Risk stratification for CIED infection: What is the clinical impact of WRAP-IT?

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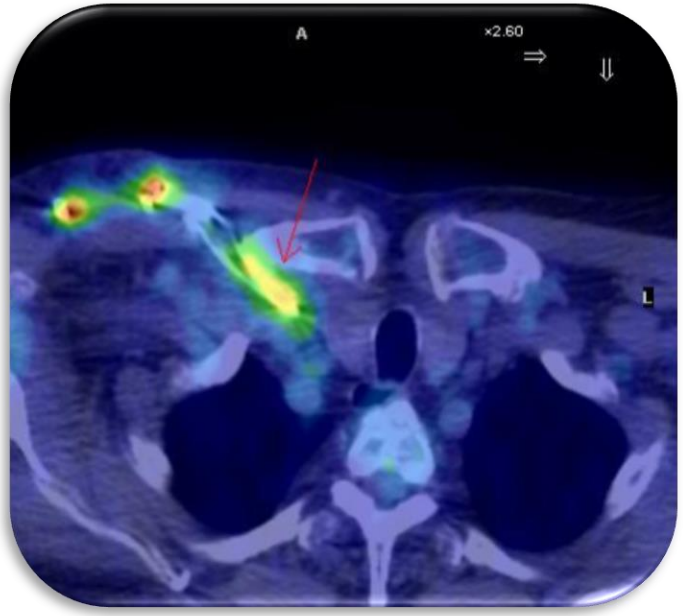
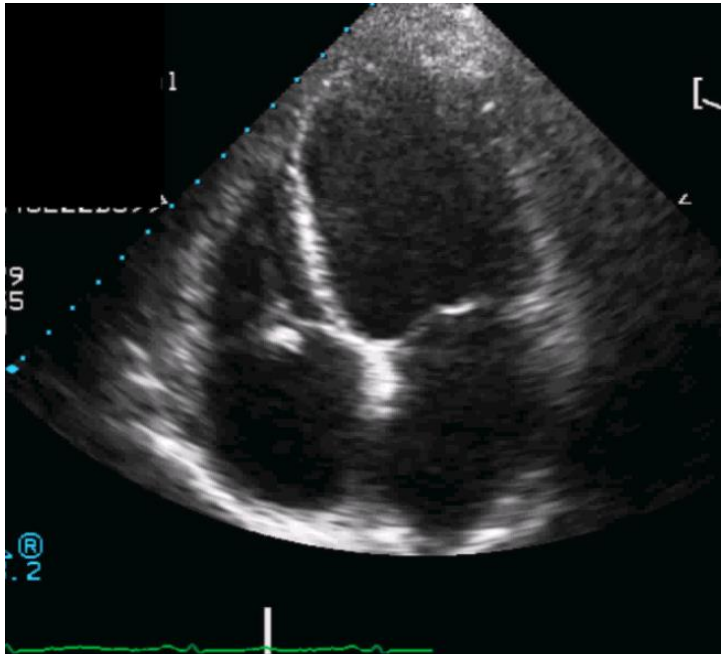
The Many Faces of CIED Infection

