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]



Courtesy of Dmitry Nemirovsky, MD, Englewood Hospital and Medical Center, NJ

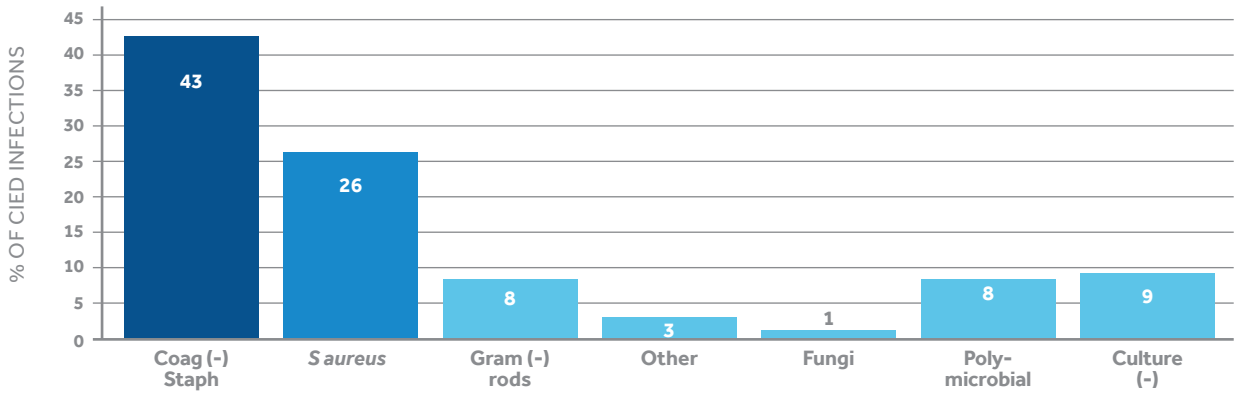


Courtesy of St. Luke's Roosevelt Hospital Center, NY



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

COAGULASE (-) *STAPHYLOCOCCUS* & *S AUREUS* ARE RESPONSIBLE FOR ~70% OF CIED INFECTIONS[4,5,8-12]



CONSEQUENCES OF CIED INFECTION ON PATIENTS AND THE HEALTHCARE SYSTEM

Infections typically cost the facility an average of ~$52,000,[20] but may exceed well over $100,000.[21]

CIED INFECTION AND LENGTH OF STAY

- The risk-adjusted average length of stay with infection was 15.5 to 24.3 days.[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).[21]
- Nearly 50% of patients with CIED Infection did not survive beyond 3 years:[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

"**THE ECONOMIC CONSEQUENCES**, INCLUDING HEALTHCARE RESOURCE UTILIZATION, OF CIED INFECTIONS **ARE SUBSTANTIAL.**"
—The AHA Update on CIED Infections and Their Management[2]

TREATING CIED INFECTIONS IS COMPLEX AND EXPENSIVE.[2,21]

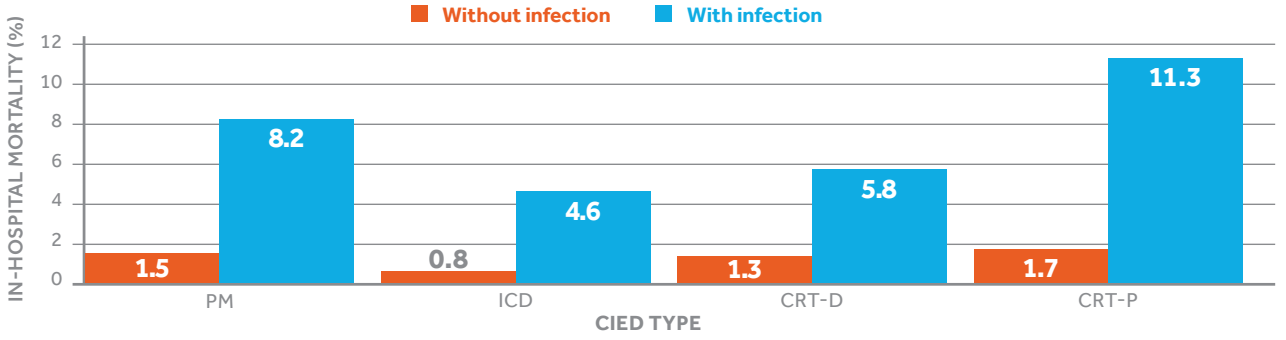
CIED Infection rates affect Centers for Medicaid and Medicare Services (CMS) reimbursement.[20]

- 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.[20]

HRS codes and physician reporting measures respond to rates of CIED Infection.[23]

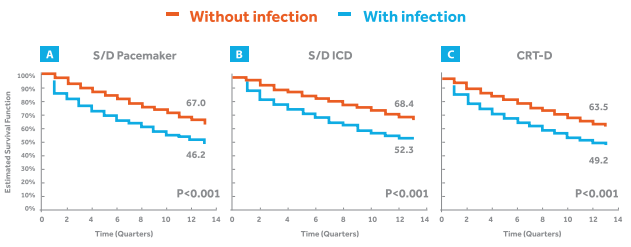
- As part of the HRS Performance Measurement Development Initiative, new physician-level performance measure coding-level specifications and code recommendations were developed and finalized in July 2012. Also included in HRS-9: Infection within 180 days of CIED Implantation, Replacement, or Revision. This proposal became active in 2015.[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. [23]

RISK-ADJUSTED MORTALITY RATES[21]



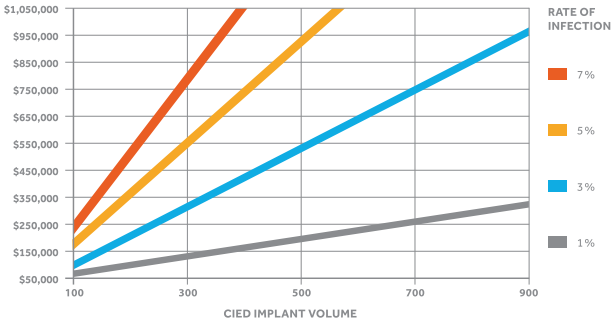
Above: Risk-adjusted admission mortality for CIED procedures without (orange) and with (blue) infection

SURVIVAL RATE FOR CIED PROCEDURES WITH AND WITHOUT INFECTIONS[22]



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[20,21,24]



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]

dviejų antibiotikų derinys

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 INFECTION[8,9,25-29]

PATIENT PROCEDURES	
Early Reintervention	15.04
CRT-D vs ICD/PM (heavier device)	7.57
>2 Leads in Place (longer procedures)	5.41
Device Replacement/Revision	3.67
Temporary Pacing Wire	2.46
PATIENT MEDICATIONS	
Corticosteroids	13.90
Oral Anticoagulant	2.82
PATIENT CHARACTERISTICS	
Dialysis-Dependent	13.39
Renal Failure	11.97
Fever <24hr Prior to Implantation	5.83
Renal Insufficiency	5.46
Diabetes	3.50
Congestive Heart Failure	2.57
Male Gender	2.23

