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

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

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

Sunday, March 17th, 2019 | #WRAPITstudy | #ACC19

The Scope of CIED* Infections

- An estimated 1.5 million patients receive a CIED worldwide every year[1]

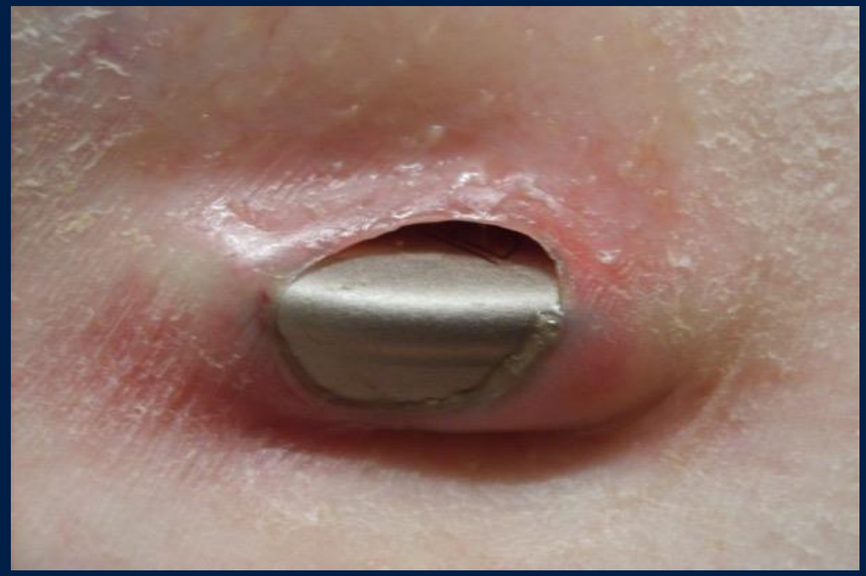
- 1-4% of procedures are associated with an infection [2]

*Cardiac Implantable Electronic Device (CIED)

1. Mond HG et al. *PACE* 2011;34:1013-27; 2. Tarakji KG et al. *Am Heart J*. 2016:180:12-21

The Consequences of CIED Infection

- Complete device and lead removal, prolonged antibiotic therapy[1]
- Long hospital stay
- Short and long term mortality[2,3]
- $44,000 - $83,000 average cost to treat[4]

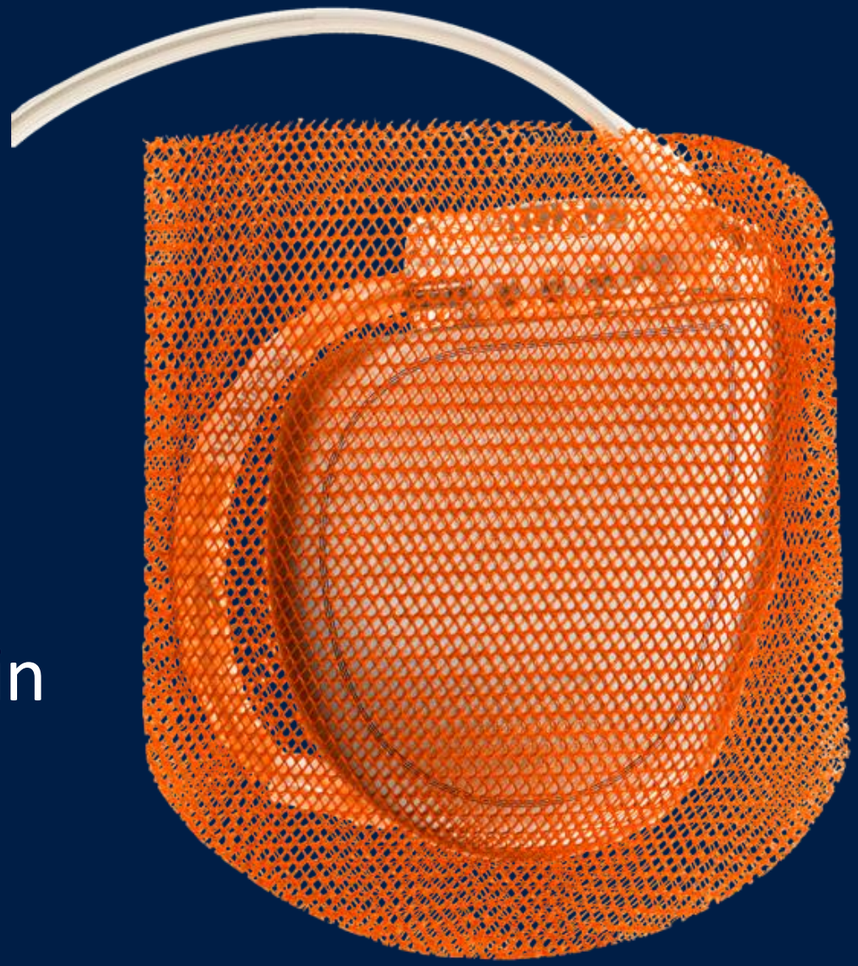


Pre-operative antibiotics are the only intervention shown to reduce the risk of CIED infection[5]

1. Kusumoto FM et. al. *Heart Rhythm* 2017;14(12):e503-551; 2. Tarakji KG et. al. *Europace* 2014 (10):1490-5; 3. Sohail MR et. al. *PACE* 2015;38(2):231-9; 4. Lopatto, et al. ACC 2017 scientific sessions; 5. de Oliveira JC et al. *Circ AE* 2009; 2:29-34

The TYRX Absorbable Antibacterial Envelope

- A single-use device, stabilizes CIED
- Absorbable multifilament knitted mesh
- Polymer-controlled antibiotic elution
- Locally delivered minocycline and rifampin sustained for 7 days
- Fully absorbed in about 9 weeks



WRAP-IT Study Aim

To evaluate the safety and effectiveness of the TYRX envelope in reducing CIED infections in addition to standard infection prevention strategies

WRAP-IT Study Design

- Prospective, randomized, controlled, multicenter, global trial
- Randomized 1:1 to TYRX Envelope vs Control (no TYRX)
- Independent Clinical Events Committee
  - Electrophysiologists & Infectious Disease specialists
- Independent Data Monitoring Committee
- Independent validation of results
  - The Cleveland Clinic Coordinating Center for Clinical Research

Tarakji KG, et al. *Am Heart J* 2016;180:12-21.