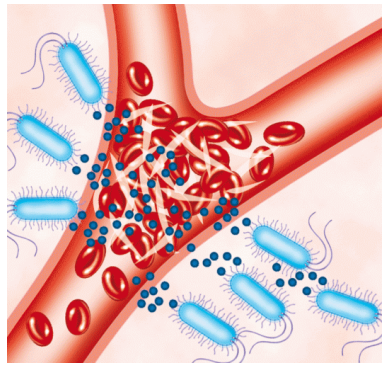
Pocket infection/erosion



Lead endocarditis : hot pocket and lead
Vegetations non-mandatory

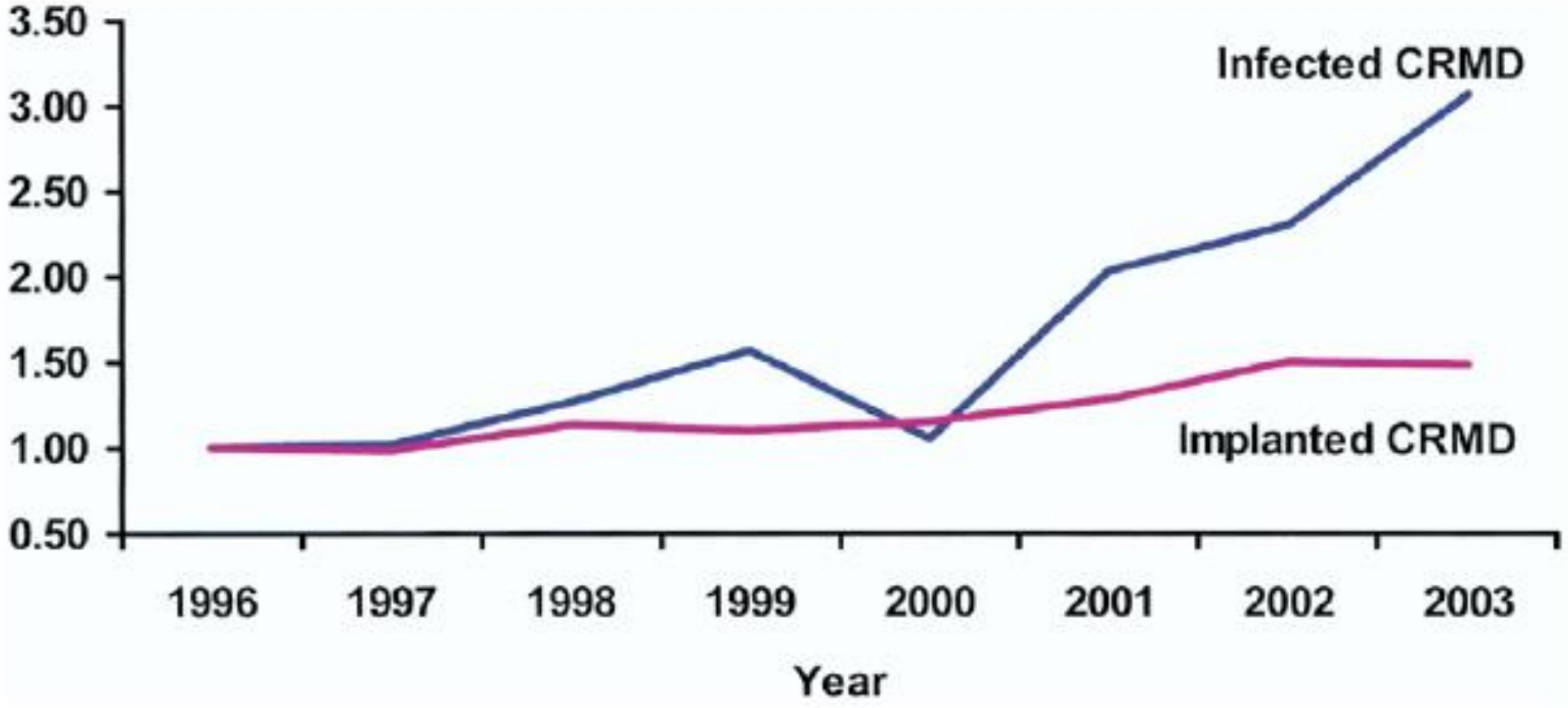
Valvular Endocarditis





Persistent Gram++ bacteremia
with no other cause

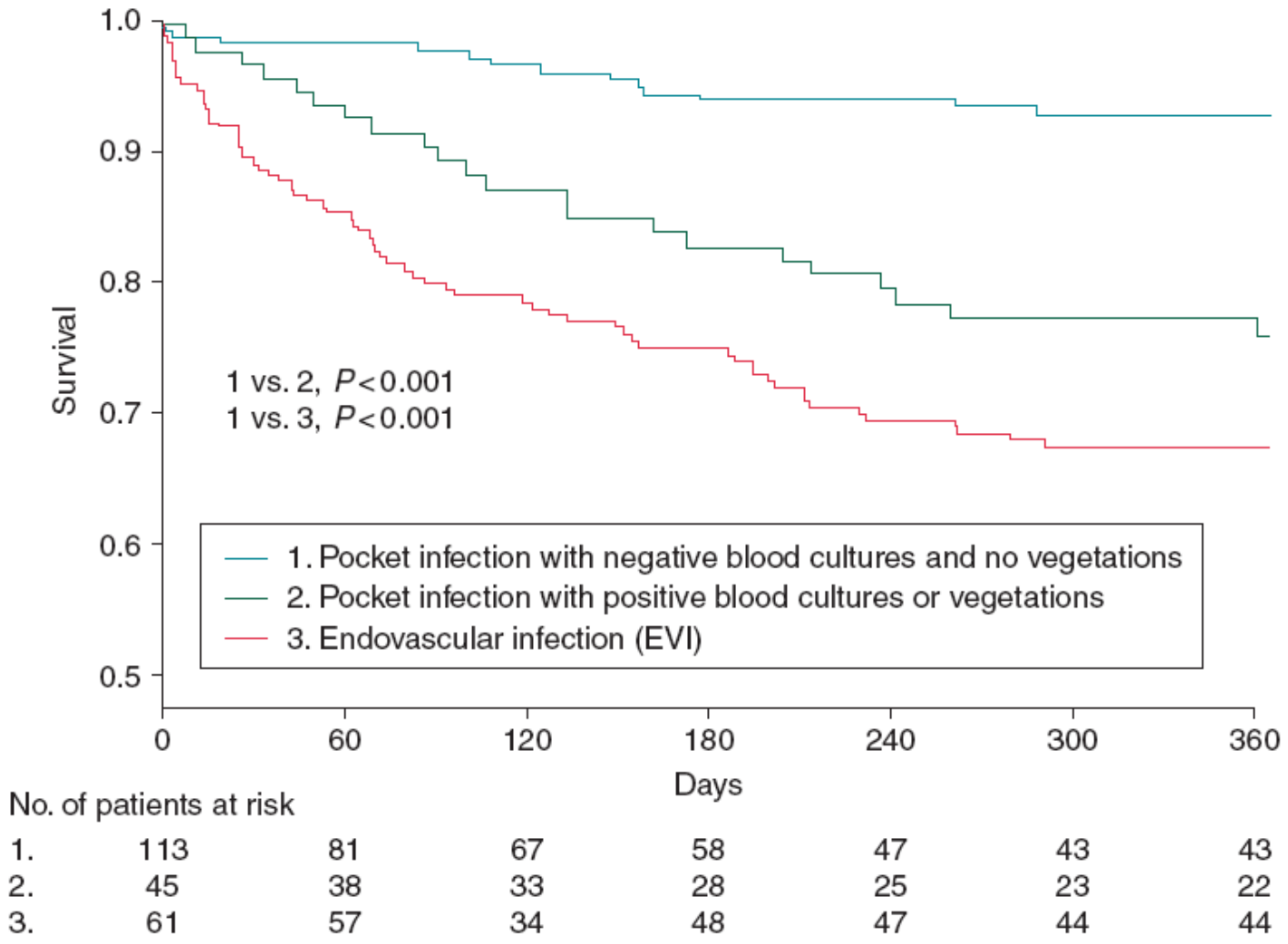
Rising Rates of CIED Infections in the US: 1996 through 2003 Current Prevalence 1-4%



Based on the National Hospital Discharge Survey (NHDS)

A. Voigt *J. Am. Coll. Cardiol.* 2006;48;590-591

Mortality after CIED removal



502 patients

58% pocket infection

42% endovascular infection only

Cause of Death

• Sepsis	6 patients
• Multiorgan system failure	10 patients
• Congestive heart failure	4 patients
• Stroke	2 patients
• Renal failure	1 patient
• Extraction related	2 patients

Infection Impact on Health Systems

- **Mortality at 12 months at least 20% for endovascular infection despite hardware removal and optimal therapy**

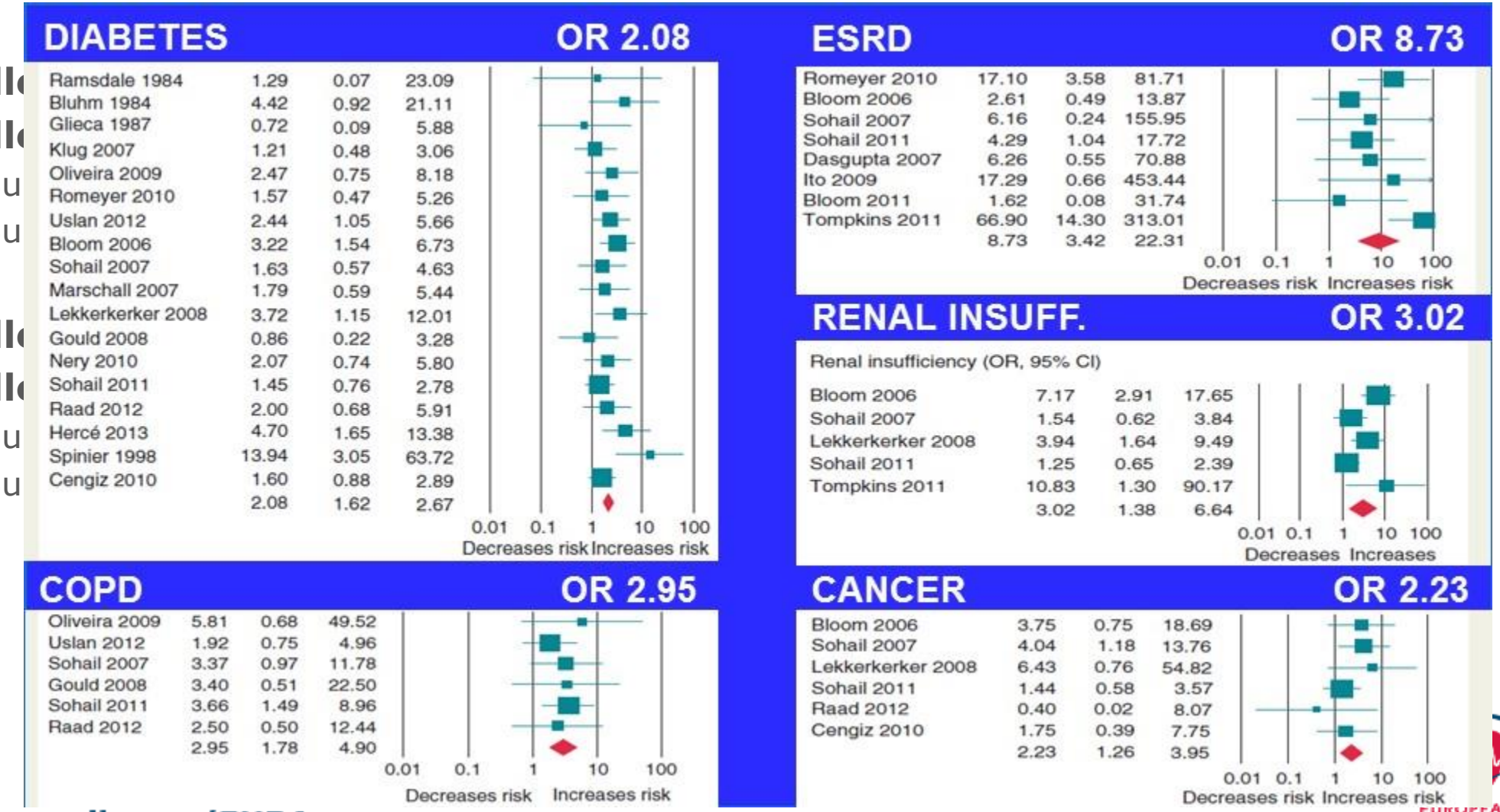
- **Costs range from 50000 to 146000 $ for infection management, with intensive care stay and management of complications accounting for the largest charge**