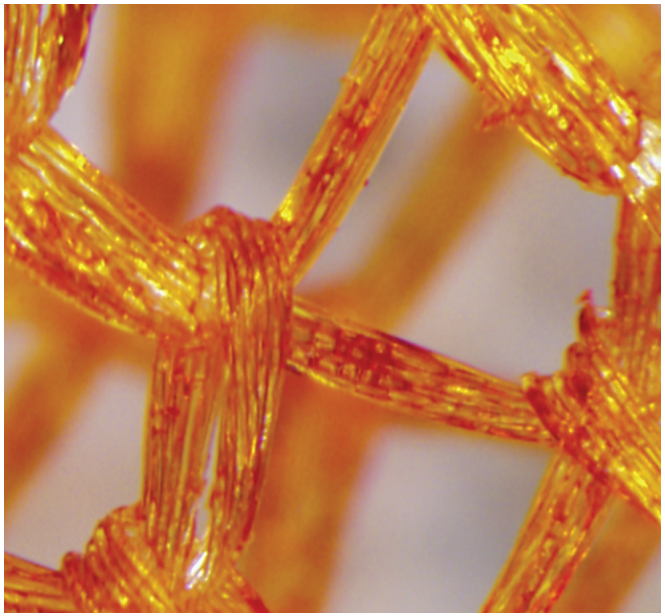
HAZARD RATIO FOR MORTALITY WITH A CIED INFECTION[34,35]

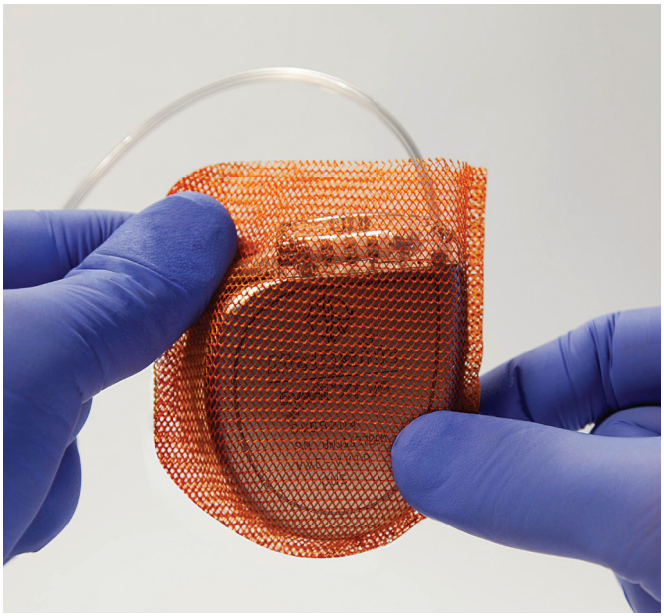
PATIENT MEDICATIONS	
Corticosteroids	1.97
PATIENT CHARACTERISTICS	
Systemic Embolization	7.11
Abnormal Right Ventricle Function	3.59
Abnormal Renal Function	2.98
Heart Failure	2.01
Acute Renal Failure	1.94

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.[20,36]





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.[37-41]

- Reduces chance of device migration, erosion, or Twiddler Syndrome.[37,38]

Synergistic combination of Minocycline and Rifampicin shown to reduce infection associated with other medical devices in multiple, randomized controlled trials.[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.[47,48]

The only antibacterial device available for CIED implants that is fully absorbable.

- Fully absorbs into the body in ~9 weeks.[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.[47]

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.

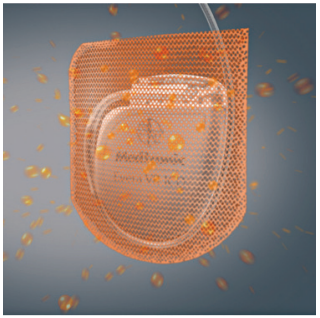
Gentamicin has variable activity against coagulase (-) *Staphylococcus* , MSSA, and MRSA, and may be effective in some infections, but not in others.[3]

Topical Ionic Silver does not cover coagulase (-) *Staphylococcus* and has no data to support coverage in *M catarrhalis* or *Corynebacterium jeikeium.*[3]

PATHOGENS RESPONSIBLE FOR CIED INFECTIONS	SINGLE-AGENT THERAPY[3]				TYRX™ [3,31-33]
	Cefazolin	Vancomycin	Gentamicin	Topical Ionic Silver	Minocycline and Rifampin
Coagulase (-) *Staphylococcus* (e.g., *S epidermidis*)			VA		
Methicillin-sensitive *S aureus* (MSSA)			VA		
Methicillin-resistant *S aureus* (MRSA)			VA		
E coli					
H influenzae					
M catarrhalis				No Data	
Corynebacterium jeikeium				No Data	

VA = Variable Activity

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



TYRX Absorbable Antibacterial Envelope after implantation[48]
Envelope is eluting Minocycline & Rifampicin.

TYRX Absorbable Antibacterial Envelope at 4 weeks[49]
Envelope is dissolving into fragments.

TYRX Absorbable Antibacterial Envelope at ~9 weeks[37]
Mesh has no physical presence and is fully absorbed.

CLINICAL SUPPORT SUMMARY
STUDIES DEMONSTRATING BENEFITS OF TYRX™ ANTIBACTERIAL ENVELOPES

TYRX™ ABSORBABLE AND NON-ABSORBABLE ANTIBACTERIAL ENVELOPE CLINICAL STUDIES REFERENCE GUIDE

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

*All subjects in this study received the TYRX Envelope.
**Comparator study

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TYRX™ ABSORBABLE AND NON-ABSORBABLE ANTIBACTERIAL ENVELOPE CLINICAL STUDIES REFERENCE GUIDE

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

*All subjects in this study received the TYRX Envelope.
**Comparator study

CLINICAL SUPPORT
COMMAND STUDY WITH THE TYRX ANTIBACTERIAL ENVELOPE*

Rate of Infection in high-risk patients implanted with the TYRX Antibacterial Envelope is significantly lower than in certain historical control cohorts[50]

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.[50]

METHODS
Patients enrolled in the COMMAND Study were at high-risk for CIED Infection, compared to the typical US electrophysiology practice.[50,51] All subjects in the study received the TYRX Antibacterial Envelope.

- Objectives were defined as:[50]
  - 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.[50]
- 624 patients met criteria for analyses.[50]

RESULTS
- >99% of implantations were successful.[50]
- There were low rates of CIED Infection following COMMAND Study procedures:[50]
  - 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.[50]
- **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.[50,52,53]**

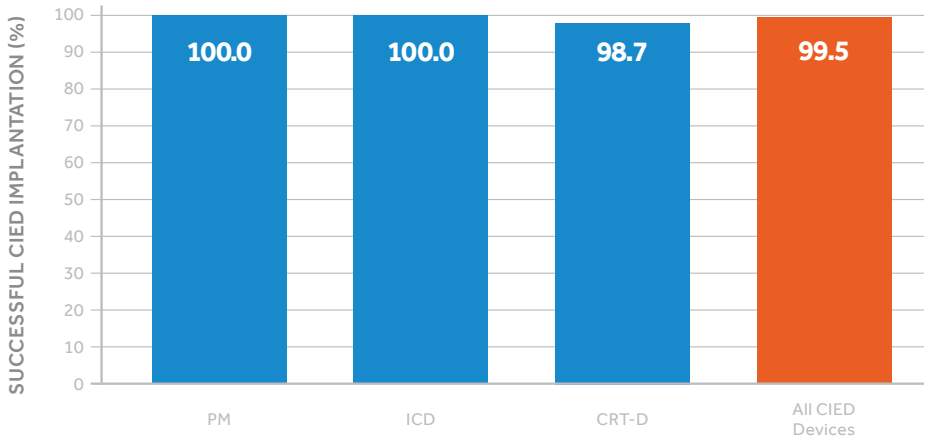
LOW RATE OF CIED INFECTION[50]