WRAP-IT Study Patients

Included

- CIED generator replacement, system upgrade, or revision
- Initial CRT-D

Excluded

- Hemodialysis or peritoneal dialysis
- Immunosuppressive agents (chronic oral or ≥20mg of prednisone)
- Recent CIED infection (<12 months)

Pacemaker (including CRT-P) randomizations were capped at 25% of the target sample size.

WRAP-IT Study Primary Objective

Rate of Major CIED Infections through 12-months post-procedure

- TYRX Envelope vs Control
- Intention-to-treat analysis
- Cox regression stratified by device class
  - Low-power and high-power devices

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

WRAP-IT Study Definitions of CIED Infection, Major Infection

CIED infections were defined as:

1) Superficial cellulitis with wound dehiscence, erosion, or purulent drainage
2) Deep incisional or generator pocket infection
3) Persistent bacteremia
4) Endocarditis

Major CIED Infections were defined as CIED infections resulting in one or more of the following:

- CIED system removal
- Any invasive procedure (e.g. pocket opened) without system removal
- Extended antibiotic therapy if the patient was not a candidate for system removal
- Death

Note: All other CIED infections including superficial incisional surgical site infections that met the CDC criteria, independent of the time from surgery, were defined as minor CIED infections unless they met the major CIED infection criteria.

WRAP-IT Study Patient Enrollment

- January 2015-July 2017
- 6,983 patients randomized
- 25 countries
- 181 centers
- 776 implanting physicians

Balanced Baseline Characteristics Between Groups

Characteristic	Envelope (N = 3495)	Control (N = 3488)
Age, (years) [Mean ± SD]	70.0 ± 12.6	70.1 ± 12.4
Female (%)	997 (28.6%)	976 (28.0%)
BMI (kg/m^2) [Mean ± SD]	29.1 ± 6.1	29.2 ± 6.3
Diabetes	1080 (31.0%)	1085 (31.2%)
Renal dysfunction	585 (16.8%)	554 (15.9%)
Baseline Medications		
Antiplatelets	2007 (57.5%)	1972 (56.6%)
Anticoagulants	1377 (39.5%)	1390 (39.9%)
Antibiotics	36 (1.0%)	37 (1.1%)
Immunosuppressive*	48 (1.4%)	85 (2.4%)
Insulin	348 (10.0%)	375 (10.8%)
Oral antidiabetic	615 (17.6%)	620 (17.8%)

*No significant differences between groups except for the use of immunosuppressive agents (p=0.001); standardized difference does not suggest imbalance

Balanced Procedure Characteristics Between Groups

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

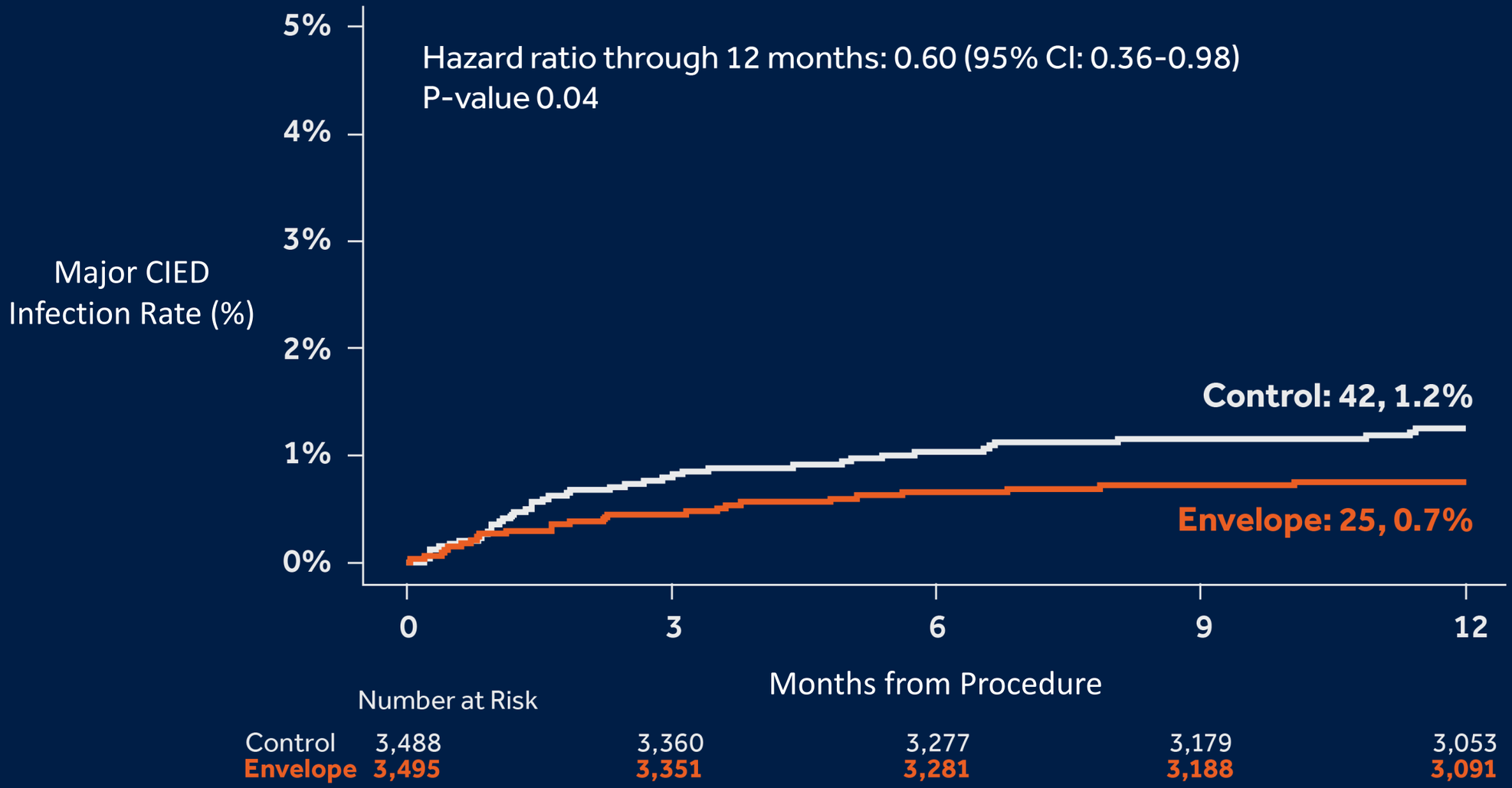
Very low cross-over rate (0.7% Control; 2.3% Envelope)