Who is at RISK of CIED Infection ?

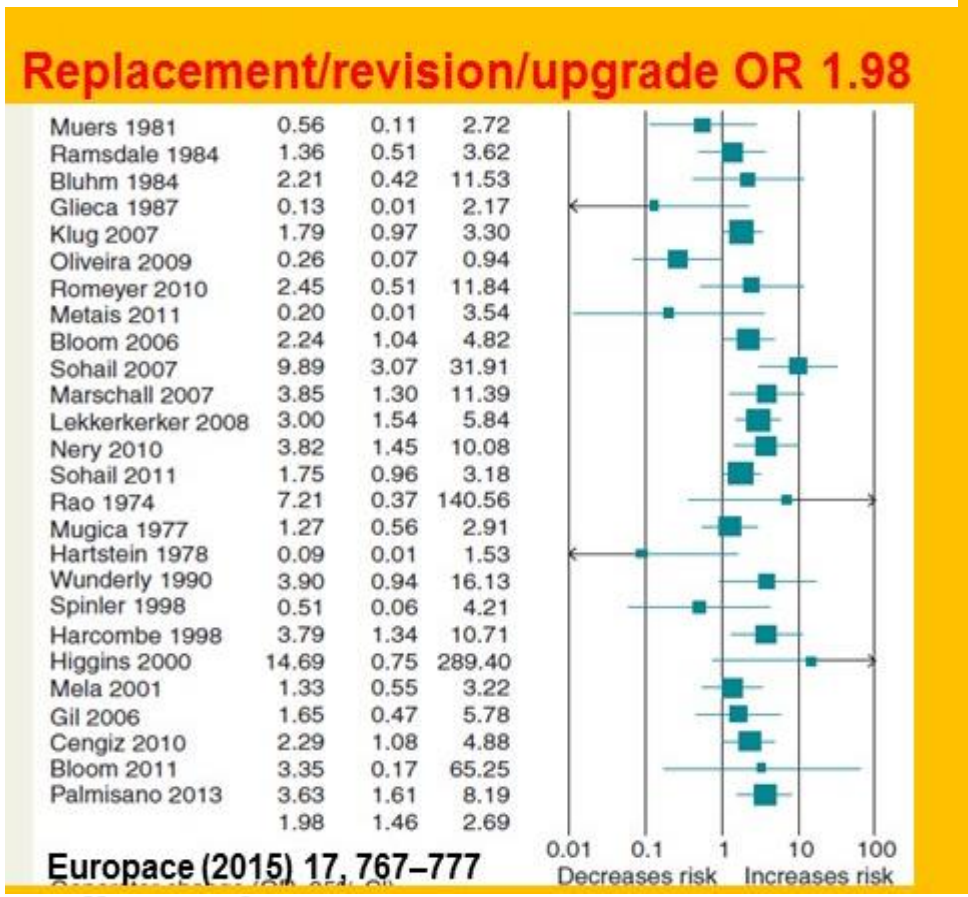
- **Patient's Profile**
- **Device Type**
- **Procedure Characteristics**