	PM	ICD/CRT	All CIED Devices
Initial Procedure	0/84 0.00%	0/117 0.00%	0/201 **0.00%**
Replacement/ Revision Procedure	0/137 0.00%	3/286 1.05%	3/423 **0.71%**
All Procedures	0/221 0.00%	3/403 0.74%	3/624 **0.48%**

THE STUDY DEMONSTRATED **60% TO 70% FEWER INFECTIONS** THAN IN SOME PREVIOUS STUDIES

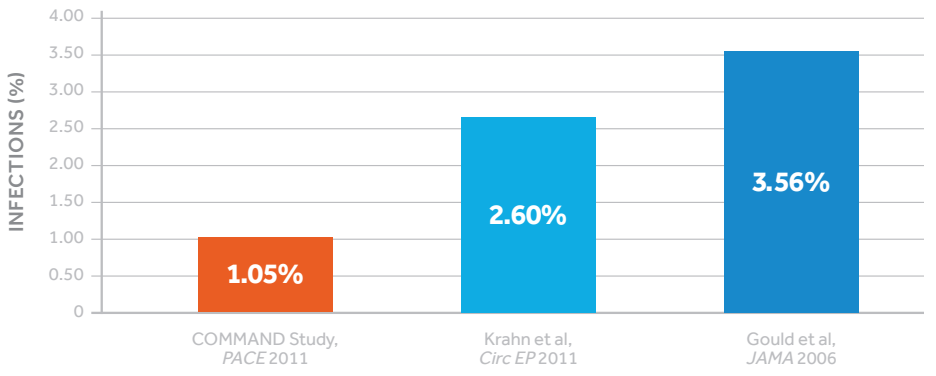
*Study performed utilizing the TYRX™ Non-Absorbable Antibacterial Envelope.

RATE OF SUCCESSFUL CIED IMPLANTATION[50]



Patients in the COMMAND Study had high rates of successful CIED Implantation across all CIED devices.

RATE OF INFECTION IN PROCEDURES FOR ICD/CRT REPLACEMENTS/REVISIONS[50,52,53]



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.

CLINICAL SUPPORT
THE VALLEY HEALTH SYSTEM STUDY WITH THE TYRX ANTIBACTERIAL ENVELOPE*

High-risk patients implanted with the TYRX Antibacterial Envelope are signifcantly less likely to develop CIED Infection than comparatively low-risk cohorts[54]

DESIGN

A retrospective, dual-cohort study was conducted in a large population of patients undergoing CIED procedures to determine the effect of the TYRX Antibacterial Envelope on CIED Infection rates, utilizing a novel scoring index to risk-stratify patients based on the specific combination of risk factors, rather than just the absolute number of risk factors.[54]

METHODS

Two cohorts of patients who underwent CIED procedures were identified: 1,651 patients before the introduction of the Envelope at the site (January 2007-October 2009) and 1,240 patients after the introduction of the Envelope (October 2009-September 2011), including 275 patients who received the Envelope. Using propensity-score matching, the 275 patients who received the Envelope were matched to 275 patients prior to the introduction of the Envelope.[54]

6-MONTH CIED INFECTION RATE: STRATIFIED BY DEVICE AND PROCEDURE TYPE(%)[54]

	Procedure Type			
Device	***DeNovo***	**Generator**	**Upgrade**	**Other**
CRT-D	4.0%	3.1%	3.9%	33.0%
ICD	1.5%	1.7%	18.2%	0.0%
PM	0.8%	0.3%	0.0%	0.0%
CRT-P	0.0%	0.0%	0.0%	0.0%

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).

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.[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).[54]

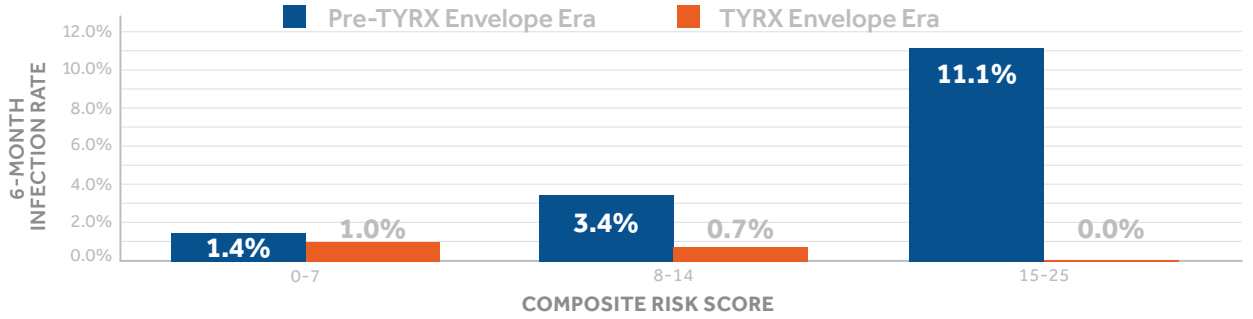
CONCLUSIONS

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

THE ENVELOPE **REDUCED INFECTIONS BY 79% AND 100%** IN THE MEDIUM- AND HIGH-RISK GROUPS, RESPECTIVELY.

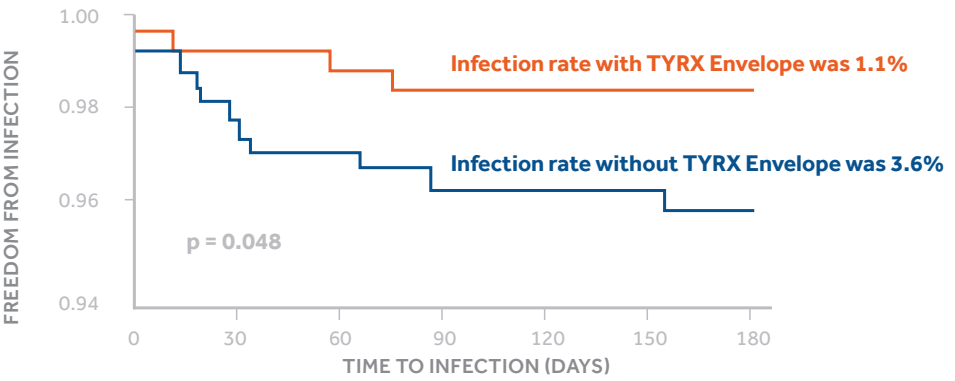
*Study performed utilizing the TYRX™ Non-Absorbable Antibacterial Envelope.