99.7% implant procedure success rate with TYRX‡

*Counts and percentages reflect subjects with procedure attempts.
†Device type planned at randomization
‡Envelope group patients with successful CIED procedure and TYRX implant attempt by 646 implanters

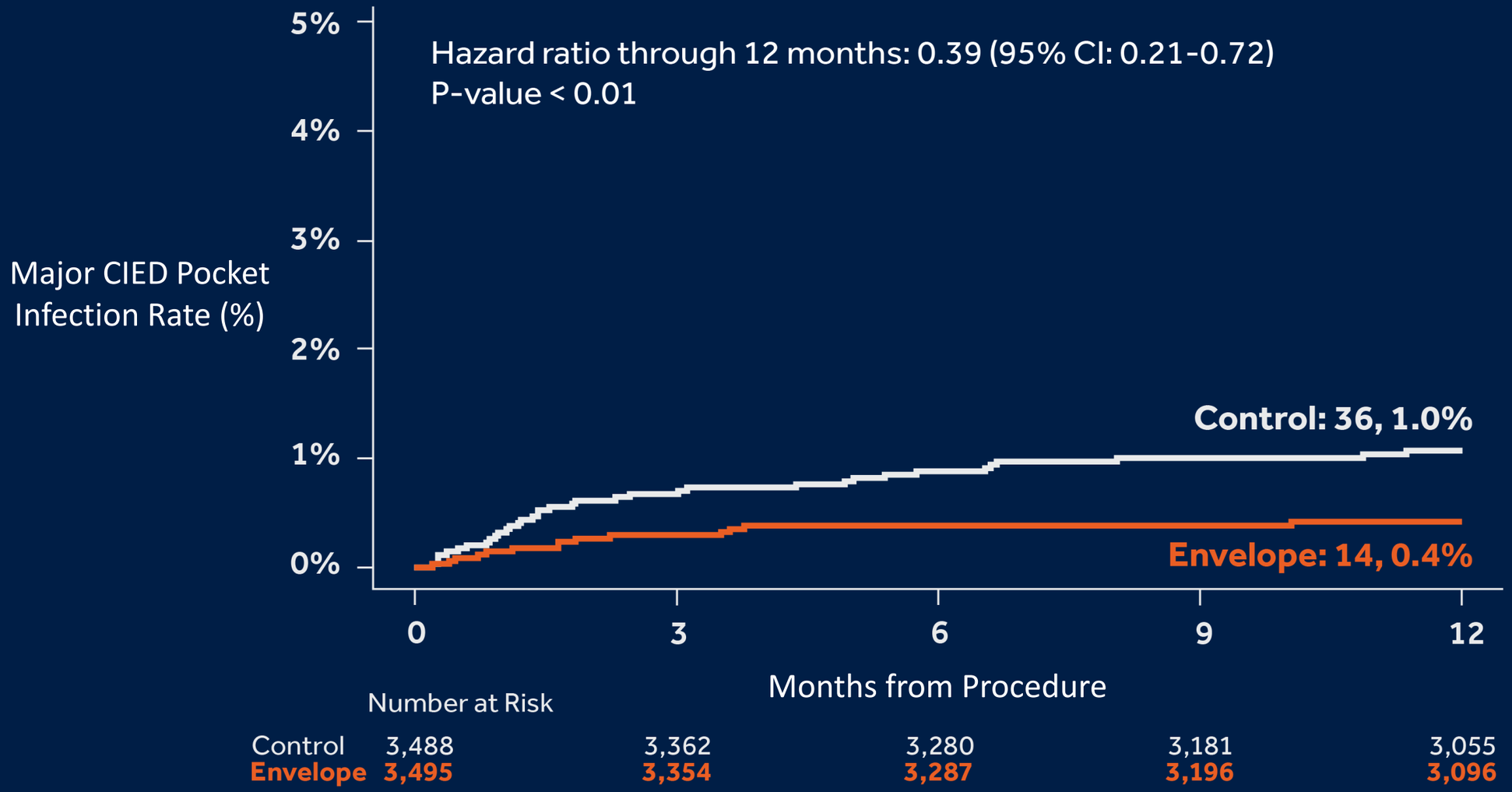
WRAP-IT Study Primary Endpoint: Major CIED Infection