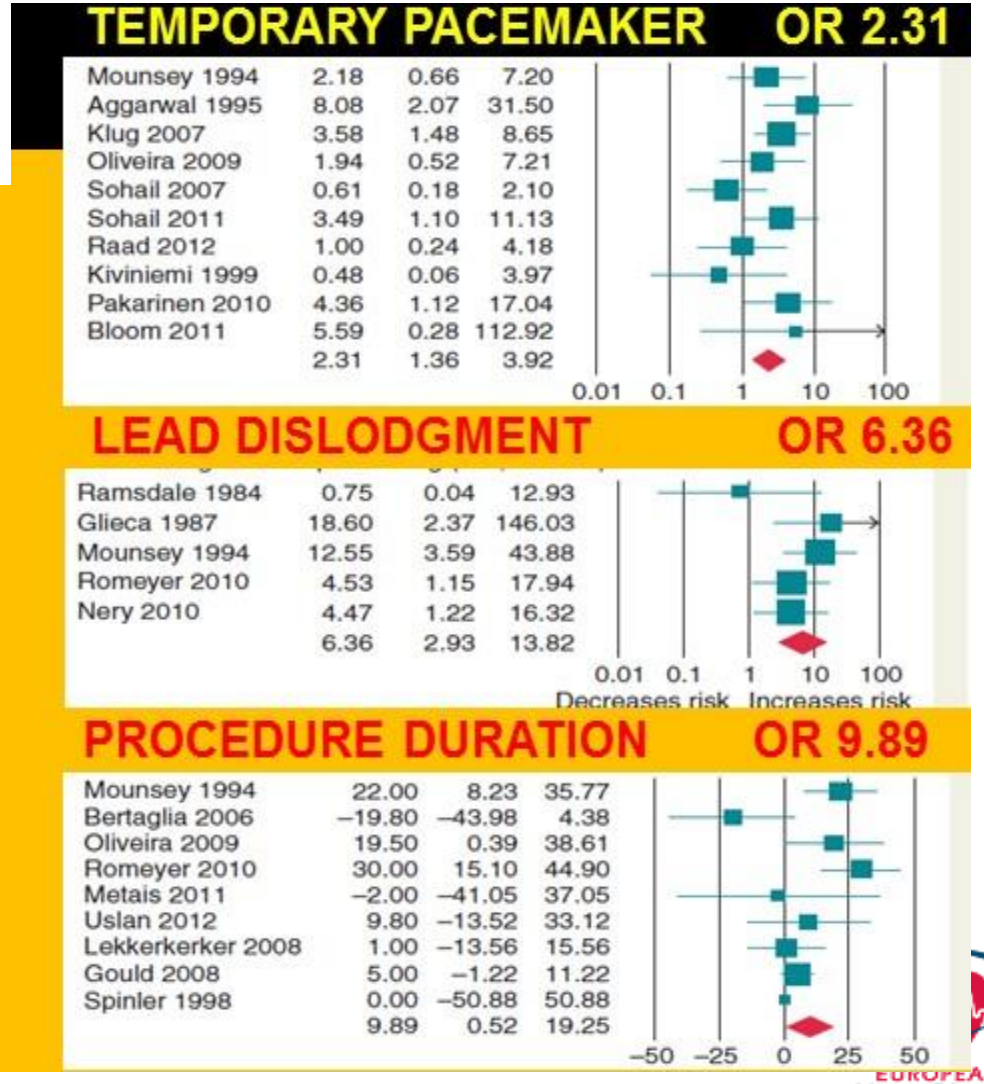
Patient's Profile

- **Bull**
- **Bull**
  - Su
  - Su
- **Bull**
- **Bull**
  - Su
  - Su

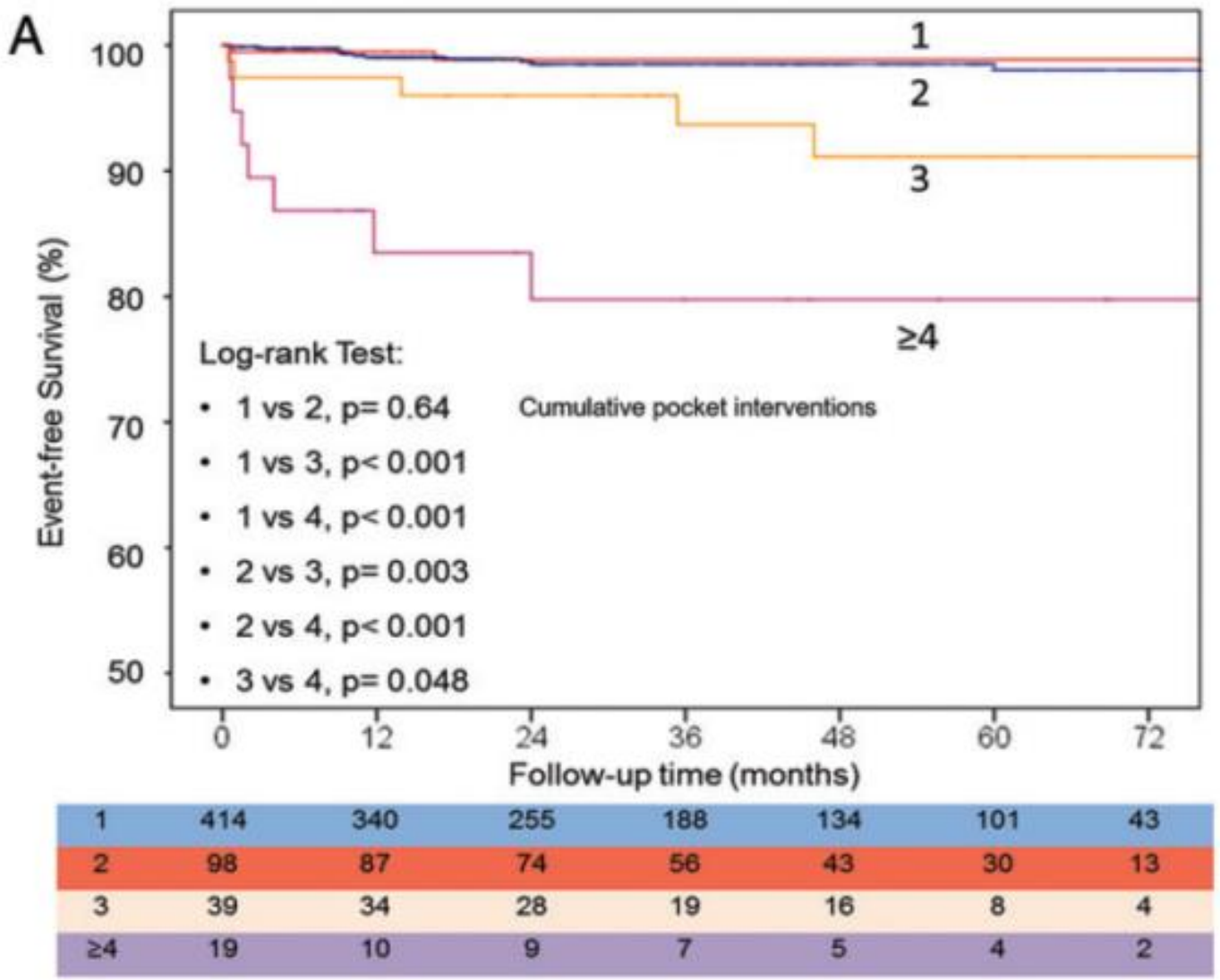


Factors related to the procedure





Infection risk at repeated CIED interventions



1	414	340	255	188	134	101	43
2	98	87	74	56	43	30	13
3	39	34	28	19	16	8	4
≥4	19	10	9	7	5	4	2

Same Observation in PADIT:

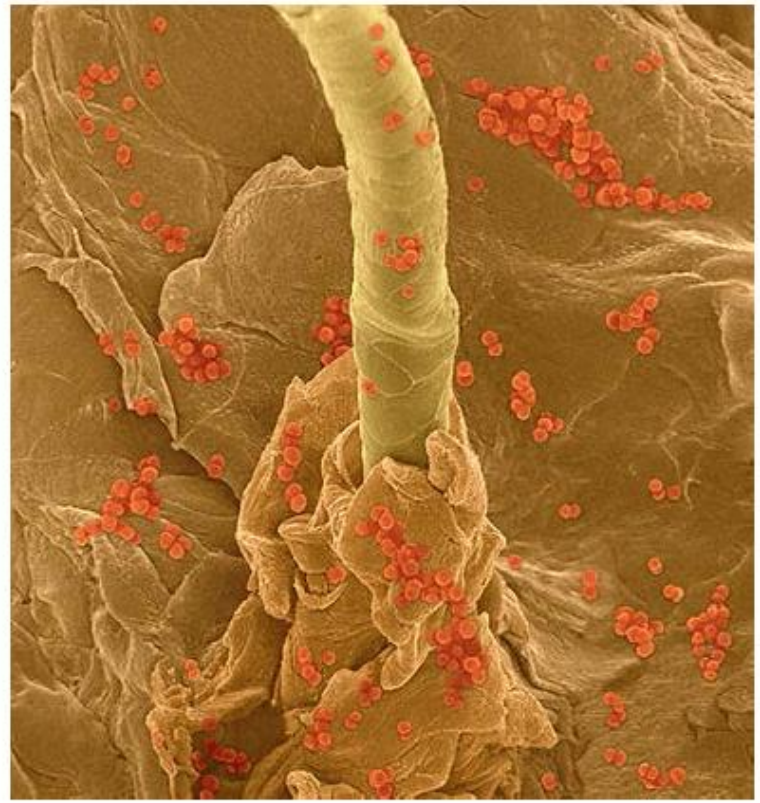
The 3rd pocket procedure increases 3-fold the infection risk

THIS is why LONGEVITY is a KEY factor in CIEDs !!!!!!!