6-MONTH CIED INFECTION RATE: LIMITED TO ICD AND CRT-D PATIENTS[54]



Pre-TYRX Envelope, n	204	416	27
TYRX Envelope, n	140	292	24
TYRX Envelope Use, n(%)	47 (34%)	16 (40%)	21(88%)

CIED INFECTION DURING THE 6 MONTHS FOLLOWING CIED IMPLANTATION FOR THOSE WITH AND WITHOUT THE TYRX ENVELOPE[54]



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.[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.[55,56]

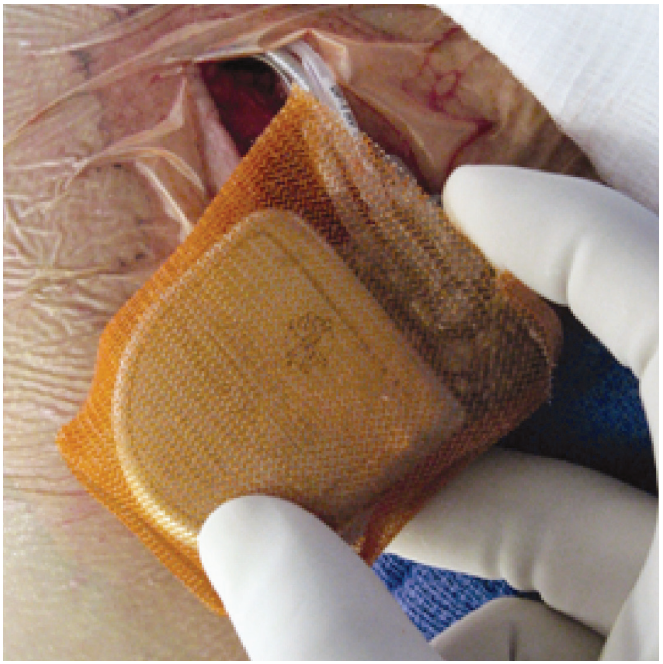


Photo courtesy of Christopher R. Ellis, MD, FACC, Vanderbilt Heart and Vascular Institute.

METHODS

Surgical procedures, medications, and patient characteristics significantly increase the risk of CIED-related Infection.[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.[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.[55,56]

A total of 488 TYRX Absorbable and Non-Absorbable Antibacterial Envelopes were implanted from November 1, 2009 to June 30, 2014.[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.[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.[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:[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)

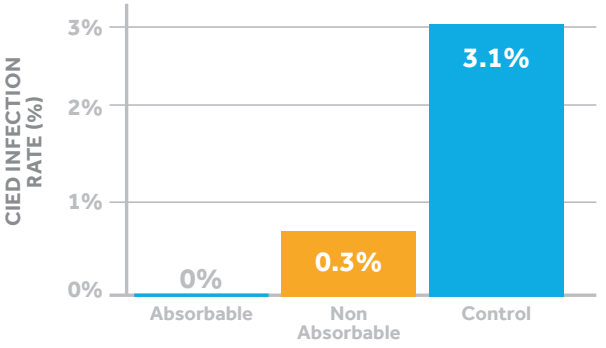
The results were adjusted using Propensity Score Matching (PSM) to control for risk factors as a confounding factor.

- 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.[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.[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.[55,56]

SIGNIFICANT REDUCTION IN CIED INFECTION RATE[55]



THERE WAS A **90% TO 100% REDUCTION IN CIED INFECTION IN HIGH-RISK PATIENTS**...

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 infection[57]
- 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.

Medtronic

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 infections[57]
- Avoided treatment costs of ~$340,000, which was comparable to the actual cost of the TYRX Envelopes at $320,000[57]
- 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

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

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]

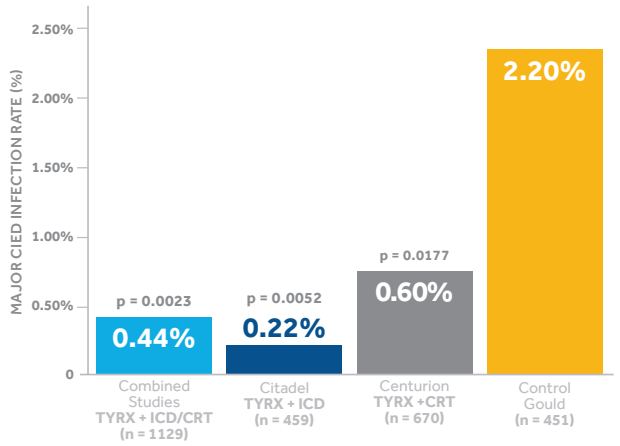
DESIGN

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.

12–MONTH INFECTION RATES[58,59]



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]
- 12-month follow-up data of the combined 1,129 patient cohort identified no significant difference between the rate of major hematomas vs. the comparator study cohort (1.55% vs. 1.60%).[58,59] Overall rates of mechanical complications were low (4.4%).[59]
- Neither the Citadel nor the Centurion patient group cohorts experienced unanticipated serious TYRX Envelope-related adverse events during the 12-month follow-up period.[58]

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

CLINICAL SUPPORT
WRAP-IT STUDY WITH THE TYRX™ ABSORBABLE ANTIBACTERIAL ENVELOPE

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

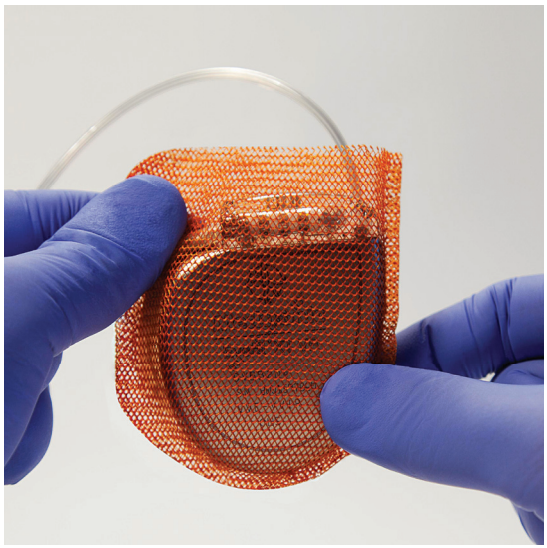
- Up to 225 investigational sites projected worldwide (including the United States, Canada, Europe, Middle East, Greater China, New Zealand, Latin America, Singapore, Malaysia, India)
- Up to 7,764 subjects projected for enrollment
- Medtronic-only generators (including upgrades, replacements, revisions)

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

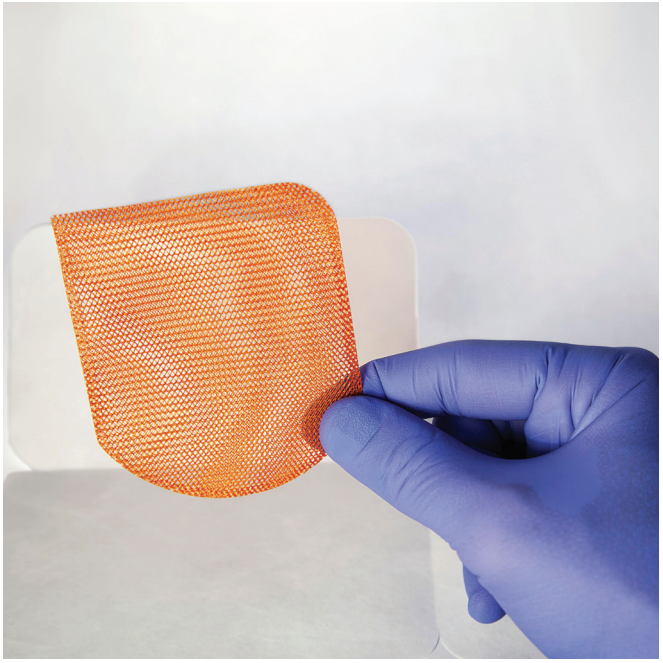
Note: All other CIED Infections including superficial incisional Surgical Site Infections (SSIs) which meet the Center for Disease Control and Prevention (CDC) criteria, independent of the time from surgery, are defined as minor CIED Infections unless they meet the major CIED Infection criteria.