40% Reduction in Major CIED Infections with TYRX through 12 Months



WRAP-IT Study: Major CIED Pocket Infections

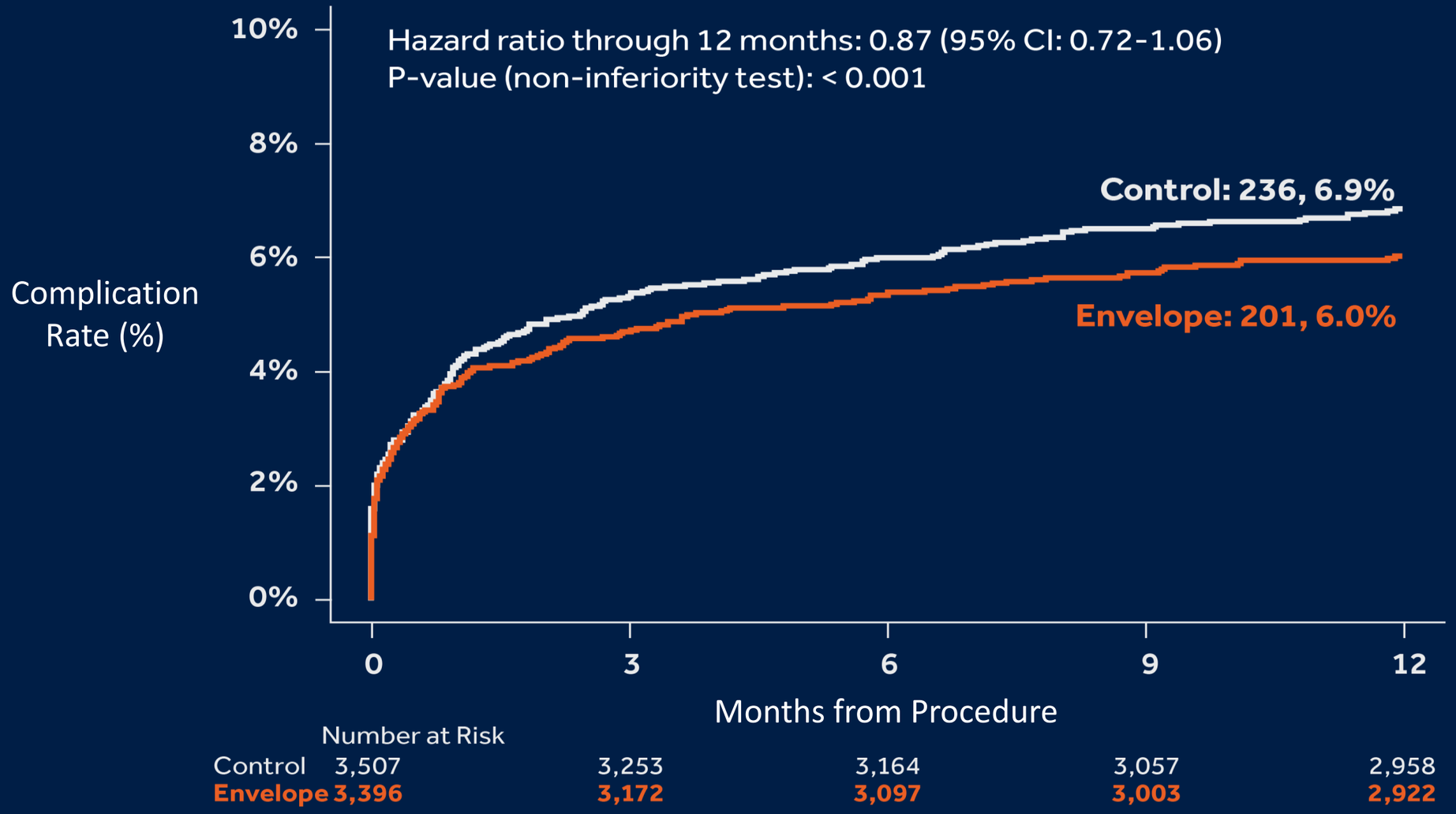
61% Reduction in Major CIED Pocket Infections with TYRX through 12 Months



74.6% of initial major CIED infections were pocket infections

WRAP-IT Study Secondary Endpoint: Safety Objective

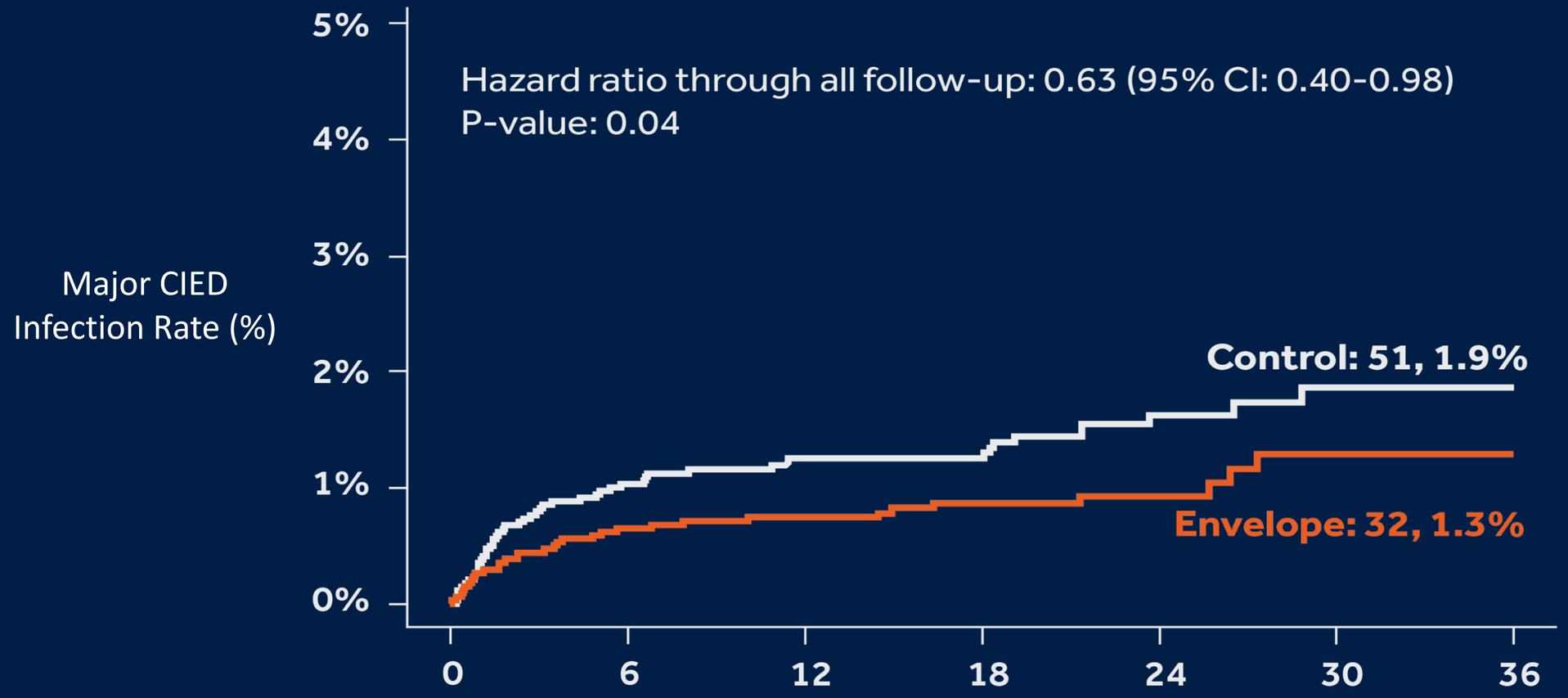
No Increased Risk of Complications with TYRX through 12 Months



Prespecified secondary analysis for non-inferiority, as treated. When excluding the primary endpoint major infections, the 12-month Kaplan-Meier complication event rates were 5.7% Envelope vs. 5.9% Control.