Eduardo Arana-Rueda et al. *Clin Cardiol 2017;40:892-898*

Bacterial Colonization of PG Pockets

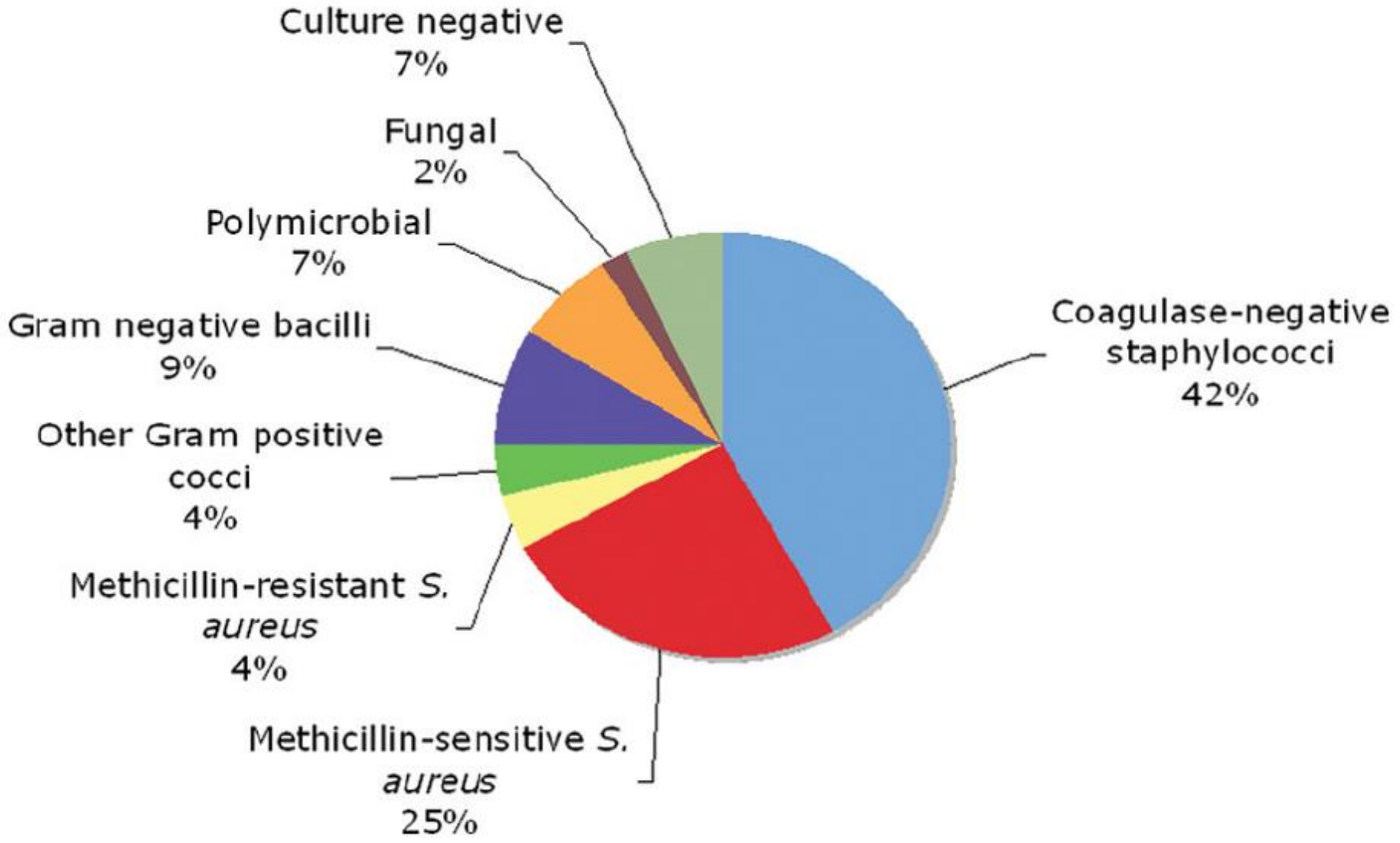
- CIED infections acquired at time of surgery, present to up to 3-6 months.
- Inoculation of Gram ++ *endogenous skin flora.*
- Contamination of device pocket during insertion is frequent
  - Bacteria recovered in 37% of patients
  - Coagulase negative Staphylococci, MSSA or MRSA.
- *122 pts without clinical infection undergoing PG replacement or lead revision. Cultures of pockets and leads obtained.
- 40/122 (33%) culture positive (coagulase negative Staph sp.).
- 7.5% of these went on to develop infection over 108 ± 73 days with same organism.



Da Costa A. et al. Circulation. 1998;97(18):1791

*Kleemann, TJ et al. Europace (2010) 12, 58–63.

Microbiology of CIED infections



Cefazolin vs. Saline RCT (2009)

Circ Arrhythmia Electrophysiol 2009 2, 29

- 1st Randomized, controlled, blinded, trial to prove that pre-operative antibiotics are effective in preventing CRMD related infections:
  - Cefazolin 0.63% vs. Saline 3.28% CRMD related infections (p=0.016)

Study Limitations:

- 100% of infections in cefazolin group were caused by cefazolin-sensitive isolates (i.e. methicillin-sensitive).
- Low number of patients w/ methicillin-resistance compared to US hospitals:

Methicillin-Resistant	de Oliveira	U.S. Hospitals
S. aureus	13%	55-60%
Coag (-) *Staph*	60%	80-90%