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

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.**

WHAT PHYSICIANS ARE SAYING ABOUT THE TYRX ANTIBACTERIAL ENVELOPE

"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

REFERENCES

1. Greenspon A et al. *J Am Coll Cardiol.* 2011;58(10):1001-1006.
2. Baddour LM et al. *Circulation.* 2010;121(3):458-477.
3. Gilbert DN et al. *The Sanford Guide to Antimicrobial Therapy.* 39th ed. 2012: Antimicrobial Therapy Inc.; Hyde Park, VT.
4. Wisplinghoff H et al. *CID.* 2004;39(3):309-317.
5. NNIS System Report. *Am J Infect Control.* 2004;32(8):470-485.
6. Tarakji KG et al. *Heart Rhythm.* 2010;7(8):1043-1047.
7. Kachroo S et al. *Ann Pharmacother.* 2006;40(3):381-385.
8. Klug D et al. *Circulation.* 2007;116(12):1349-1355.
9. Lekkerkerker JC et al. *Heart.* 2009;95(9):715-720.
10. de Oliveira JC et al. *Circ Arrhyth Electrophysiol.* 2009;2(1):29-34.
11. Da Costa A et al. *Circulation.* 1998;97(18):1791-1795.
12. Chua J et al. *Ann Intern Med.* 2000;133(8):604-608.
13. Kuhlkamp V et al. *J Am Coll Cardiol.* 2002;39(5):790-797.
14. Thomas AC et al. *Pacing Clin Electrophysiol.* 1988;11(11):2053-2058.
15. Cleland JG et al. *N Engl J Med.* 2005;352(15):1539-1549.
16. Fahraeus T et al. *Europace.* 2003;5(3):279-281.
17. Hill PE. *Pacing Clin Electrophysiol.* 1987;10(3):564-570.
18. Dursun I et al. *Clin Res Cardiol.* 2006;95(10):547-549.
19. Sullivan R. Revisiting Twiddler's. HRS Poster Session, P006-1, May 16, 2009.
20. Centers for Medicare & Medicaid Services, U.S. Department of Health and Human Services Inpatient Prospective Payment System (IPPS) Final Rule FY13.
21. Sohail MR et al. *Arch Intern Med.* 2011;171(20):1821-1828.
22. Sohail MR et al. *PACE.* 2015;38(2):231-239.
23. Heart Rhythm Society (HRS) Performance Measurement Development Initiative, Cycle 2, 2012.
24. Based on TYRX analysis of the Medicare Standard Analysis File (SAF) for 2008 in patient claims, performed in conjunction with the health care consulting firm Braide-Forbes Health Research.
25. Margey R et al. *Europace.* 2010;12(1):64-70.
26. Sohail MR et al. *Clin Infect Dis.* 2007;45(2):166-173.
27. Bloom HL et al. *Pacing Clin Electrophysiol.* 2006;29(2):142-145.
28. Hercé B et al. *Europace.* 2013;15(1):66-70.
29. Romeyer-Bouchard C et al. *Eur Heart J.* 2010;31(2):203-210.
30. Wilkoff B et al. *Heart Rhythm.* 2007;4(11):1467-1470.
31. Zinner SH et al. *J Infect Dis.* 1981;144(4):365-371.
32. Darouiche RO et al. *Int J Antimicrob Agents.* 1995;6(1):31-36.
33. Segreti J et al. *Diagn Microbiol Infect Dis.* 1989;12(3):253-255.
34. Habib A et al. *Am J Cardiol.* 2013;111(6):874-879.
35. Baman TS et al. *Circ EP.* 2009;2:129-134.
36. Data on File, 061715-1.
37. Huntingdon Life Sciences Study TR-2011-054.
38. Hirsh J. *EP Lab Digest,* July 2012;12(7).
39. Klinge U et al. Influence of Polyglactin-Coating on Functional Morphological Parameters of Polypropylene-Mesh Modifications For Abdominal Wall Repair. *Biomaterials.* 1999;20:613-623.
40. Pillai CKS et al. Absorbable Polymeric Surgical Sutures: Chemistry, Production, Properties, Biocompatibility and Performance. *J Biomater Appl.* 2010;25:291-366.
41. Ferrando JM et al. Early Imaging of Integration Response to Polypropylene Mesh in Abdominal Wall by Environmental Scanning Electron Microscopy: Comparison of Two Placement Techniques and Correlation with Tensiometric Studies. *World J Surg.* 2001;25:291-366.
42. Hanna H et al. *J Clin Oncol.* 2004;22(15):3163-3171.
43. Leon C et al. *Intensive Care Med.* 2004;30(10):1891-1899.
44. Zambramski JM et al. *J Neurosurg.* 2003;98(4):725-730.
45. Chatzinikolaou I et al. *Am J Med.* 2003;115(5):352-357.
46. Raad I et al. *Ann Intern Med.* 1997;128(4):267-274.
47. TYRX Absorbable Antibacterial Envelope Instructions For Use.
48. Huntingdon Life Sciences Study TR-2013-001.
49. Data on File, 093013-1.
50. Bloom HL et al. *Pacing Clin Electrophysiol.* 2011;34(2):133-142.
51. Hammill SC et al. *Heart Rhythm.* 2009;6(9):1397-1401.
52. Krahn D et al. *Circ EP.* 2011;4(2):136-142.
53. Gould PA et al. *J Am Med Assoc.* 2006;295(11):1907-1911.
54. Mittal S et al. *Heart Rhythm.* 2014;11(4):595-601.
55. Kolek MJ et al. *Pacing Clin Electrophysiol.* 2013;36(3):354-361.
56. Kolek MJ et al. *J Cardio Electrophysiol.* 2015;26(10):1111-1116.
57. Shariff N et al. *J Cardio Electrophysiol.* 2015. Online publication.
58. Henrikson CA, Citadel and Centurion Study Results: Use of Antibacterial Envelope is Associated With Low 12-Month CIED Infection Rates. Oral presentation at Heart Rhythm Society Annual Scientific Sessions, *Heart Rhythm* May Supplement. 2015;12(5).
59. Gould PA et al. *Heart Rhythm.* 2008;5(12):1675-1681.