WRAP-IT Study Secondary Endpoint: Major CIED Infections All Follow-up

Effect Sustained with TYRX through Follow-up

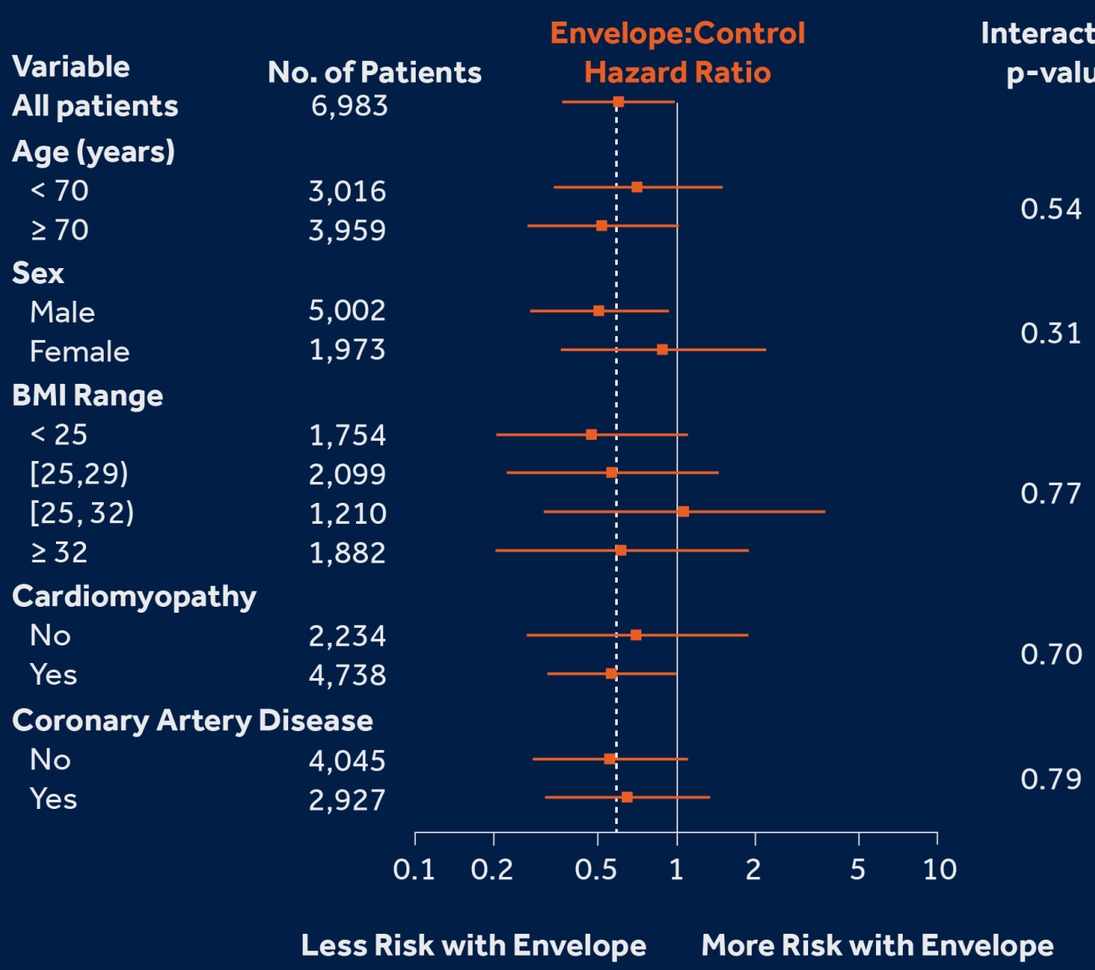


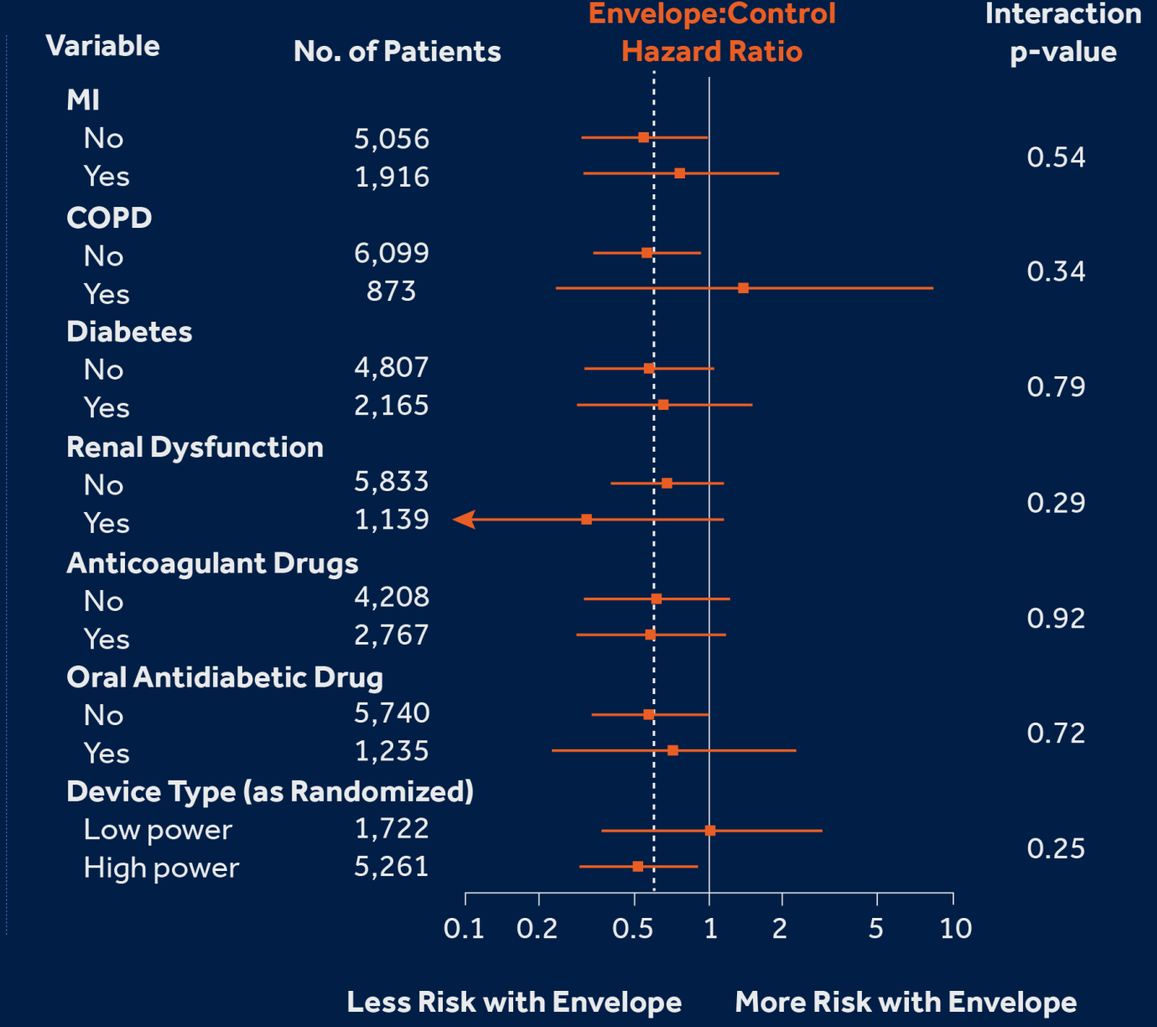
Number at Risk							
Control	3,488	3,277	3,053	2,193	1,408	571	130
Envelope	**3,495**	**3,281**	**3,091**	**2,178**	**1,395**	**581**	**121**