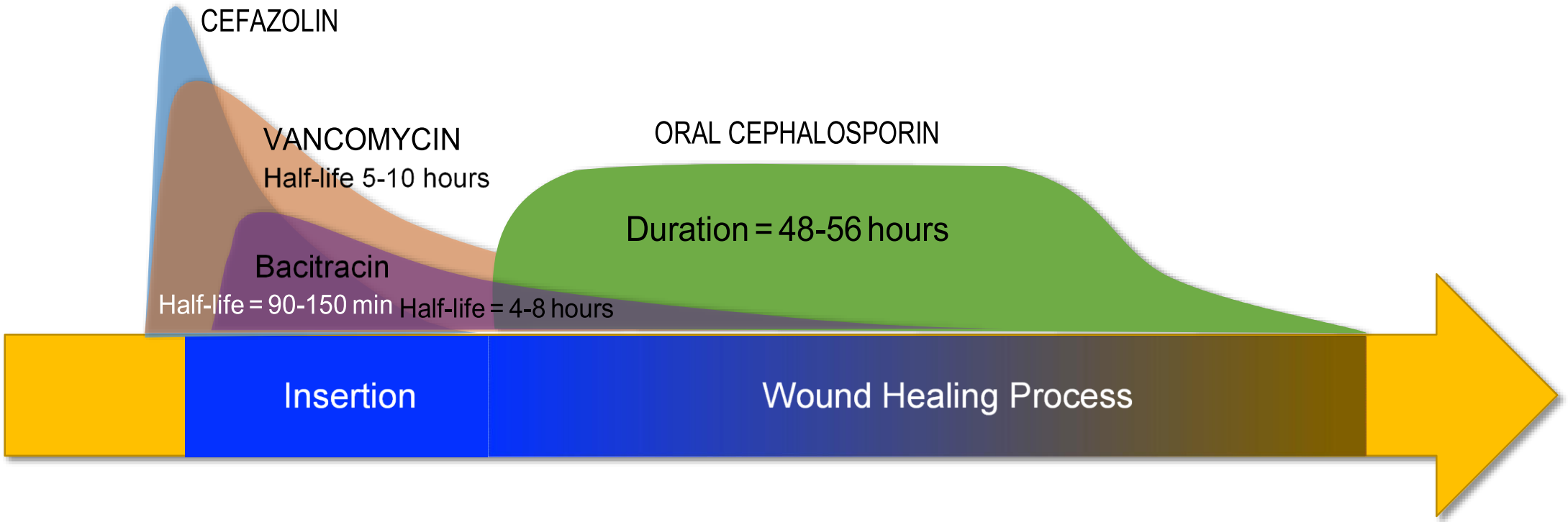
- "High Risk" patients excluded:
  - antibiotic use, surgery w/in 30 days, previous infection w/in 30 days.
  - prosthetic heart valves, lead revision for dislodgement

The Problem of "Prolonged Prophylaxis" in medical device recipients

- Persistence of the Device in human body
- Biofilm Formation on the Device Surface
- Sealing of tissue takes time
- Prophylaxis should prolong until tissue sealing at the Entry site

MOST DIFFICULT CASE → *Central Venous Lines, Dyalisis Catheters*

PADIT - Incremental prophylaxis



Hospitalization attributed to device infection

ADJUNCTIVE ANTIBIOTIC PROPHYLAXIS

PATHOGENS RESPONSIBLE FOR CIED INFECTIONS	SINGLE-AGENT THERAPY				TYRX
	Cefazolin[1]	Vancomycin[1]	Gentamicin[1]	Topical Ionic Silver[2-5]	Minocycline & Rifampicin[1,6-8]
Coagulase *(-) Staphylococcus (*e.g., *S epidermidis)*			Variable Activity		
Methicillin-sensitive *S aureus* (MSSA)			Variable Activity		
Methicillin-resistant *S aureus* (MRSA)			Variable Activity		
E coli					
H influenzae					
M catarrhalis				No Data	
Corynebacterium jeikeium				No Data	

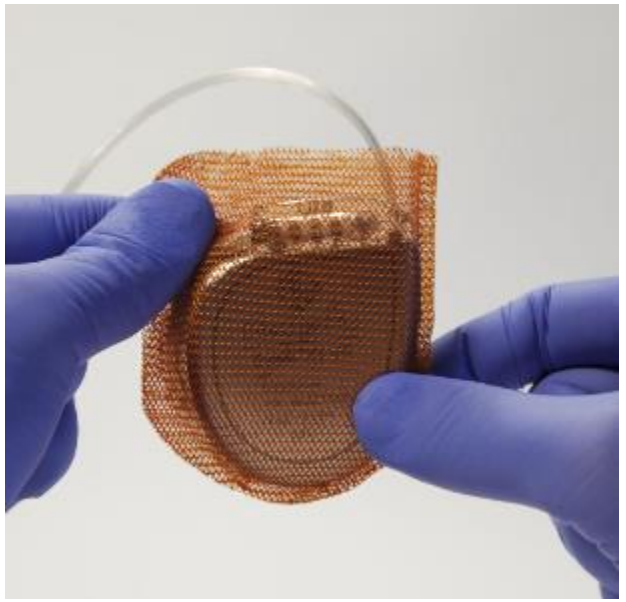
- **Cefazolin & vancomycin** are rarely used in combination and have important clinical deficiencies when used as a single agent to help prevent CIED Infections.[1]
  - Substantial overlap; both have activity against gram (+) organisms[1]
  - Neither has a strong profile against gram (-) organisms[1]
- **Gentamicin** has variable activity against coagulase (-) *Staphylococcus* , MSSA, and MRSA, and may be effective in some infections, but not reliably effective in others.[1]
- **Topical Ionic Silver** does not have activity against coagulase (-) *Staphylococcus* and has no data to support coverage in *M catarrhalis or Corynebacterium jeikeium.*[2-5]

1. The Sanford Guide to Antimicrobial Therapy. Web Edition. 2015: Antimicrobial Therapy Inc.; Hyde Park, VT. 2. Lansdown A et al. Issues in Toxicology. 2010:5.3:123. 3. Percival SL et al. Wound Repair Regeneration. 2011;19(6): 767-774. Online publication. 4. Argentum Medical. Silverlon® Product Brochure. 5. Townsend Letter for Doctors & Patients. April 2006; Issue 273: 66-72. 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.

Prolonged topical Prophylaxis

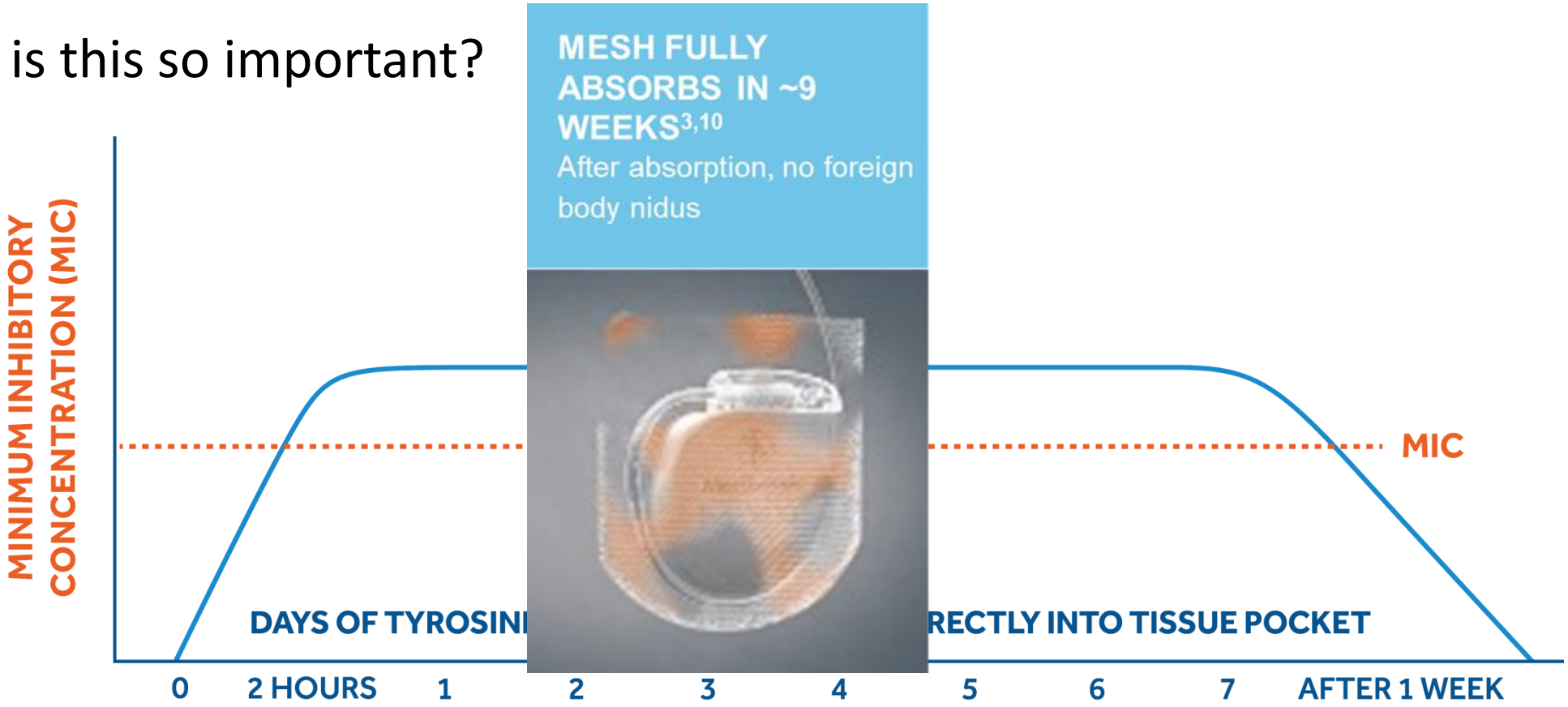
- Provides bactericidal activity sustained for 7-14 days >>> longer than PADIT
- Effective against methicillin resistant cocci
- Effective against NON-staph pathogens
- High topical concentration without systemic effects