THE TYRX™ ABSORBABLE ANTIBACTERIAL ENVELOPE: THE ONLY ANTIBACTERIAL DEVICE AVAILABLE FOR CIED STABILIZATION AND INFECTION PREVENTION THAT IS FULLY ABSORBABLE.[37]

- Specifically designed to aid in the **stabilization** of CIED placement.
- Synergistic combination of Minocycline & Rifampicin has been shown to **reduce** medical device **infections.**[42-46]
- 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.[47,48]
- Fully **absorbs** into the body in ~9 weeks.[37]
- Associated with 70% to 100% **fewer infections** compared to patients without it.[50, 54, 56-58]

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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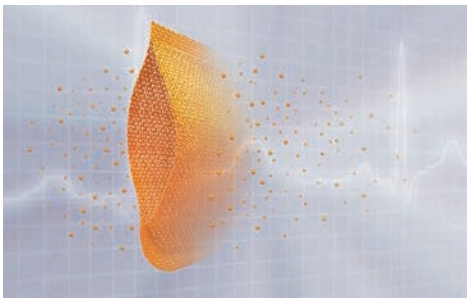
Medtronic

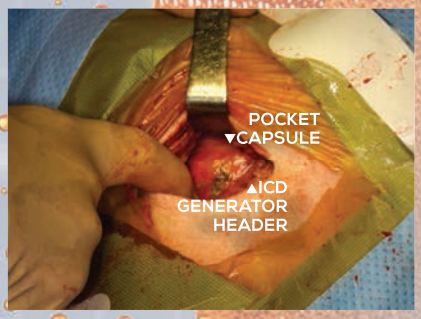
PERFECT-POCKET™ PROTECTION
WITH THE NEW, REVOLUTIONARY AIGISRx® R FULLY RESORBABLE ANTIBACTERIAL ENVELOPE

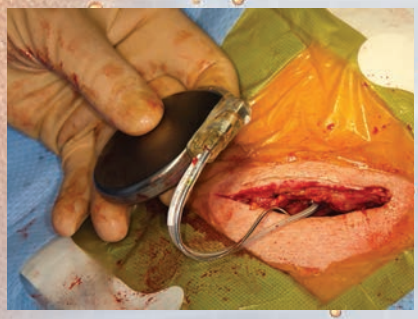


Stabilizes CIED Placement Helps Prevent CIED Infection

Unique Bioresorbable Mesh

- Fully resorbs into the body in ~9 weeks[1]
- Requires no adjustment to standard surgical techniques during replacement or revision procedure



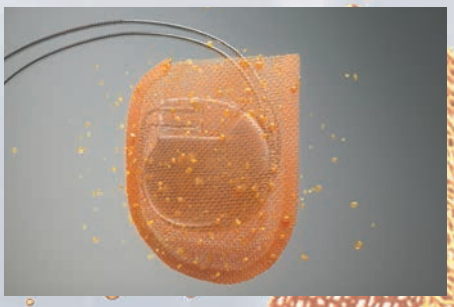


Bioresorbabilty of AIGISRx R in Patients

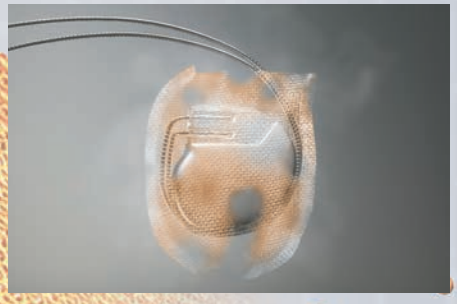
- Dual chamber ICD implanted with AIGISRx R Antibacterial Envelope
- Dislodged lead revised ~5 weeks later
- No visible remnant of the AIGISRx R, generator easily removed

Photos courtesy of Francois Philippon, MD Laval University Hospital, Quebec City, Canada

Time sequence demonstrating bioresorbability of AIGISRx R after ~9 weeks



AIGISRx R after implantation[2]
Envelope is eluting minocycline & rifampin.



AIGISRx R at 4 weeks[3]
Envelope is dissolving into fragments.

AIGISRx R at ~9 weeks[1]
Mesh has no physical presence and is fully resorbed.

NOW, FULLY RESORBABLE.
PLUS ALL THE PROTECTION OF THE ORIGINAL AIGISRx

Designed to Aid in the Stabilization of CIED Placement

- **Use of the AIGISRx R Antibacterial Envelope anchors the CIED in the tissue pocket.[1]**
- **Reduces chance of device migration or erosion due to Twiddler's Syndrome.[1, 4]**
- **AIGISRx R and AIGISRx are safe and effective at stabilizing a CIED generator within a tissue pocket and preventing migration. There is no clinically significant difference between their performances.[1]**

Helps Prevent CIED Infections

- **AIGISRx R contains the antimicrobial agents minocycline and rifampin which are released locally into the tissue to help reduce CIED infection following implantation.**
  - The amount of drug dose contained in the AIGISRx R is <10% of the recommended daily oral dose of minocycline and rifampin.[5]
- **The AIGISRx R and the original AIGISRx have identical antibiotic efficacy.**

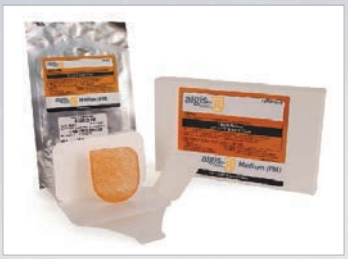
PATHOGENS RESPONSIBLE FOR CIED INFECTIONS	SINGLE-AGENT THERAPY		AIGISRx R AND AIGISRx[5-8]
	cefazolin	vancomycin	minocycline and rifampin
Coagulase (-) Staphylococcus (eg, S. epidermidis)		■	■
Methicillin-sensitive S. aureus (MSSA)	■	■	■
Methicillin-resistant S. aureus (MRSA)		■	■
Escherichia coli	■		■
Haemophilus influenzae	■		■
M. catarrhalis			■
Corynebacterium jeikeium		■	■

- **Multiple studies show that patients at high-risk for CIED infection who are implanted with the AIGISRx Antibacterial Envelope had 70% to 100% fewer device infections than similar patients who did not receive the AIGISRx.[9-11,17]**

AIGISRx R

AIGISRx R Perfect-Pocket™ Protection

- **Fully Resorbs in ~9 Weeks.[1]**
- **Specifically designed to aid in the stabilization of CIED Placement.**
- **Combination of rifampin & minocycline has been shown to reduce medical device infections.[12-16]**
- **Associated with 70% to 100% fewer infections compared to patients without it.[9-11]**
- **Cost Effective –Your facility may reduce costs by as much as $100,000 for every 100 Envelopes used with your high-risk CIED patients.[3,10,17-19]**



AIGISRx R Medium Fully Resorbable Antibacterial Envelope
Size: 2.5" (6.3cm) x 2.7" (6.9cm)
SKU # CMRM-6122US-B

AIGISRx R Large Fully Resorbable Antibacterial Envelope
Size: 2.9" (7.4cm) x 3.3" (8.5cm
SKU # CMRM-6133US-B