P-value shown was not adjusted for multiple comparisons. After the prespecified adjustment for multiple comparison was done, the adjusted p-value was not significant. Patients were followed for an average of 20.7±8.5 months.

WRAP-IT Study Subgroup Analysis

Reduction in Major CIED Infections Consistent Across Sub-groups





The subgroup analysis was conducted to test for interaction among various baseline variables for the primary end point through 12 months.

WRAP-IT Study Limitations

- One manufacturer’s devices, non-sequential patients
- Commercial availability of TYRX Envelope allowed for possible selection bias
- Immunosuppressive use at baseline was not balanced between cohorts

WRAP-IT Study Conclusions

In patients undergoing CIED generator replacement, system upgrade, or revision or initial CRT-D implantation

- The rate of major CIED infections was 1.2% at 1 year
- The TYRX envelope significantly reduced major CIED infections by 40%, without increasing complications
- Major pocket infections were reduced by 61%

This study provides comprehensive data on CIED infection and strong evidence for the use of the TYRX envelope for infection prevention in this patient population

WRAP-IT Study Committees

Steering Committee

Bruce Wilkoff, MD (Chair)
Cleveland Clinic

Ralph Corey, MD
Duke Clinical Research Institute

Charles Kennergren, MD
Sahlgrenska University Hospital

Suneet Mittal, MD
Valley Health System

Jeanne Poole, MD
University of Washington

Khaldoun Tarakji, MD MPH
Cleveland Clinic

Clinical Events

Ken Ellenbogen, MD (Chair)
Medical College of Virginia

Frank Bracke, MD
Catharina Hospital

Antonio Curnis, MD
University of Brescia

Arnold Greenspon, MD
Jefferson University

Rizwan Sohail, MD
Mayo Clinic

Charles Swerdlow, MD
UCLA

Data Monitoring

Andrew Krahn, MD (Chair)
University of British Columbia

Helen Boucher, MD
Tufts Medical Center

Anne Curtis, MD
Buffalo General Medical Center

Thomas Heywood, MD
Scripps Clinic

Kerry Lee, PhD
Duke Clinical Research Institute

WRAP-IT Study Centers

1. Edward Schloss, MD, The Lindner Research Center, US
2. Jose Gallastegui, MD, Clearwater Cardiovascular & Interventional Consultants, US
3. Robert A. Pickett, MD, Saint Thomas Research Institute LLC, US
4. Rudolph Evonich, MD, Upper Michigan Cardiovascular Associates, US
5. Francois Philippon, MD, IUCPQ - Institut Universitaire de Cardiologie et de Pneumologie, Canada
6. Janet McComb, MD, The Newcastle upon Tyne Hospitals, UK
7. Steven Roark, MD, Cardiology Associates of Gainesville, US
8. Denise Sorrentino, MD, Iowa Heart Center, P.C. (West Des Moines), US
9. Darius Sholevar, MD, Lourdes Cardiology Services, US
10. Khaldoun Tarakji, MD MPH, Cleveland Clinic, US
11. Edmond Cronin, MD, Hartford Hospital, US
12. Brett Berman, MD, Chula Vista Cardiac Center, US
13. David Riggio, MD, AZ Arrhythmia Consultants, US
14. Mauro Biffi, MD / Igor Diemberger, MD, Policlinico Sant' Orsola, Malpighi, Italy
15. Hafiza Khan, MD, Baylor Research Institute, US
16. Marc Silver, MD, WakeMed Heart and Vascular, US
17. Jack Collier, MD, Oklahoma Heart Hospital, US
18. Zayd Eldadah, MD, MedStar Heart and Vascular Institute, US
19. David Justin Wright, MD, Liverpool Heart and Chest Hospital, UK
20. JoEllyn Moore, MD, Minneapolis Heart Institute, US
21. Kamel Addo, MD, Mount Carmel East, US
22. R. Chris Jones, MD, Centennial Heart Cardiovascular Consultants, US
23. Robert Schaller, MD, University of Pennsylvania, US
24. Joaquin Martinez-Arraras, MD / Ismaile Abdalla, MD, Amarillo Heart Group, US
25. Ziad Issa, MD, Prairie Education & Research Cooperative, US
26. Calum Redpath, MD, Ottawa Heart Institute, Canada
27. Jean Moubarak, MD, Hamot Medical Center / Medicor Associates, US
28. Surinder Kaur Khelea, MD, Institute Jantung Negara, Malaysia
29. Berit Thornvig Philbert, MD, Rigshospitalet, Denmark
30. Timothy A.Simmers, MD, Catharina Ziekenhuis, Netherlands
31. Lucas V.A. Boersma, MD, St. Antonius Ziekenhuis, Netherlands
32. Panagiotis Korantzopoulos, MD, University Hospital of Ioannina, Greece
33. John Love, MD, Maine Medical Center, US
34. Ralph Augostini, MD, The Ohio State University, US
35. Havard Keilegavlen, MD / Svein Faerestrand, MD, Haukeland Universitetssjukehus, Norway
36. Suneet Mittal, MD, The Valley Hospital, US
37. Scott Wiggins, MD, Ark-La-Tex Cardiology, US
38. Jeff Healey, MD, Hamilton General Hospital, Canada
39. Brian Ramza, MD, Mid America Heart Institute, US
40. Riple Hansalia, MD, Jersey Shore University Medical Center, US
41. Chad Brodt, MD / Paul Wang, MD, Stanford Hospital & Clinics, US
42. Attila Mihalcz, MD, Universitatsklinikum Krems, Austria