TYRX™ Absorbable
Antibacterial Envelope



Tyrosine controlled elution – The polymer is The Science!

- Why is this so important?



Proprietary combination of polymer with antibiotic agents Minocycline & Rifampicin. Tyrosine-based polymer controls the drug release – MIC maintained in 2 hours, MIC for minimum of 7 days[1]

1. Huntingdon Life Sciences Study TR-20 13-001.

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*

WRAP-IT Study Definitions of CIED Infection, Major Infection

CIED infections were defined as:

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

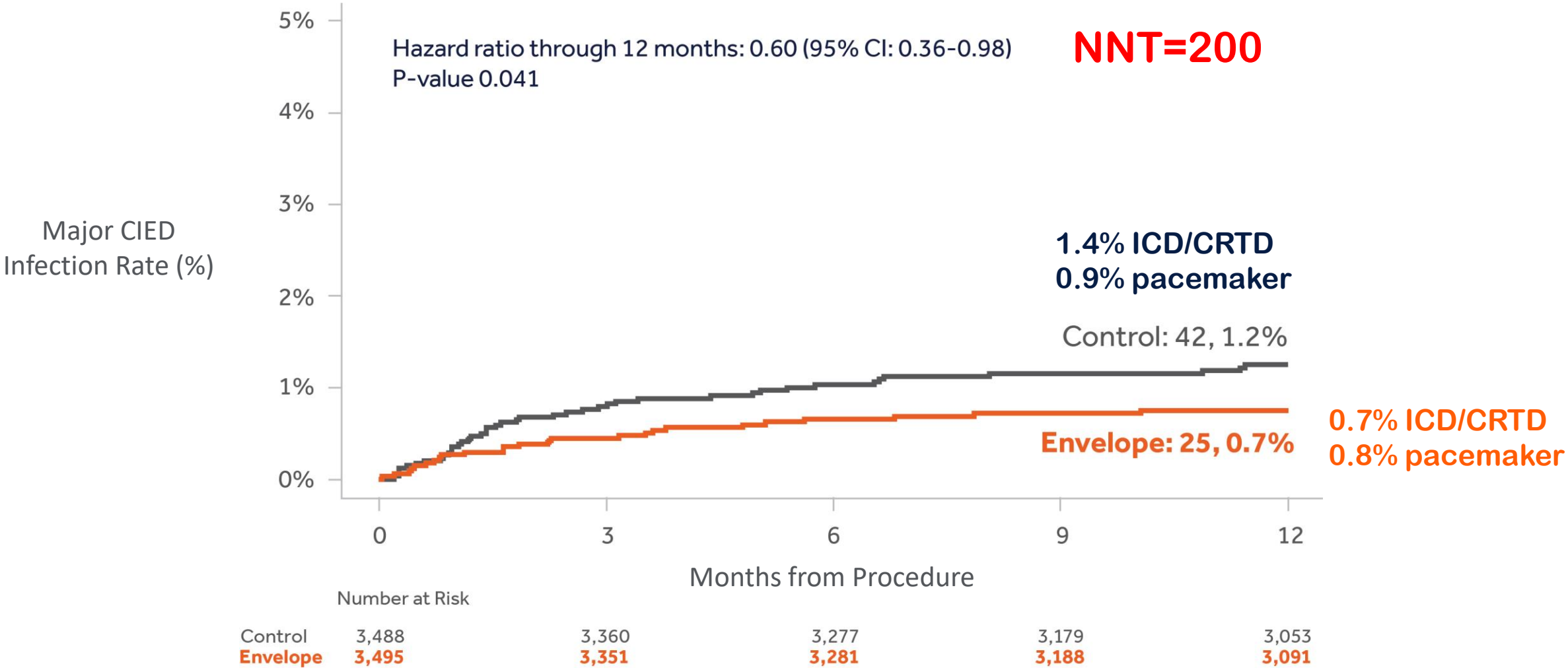
Major CIED infections were defined as CIED infections resulting in one or more of the following:

- 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 meet 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 Primary Endpoint: Major CIED Infection

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



Tarakji KG. *N Engl J Med* 2019; 380(20): 1895-1905

WRAP-IT Study Primary Endpoint: Major CIED Infection

67% Reduction in Major CIED Infections in ICD/CRTD “second surgery”

	Control Group (3485)	TYRX group (3490)
Low Power	7/866 (0.8%)	7/856 (0.8%)
First CRTD implants	3/586 (0.5%)	7/536 (1.3%)
ICD/CRTD replacement-upgrade-revision	32/2033 (1.57%)	11/2098 (0.52%)

NNT=100

Biffi M. *J Cardiovasc Electrophysiol* 2019; 30(8): 1191-1196

Key Facts of WRAP-IT and PADIT

- Nearly 27,000 patients randomized

- **Very low infection rate in control arms !!**
- **Hard to prove statistical significance …….**

IS THIS THE REAL WORLD ??????

A Strict Prospective Strategy of Prevention *by itself HALVES CIED infections*

TABLE 3 Infection rate in retrospective and prospective studies

Study	Enrollment period	Study type	TYRX use	Patients	CIED type	Procedure	FU time	Infection rate, %
Ludwig[19]	2010-2013	Retrospective	No	4699	ICD/CRTD	All	12 mo	3.4
Clémenty[18]	2012	Retrospective	No	9465	ICD/CRTD	All	12 mo	2.3
REPLACE[32]	2007-2008	Prospective	No	1744	All	All	6 mo	1.3
Ahsan[13]	2004-2009	Retrospective	No	1798	All	All	12 mo	1.33
		Prospective	No	981				0.62
Kolek[27]	2005-2010	Retrospective	No	636	All	All	300 d	3.1
	2009-2014	Prospective	Yes	488				0.2
PADIT[15]	2013-2016	Prospective	No	12 826	All	All	12 mo	1.03, conventional antibiotic
								0.78, incremental antibiotic
DECODE[31]	2013-2015	Prospective	No	983	ICD/CRTD	All	12 mo	1.2

Abbreviations: CIED, cardiac implantable electronic device; CRTD, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; FU, follow-up.