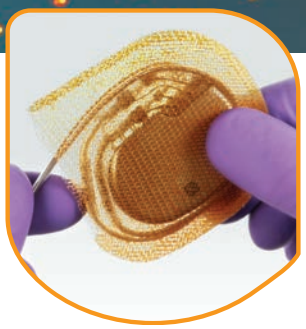
1 Huntington Study TR-2011-054. **2** Huntington Study TR-2013-001. **3** Data on file, 093013-1. **4** Hirsh J. *EP Lab Digest.* July 2012; 12(7); Clinical Case Report; Recurrent Twiddler's Syndrome. **5** Gilbert DN et al. *The Sanford Guide to Antimicrobial Therapy.* 42nd ed. 2012: Antimicrobial Therapy Inc.; Hyde Park, VT. **6** Zinner SH et al. *J Infect Dis.* 1981; 144(4):365-371. **7** Darouiche RO et al. *Int J Antimicrob Agents.* 1995; 6(1):31-36. **8** Segreti J et al. *Diagn Microbiol Infect Dis.* 1989; 12(3):253-255. 35. **9** Bloom H et al. *Pacing Clin Electrophysiol.* 2011; 34(2):133-142. **10** Kolek MJ et al. *Pacing Clin Electrophysiol.* 2013; 36(3):354-361 **11** Henrickson CA. Citadel & Centurion Studies. Presented at the Late Breaking Clinical Trials session at the European Heart Rhythm Association (EHRA), *Europace.* 2013. **12** Hanna H et al. *J Clin Oncol.* 2004; 22(15):3163-3171. **13** Leon C et al. *Intensive Care Med.* 2004; 30(10):1891-1899. **14** Zabramski JM et al. *J Neurosurg.* 2003; 98(4):725-730. **15** Chatzinikolaou I et al. *Am J Med.* 2003; 115(5):352-357. **16** Raad I et al. *Ann Intern Med.* 1997; 128(4):267-274. **17** Mittal S et al. 2013 HRS Scientific Session, PO 05-43, NY/NJ Valley Health System. **18** Inpatient Prospective Payment System (IPPS) Final Rule FY13. **19** Data on file, 092713-1.

MKT-23-211 Rev 1B

TYRX, Inc. , 1 Deer Park Drive, Suite G, Monmouth Junction, NJ 08852 Customer Service: 866.908.8979 | TYRX.com | HeartDeviceInfection.com

aigisRx®

Antibacterial Envelope Product Specifications



Product:
AIGISRx® is an Antibacterial Envelope is made from knitted polypropylene mesh substrate, coated with a polyarylate bioresorbable polymer containing two antimicrobial agents, minocycline and rifampin. AIGISRx is a dual component (resorbable and non-resorbable), sterile prosthesis designed to reduce infection and to stabilize the implantable pacemaker or defibrillator when implanted in the body.

AIGISRx Polypropylene Mesh:
Performance Properties
Burst Strength = 49.3 PSI - 180 PSI
Break Strength ≥ 150N

Product Indications:
AIGISRx is intended to securely hold the pacemaker pulse generator or defibrillator in order to create a stable environment when implanted in the body. AIGISRx contains the antimicrobial agents, rifampin and minocycline, which have been shown to reduce infection in an *in vivo* model of bacterial challenge following surgical implantation of the generator or defibrillator. This device is only intended to be used in conjunction with pacemakers and implantable defibrillators.

Non-resorbabale Mesh Substrate:
A large-pore mesh knitted from monofilament polypropylene filaments, similar in composition and diameter to 5-0 suture. The knitted mesh comprises over 90% of the entire AIGISRx device by weight.

Resorbabale Polymer Coating:
A bioresorbable, biocompatible polymer based upon the amino acid, tyrosine, which breaks down linearly, primarily via hydrolysis and is resorbed in approximately 140 days. This bioresorbable polymer breaks down into naturally occurring components which are considered Generally Regarded As Safe (GRAS). The primary purpose of this polymer is to act as a carrier for the antimicrobial agents, minocycline and rifampin. The tyrosine polymer and drug combination, which are spray coated onto the polypropylene mesh, comprise the remaining 10% of the entire AIGISRx device by weight.

Antibiotics:
Minocycline is a bacteriostatic antimicrobial which inhibits protein synthesis of the cell wall.

Minocycline has been shown to be effective against Gram positive (+) bacteria such as S. *aureus* and *S. pneumoniae* and Gram negative (–) bacteria such as *E. coli, E. aerogenes, H. influenza* and *A. baumannii.*

Minocycline dose per AIGISRx device: up to 11mg (Pacemaker), 16mg (ICD). Sustained released over 7 to 10 days.

Rifampin is a bacteriocidal antimicrobial which interferes with DNA-dependent RNA polymerase activity.

Rifampin has been shown to be effective against Gram positive (+) bacteria such as *S. aureus* (including *MRSA*) and *S. epidermidis* and Gram negative (–) bacteria such as *H. influenza*.

Rifampin dose per AIGISRx device: up to 11mg (Pacemaker) 16mg (ICD). Sustained released over 7 to 10 days.

AIGISRx PM Antibacterial Pacemaker Envelope
Size: 2.5” (6.4cm) x 2.75” (7.0cm)
SKU # CMRM-3122-B (box of 6 individuals)
Single Use Only: Do Not Resterilize
Storage: Store between 36–77° F (2–25° C)

Each AIGISRx polymer-coated envelope is placed in a Tyvek folder insert which is packaged inside a single-barrier foil pouch.

AIGISRx ICD Antibacterial Defibrillator Envelope
Size: 3.0” (7.6cm) x 3.35” (8.5cm)
SKU # CMRM-3133-B (box of 6 individuals)
Single Use Only: Do Not Resterilize
Storage: Store between 36–77° F (2–25° C)

Each AIGISRx polymer-coated envelope is placed in a Tyvek folder insert which is packaged inside a single-barrier foil pouch.

For full prescribing information see minocycline and rifampin package inserts. For full prescribing information for AIGISRx, including warnings, cautions and contraindications, see package insert.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a licensed medical practitioner.

MKT-23-097 Rev 4

1 Deer Park Drive • Suite G • Monmouth Junction, NJ 08852
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TYRX®

Medtronic

TYRX™
Antibacterial Envelope

TYRX™ Antibacterial Envelope
(Tyrosine Polyarylate-coated, Monofilament Polypropylene Mesh Envelope
Containing the Antimicrobials Rifampin and Minocycline)

INSTRUCTIONS FOR USE
USA

STERILE: Contents sterile unless package has been opened or damaged. Single Use Only. Do Not Resterilize.

CAUTION: Read instructions prior to use.

Rx Only

PRODUCT DESCRIPTION

The TYRX™ Antibacterial Envelope is a dual component (absorbable and non-absorbable), sterile prosthesis designed to hold a pacemaker pulse generator or defibrillator to create a stable environment when implanted in the body.

The antibacterial envelope is constructed of knitted filaments of polypropylene that are coated with an absorbable polyarylate polymer.

The antibacterial envelope absorbable polymer coating contains the antimicrobial agents rifampin and minocycline in concentrations of 86 µg/cm^2.

INDICATIONS FOR USE

The antibacterial envelope is intended to securely hold a pacemaker pulse generator or defibrillator in order to provide a stable environment when implanted in the body. The antibacterial envelope contains the antimicrobial agents rifampin and minocycline which have been shown to reduce infection in an *in vivo* model of bacterial challenge following surgical implantation of the generator or defibrillator. This device is only intended to be used in conjunction with pacemakers and implantable defibrillators.

ACTIONS

The antibacterial envelope is constructed of knitted filaments of polypropylene that are coated with a absorbable polyarylate polymer. The purpose of the absorbable coating is to act as a carrier for the antimicrobial agents. Once placed, the polymer absorbs in approximately 140 days, leaving a lightweight permanent mesh incorporated into the tissue.

The antibacterial envelope releases the antimicrobial agents rifampin and minocycline for a minimum of 7 days to reduce the risk of infection of the implanted pulse generator following surgery. In *in vitro* studies, the antibacterial envelope demonstrated antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus, Staphylococcus epidermidis, Acinetobacter baumannii, Enterobacter aerogenes,* and *Proteus mirabilis*.