43. Daniel Gras, MD, Nouvelles Cliniques Nantaises, France
44. Ulrika Maria Birgersdotter-Green, MD, University of California San Diego, US
45. Ethan Fruechte, MD / Douglas Hodgkin, MD, North Memorial Health Heart & Vascular Center, US
46. Daniel Lustgarten, MD, Fletcher Allen Health Care, US
47. Gery Tomassoni, MD, Lexington Cardiac Research Foundation, US
48. Fozia Ahmed, MD, Central Manchester University Hospital NHS, UK
49. Cecilia Rorsman, MD, Sjukhuset i Varberg, Sweden
50. Pugazhendhi Vijayaraman, MD, Geisinger Clinic, US
51. Judith Mackall, MD / Harish Manyam, MD, University Hospitals Case Medical Center, US
52. Allan Nichols, MD, Ohio Health Corporation, US
53. Serge David Bar-Lev, MD, Sheba Medical Center Tel Hashomer, Israel
54. James Merrill, MD, Wellmont CVA Heart Institute, US
55. Wayne Adkisson, MD, University of Minnesota, US
56. Juan José Olalla, MD, Hospital Marques de Valdecilla, Spain
57. Nagib Chalfoun, MD, Spectrum Health, US
58. Eric Johnson, MD, The Stern Cardiovascular Center, US
59. Jorge Massare, MD, Longview Regional Medical Center, US
60. Camille-Frazier Mills, MD, Duke University Medical Center, US
61. John Chenarides, MD, Allegheny General Hospital, US
62. Mohammad Jazayeri, MD, Bellin Health, US
63. Kevin Boran, MD, Cardiovascular Consultants Heart Center, US
64. John Schoenhard, MD / Simon Milstein, MD, CentraCare Heart & Vascular Center, US
65. John Bailey, MD / Mark Kremers, MD, Novant Health Heart and Vascular Institute, US
66. Thomas Burkart, MD, University of Florida Health Sciences Center Gainesville, US
67. Wilfried Mullens, MD, ZOL, Belgium
68. Jay Franklin, MD, Baylor Research Institute, US
69. Frederick Ehlert, MD, New York Presbyterian Hospital, US
70. Charles Henrikson, MD, Oregon Health & Science University (OHSU), US
71. Ilana Kutinsky, MD, William Beaumont Hospital, US
72. Ignasi Anguera, MD, Hospital Universitari Bellvitge, Spain
73. Michael Springer, MD, Norton Cardiovascular Associates
74. Grant Simons, MD, Englewood Hospital & Medical Center, US
75. Frederic Anselme, MD, Hopital Charles Nicolle - CHU Rouen, France
76. David Sandler, MD, Oklahoma Heart Institute, US
77. Luca Bontempi, MD Azienda Ospedaliera Spedali Civili di Brescia, Italy
78. Laurence Marie-Pierre Guedon-Moreau, MD, CHRU de Lille, France
79. Sei Iwai, MD, Westchester Medical Center, US
80. John McAnulty, MD / Eric Putz, MD, Legacy Medical Group, US
81. Gregory Golovchiner, MD, Rabin Medical Center - Beilinson Hospital, Israel
82. David Juang, MD, University of Rochester Medical Center, US
83. Peter Ammann, MD, Kantonsspital St.Gallen, Switzerland
84. Randy Jones, MD, Providence Health & Services, US
85. Allan Katz, MD, Saint Elizabeth Health Center, US
86. Malini Madhavan, MD, Mayo Clinic, US
87. Martin Emert, MD, The University Kansas Medical Center Research Institute, US
88. António Cândido de Freitas Fernandes Hipólito Reis, MD, Centro Hospitalar do Porto, Portugal
89. Tina Salo, MD, Sisataudit TYKS, Finland,
90. Christopher Cole, MD, Penrose Hospital, US
91. Stephen Keim, MD, Delmarva Heart, LLC, US
92. George Thomas, MD, Cornell University, US
93. Chanta Chakrabarti, MD, Saint Paul's Hospital, Vancouver, BC, Canada
94. Christina Murray, MD, Oklahoma University Health Science Center, US
95. Pierce Vatterott, MD, United Heart and Vascular Clinic, US
96. Robert Sangrigoli, MD, Doylestown Cardiology Associates – VIAA, US
97. Theofanie Mela, MD, Massachusetts General Hospital, US
98. Mark John Mason, MD, Royal Brompton & Harefield NHS Foundation Trust, UK
99. Robert Winslow, MD, Danbury Hospital, US
100. Shang-Chiun Lee, MD, Mercy Hospital Springfield, US
101. Przemyslaw Mitkowski, MD, Szpital Kliniczny Przemienienia Panskiego, Poland
102. Antoine Da Costa, MD, Cen Hosp Univ Saint Etienne - Hopital Nord, France
103. Girish Nair, MD, Saint Vincent Heart Center of Indiana, US
104. Westby Fisher, MD, NorthShore University Health System, US
105. Jean-Claude Deharo, MD, Hopital de la Timone - CHU de Marseille, France
106. Mark Castellani, MD / David Rhine, MD, Sparrow Clinical Research Institute, US
107. Hamid Ghanbari, MD, University of Michigan Cardiovascular Center, US
108. Gautham Kalahasty, MD, Virginia Commonwealth University Medical Center, US
109. Daniel Anderson, MD, University of Nebraska, US
110. Daniel Frisch, MD, Thomas Jefferson University, US
111. Larry Chinitz, MD / Charles Love, MD, NYU – Langone Medical Center, US
112. Andrew Rubin, MD, Eisenhower Medical Center, US
113. Timothy Lessmeier, MD, Heart Clinics Northwest, P.S., US
114. Steven Compton, MD, Alaska Heart Institute, US