The antibacterial envelope also demonstrated *in vivo* effectiveness in reducing infections in a series of studies in which a pulse generator canister placed into an antibacterial envelope and generator canister alone (Control) were implanted into appropriate models of infectivity (dogs or rabbits). Both the antibacterial envelope and the Control groups were inoculated with bacteria and observed for a minimum of 7 days to validate the presence of infection in the animals. The bacteria tested included *Staphylococcus aureus, Staphylococcus epidermidis, Acinetobacter baumannii,* and *Escherichia coli* which represent a majority of the infections reported in pacemaker-related endocarditis.

It should be noted that the *in vitro* and *in vivo* activity of the antibacterial envelope antimicrobials is variable against non-*epidermidis* strains of coagulase-negative staphylococci.

CONTRAINDICATIONS

The antibacterial envelope is **NOT** indicated for use in the following situations:

- Allergy or history of allergy to tetracyclines, or rifampin, or polypropylene.
- In patients with systemic lupus erythematosus (SLE) because minocycline has been reported to aggravate this condition.
- Use of the antibacterial envelope in contaminated or infected wounds.

WARNINGS

This device is supplied sterile. Inspect the packaging to be sure that it is intact and undamaged prior to use.

This device is for single use only. Do not resterilize. Product should be used once the exterior foil wrapper has been broken. Do not store for later use. Unused portions of the prosthesis should be discarded.

If the unused prosthesis has been in contact with instruments or supplies used on a patient or contaminated with bodily fluids, discard with care to prevent risk of transmission of any disease.

The use of any permanent mesh in a contaminated or infected wound could lead to fistula formation and extrusion of the prosthesis. If infection develops, treat the infection aggressively as per standard practice. The prosthesis may not have to be removed. An unresolved infection may require removal of the prosthesis.

As in any antimicrobial therapy, the possible teratogenic potential in women capable of having children should be carefully weighed against the benefit of therapy.

This device has not been evaluated in pediatric patients.

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 carefully considered since rifampin and minocycline can cause additional stress on the hepatic and renal systems. Patients who are implanted with this device and are also taking methoxyflurane should also be carefully monitored for signs of renal toxicity.

Patients who are implanted with this device who are also taking warfarin should have their International Normalized Ratio (INR) time monitored because tetracyclines have also been reported to potentiate the anticoagulant effect of warfarin. The use of this product in patients being treated with thionamides, isoniazid, or halothane should be carefully considered due to potential hepatic side effects that have been reported in patients using these drugs and higher doses of rifampin.

The contraindications, warnings and precautions applicable to the use of specific antibiotic prophylaxis should be followed when prophylaxis is administered in conjunction with implantation of a pacemaker pulse generator or defibrillator enclosed in an antibacterial envelope.

Development of a hypersensitivity reaction should be followed by removal of the device and appropriate treatment initiated at the discretion of the attending physician.

Use of the antibacterial envelope in contaminated wounds is not recommended. The device is not indicated for the treatment of infection. Because the antibacterial envelope is impregnated with a combination of the antimicrobial agents rifampin (a derivative of rifamycinB) and minocycline (a derivative of tetracycline), the contraindications, warnings, and precautions regarding the use of these antimicrobials apply and should be adhered to when using this device.

CAUTIONS
Only physicians qualified in the placement of pulse generators or defibrillators should use this prosthesis.

Rx Only

There are no known interactions between rifampin and minocycline. As with many drugs, the effectiveness of minocycline and rifampin may be reduced after direct contact with solutions containing iodine.

Do not alter usual practice of pre-, peri-, or post-operative administration of local or systemic antibiotics.

COMPLICATIONS AND ADVERSE REACTIONS
Possible complications for these procedures include bleeding and infection. (See **WARNINGS**.) There is currently no long-term data available to determine whether tissue reactions to the antibacterial envelope will be equivalent to the Parsonnet™ Pacemaker Pouch. As with any surgical procedure involving the implantation of a pacemaker/defibrillator, there may be complications including seroma, adhesions, hematoma, inflammation, extrusion, or fistula formation. If infection develops, treat the infection aggressively as per standard practice, including removal of the prosthesis, if indicated. Please report any device-related adverse events to Medtronic, Inc. at 1-800-848-9300.

STORAGE: The antibacterial envelope should be stored between 36 – 77 ºF (2 – 25 ºC). Do not freeze.

HANDLING: Use clean, sterile gloves and/or atraumatic instruments when handling the mesh.

MAINTAINING ASEPSIS
To help maintain strict asepsis during surgery, special precautions and careful preoperative site preparations are necessary. Any postoperative infection should be aggressively treated as soon as possible. Any unresolved infection may require removal of the prosthesis.

PREPARATION
It is recommended that the antibacterial envelope be completely immersed for a few seconds in standard irrigation solution to facilitate placement.

INSERTION TECHNIQUE
Prepare the pulse generator or defibrillator as per manufacturer's instructions, making sure to secure the leads. Slide the pulse generator/defibrillator into the opening in the envelope with lead wires emerging straight out as shown in Figure 1. It is important to make sure that the pocket is created large enough to accommodate the additional volume of the antibacterial envelope, to ensure that closure of the incision does not place too much tension on the sutures on the adjacent skin, and that the layers of suture do not inadvertently ensnare the envelope. Place generator/defibrillator into the patient as per standard practice. If the dimensions of the pulse generator/defibrillator are larger than the opening, but of similar dimension to the antibacterial envelope, the opening can be widened to accommodate placement. (NOTE: The antibacterial envelope cannot be used with generators and defibrillators that are larger than its internal dimensions.) For generators and defibrillators that are significantly smaller than the antibacterial envelope, the generator/defibrillator should be placed as shown in Figure 2. Nonabsorbable or absorbable monofilament sutures can be used to tack the opening of the envelope to secure the generator/defibrillator prior to implantation.

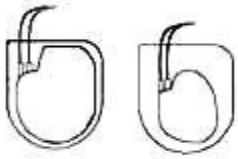

Figure 1 Figure 2

REMOVAL OF PULSE GENERATOR FROM INCORPORATED ENVELOPE
It may be necessary to remove the pacemaker or defibrillator from the envelope after a period of implantation. First, surgically expose the envelope. Make an incision on the flat side of the envelope, approximately the width of the pacemaker or defibrillator. Disconnect the electrode leads. Remove the pacemaker/defibrillator through the opening in the side of the envelope. If required, insert a drainage tube. A new pacemaker/defibrillator may be inserted into the envelope through the side opening. Connect the electrical leads. Suture the envelope closed. Complete the procedure following standard accepted surgical techniques. Familiarization with the device and following proper surgical techniques are important when explanting a device. Always use standard of care subject to the patient's condition and the surgical presentation in removing an implant.

TRACEABILITY
A traceability label, which identifies the type, size and lot number of the prosthesis, is attached to the foil label in every package. This traceability label should be peeled off and affixed to the patient's permanent medical record to clearly identify the device that was implanted.

HOW SUPPLIED
The antibacterial envelope is supplied sterile in foil pouches in two sizes, a Medium and Large envelope.

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TYRX products are protected under one or more patents which can be found at www.TYRX.com

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