115. Mark Mitchell, MD, Forsyth Medical Center, US
116. Katherine Fan, MD, Grantham Hospital, Hong Kong
117. Saeed Bandar Al Ghamdi, MD, King Faisal Specialist Hospital, Saudi Arabia
118. Gabriela Kaliska, MD, Stredoslovensky Ustav srdcovych a cievnych chorob (SUSCCH), Slovakia
119. Peter Margitfalvi, MD, NUSCH a.s. Bratislava, Slovakia
120. Glenn Meininger, MD, MedStar Health Research Institute, US
121. Aamir Cheema, MD, Saint Mary's Medical Center, US
122. Maria Grazia Bongiorni, MD, Azienda Ospedaliero Univ Pisana - Stabilimento di Cisanello, Italy
123. Jeffrey Luebbert, MD, Pennsylvania Hospital, US
124. Michael Pelini, MD, Northeast Ohio Cardiovascular Specialists, US
125. Silvia Misikova, MD, VUSCH, Slovakia
126. Jerome Kuhnlein, MD, Great Lakes Heart & Vascular Institute, PC, US
127. Robert Schweikert, MD, Akron General Medical Center, US
128. Jean-Manuel Herzet, MD, CHR La Citadelle, Belgium
129. Stefano Pedretti, MD, Presidio Ospedaliero Sant Anna, Italy
130. Byron Lee, MD, University of California San Francisco, US
131. Peter Santucci, MD, Loyola University Medical Center, US
132. Jonas Hörnsten, MD, Karolinska Universitetssjukhuset, Sweden
133. Samir Saba, MD / Evan Adelstein, MD / Stuart Mendenhall, MD, University of Pittsburgh Medical Center
134. Ngai-Yin Chan, MD, Princess Margaret Hospital, Hong Kong
135. Shabbar Jamaly, MD, Sahlgrenska Universitetssjukhuset, Sweden
136. Javier Moreno, MD, Hospital Universitario Ramon y Cajal, Spain
137. Tiziano Moccetti, MD, Cardio Centro Ticino, Switzerland
138. Paresh Shah, MD, Sinai Hospital of Baltimore, US
139. John Douglas Pappas, MD, Cardiology Associates of Corpus Christi, US
140. Thomas Blum, MD, Universitaets-Herzzentrum Freiburg Bad Krotzingen, Germany
141. Etienne Pruvot, MD, CHUV - University Hospital, Switzerland
142. Anthony Chu, MD, The Miriam Hospital, US
143. Chetan Gangireddy, MD / Joshua Cooper, MD, Temple University Hospital, US
144. Walter Chien, MD, Saint Joseph's Medical Center, US
145. Ali Al-Mugamgha, MD, Saint Joseph's Hospital Health Center, US
146. Matthew Smelley, MD, Asheville Cardiology Associates, PA, US
147. Heath Saltzman, MD, Drexel University College of Medicine, US
148. Arun Kolli, MD, Tri-City Cardiology Consultants, US
149. William Kostis, MD / Sluja Amardeep, MD, Robert Wood Johnson Medical School, US
150. Charles Kennergren, MD, Sahlgrenska University Hospital, Sweden
151. Rajiv Handa, MD, Saint Anthony's Medical Center, US
152. Emmanuel Simantirakis, MD, University Hospital of Heraklion, Greece
153. Tony Simmons, MD, Wake Forest University Health System, US
154. Randel Smith, MD, Hattiesburg Clinic/Forrest General, US
155. Marye Gleve, MD, Washington University School of Medicine, US
156. George N. Theodorakis, MD, Onassis Cardiac Surgery Center, Greece
157. Emad Aziz, MD, Mount Sinai Saint Luke's Hospital, US
158. Scott Burke, MD, St. Mary's Medical Center, US
159. Kah Leng Ho, MD, National Heart Center, Singapore
160. Carlo De Asmundis, MD, Heart Rhythm Management Centre, UZ Brussels VUB Brussel, Belgium
161. Kenneth Civello, MD, Our Lady of the Lake, US
162. Tan Vern Hsen, MD, Changi General Hospital, Singapore
163. Darryl Wells, MD, Swedish Medical Center Cherry Hill, US
164. Hüseyin Ince, MD, Universitatsklinikum Rostock, Germany
165. Sami Pakarinen, MD, Helsingin Seudun Yliopistollinen Keskussairaala, Finland
166. Jodie Hurwitz, MD, North Texas Heart Center, US
167. Vinay Mehta, MD, Aurora BayCare Medical Center, US
168. Imra Zainal Abidin, MD, Universiti Malaya Medical Centre, Malaysia
169. Michael Osayamen, MD, Jackson Clinic, US
170. Javier Banchs, MD, Scott & White Hospital, US
171. Kelly Kim, MD, SCL Physicians Heart Institute of Colo, US
172. Andrzej Kutarski, MD, Samodzielny Publiczny Szpital Kliniczny nr 4 w Lublinie, Poland
173. João Manuel Frazão Rodrigues de Sousa, MD, Hospital de Santa Maria-Centro Hospitalar Lisboa Norte, EPE, Portugal
174. Senthil Tambidorai, MD, Plaza Medical Center of Fort Worth, US
175. James Sandberg, MD, Lehigh Valley Hospital, US
176. Rubén Aguayo, MD, Hospital San Juan de Dios, Chile
177. Darren Traub, MD, St. Lukes Hospital and Health Network, US
178. Siddarth Mukerji, MD / Rajesh Venaktaraman, MD / Ramesh Hariharan, MD, EP Heart LLC, US
179. Saravanan Krishinan, MD, Hospital Sultanah Bahiyah, Malaysia
180. Jorge Silvestre, MD, Hospital Universitario La Paz, Spain
181. Vladimir Rankovic, MD, Florida Electrophysiology Associates, US

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibacterial Envelope to Prevent Infections of Cardiac Implantable Devices

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