Biffi M. *J Cardiovasc Electrophysiol* 2019; 30(8): 1191-1196

Detect long-term complications after ICD/CRTD replacement (DECODE)

Purpose: To evaluate patient's profile and procedure characteristics as potential predictors of major AEs over 12 months after **ICD/CRT-D replacement/upgrade** in a large real-world population.

- Prospective, single-arm, **multicenter cohort study of CONSECUTIVE ALL-COMERS**
- ICD/CRT-D replacement/upgrade from 2013 to 2015 **ALL MANUFACTURERS**
- All clinical and survival data of these patients at 12-month follow-up
- Death from any causes, surgical interventions to treat complications related to the procedure and overall infective AEs during follow-up.

Clinical and demographic data	
Age, y	71 [63-77]
LVEF, %	35 [30-45]
BMI	26.3 [24-29.4]
eGFR	63.3 [44.5-84]
Gender Male, n (%)	750 (76.3)
NYHA I	191 (19.4)
NYHA II	553 (56.3)
NYHA III	225 (22.9)
NYHA IV	14 (1.4)
History of AF, n (%)	372 (37.8)
AV node ablation, n (%)	41 (4.2)
Ischemic Cardiomyopathy, n (%)	537 (54.6)
PTCA/CABG within 6 months prior to the procedure, n (%)	95 (9.7)
Diabetes, n (%)	282 (28.7)
Hypertension, n (%)	608 (61.9)
Chronic Kidney Disease, n (%)	249 (25.3)
Hospitalization within 30 days prior to the procedure, n (%)	73 (7.4)

Device Replaced	
Single-chamber/VDD	26.6
Double-chamber	26.6
CRT-D, %	46.8

Results:

- **983 consecutive patients**
- mean follow-up duration of 353±49 days
- 7% of the patients died (60.6% for CV reasons)

- **CIED infection in 12 (1.2%) patients**
- **Bleeding complications in 25 (2.5%)**
- **Lead related complications in 26 (2.6%)**

Biffi M. *Europace* 2019; 21: 1527-1536

Europace (2014) 16, 1482–1489
doi:10.1093/europace/euu126

CLINICAL RESEARCH
Pacing and resynchronization therapy

A simple infection-control protocol to reduce serious cardiac device infections

Syed Y. Ahsan*, Bunny Saberwal, Pier D. Lambiase, Chieh Y. Koo, Simon Lee, Aerokondal B. Gopalamurugan, Dominic P. Rogers, Martin D. Lowe, and Anthony W. C. Chow

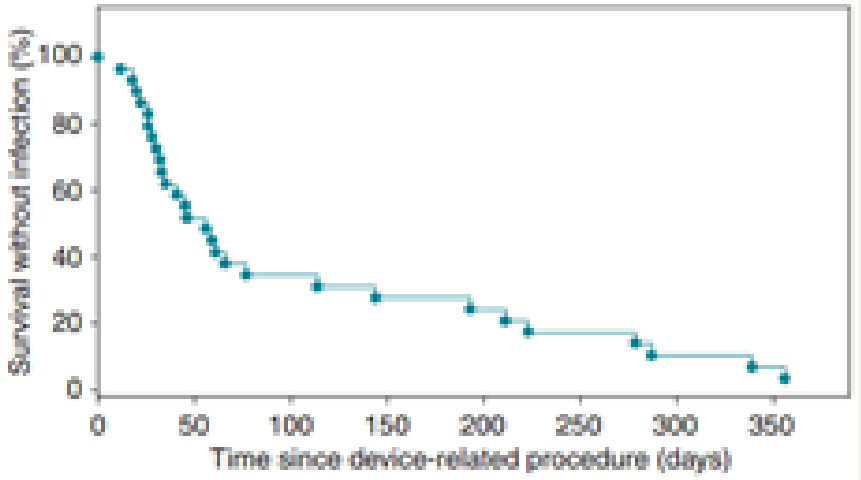


Table 2 Infection rates for all device procedures

Year	Procedure number (*n*)	Infections (*n*)	Rate (%)	95% CI (%)	Reduction in infection rate (*P*)
2004–5	643	9	1.40	0.7–2.7	N/A
2005–6	598	7	1.17	0.5–2.5	N/A
2006–7	557	8	1.44	0.7–2.9	N/A
Pre-intervention total	1798	24	1.33	0.9–2.0	N/A
2007–8	617	3	0.49	0.1–1.5	0.041
2008–9	364	3	0.82	0.2–2.5	0.370
Post-intervention total	981	6	0.62	0.3–1.4	0.028

†Table showing infection rates by year, as well as total pre- and post-intervention rates.

Ahsan SY. *Europace* 2014; 16: 1482-1489

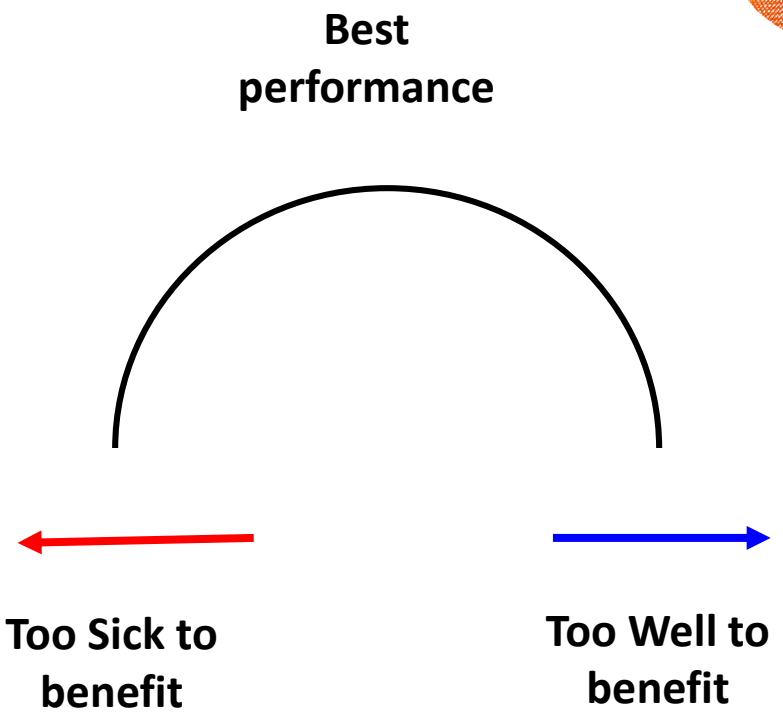
NEED to assess TYRX efficacy in

NNT = 200

- Re-Do CIED surgery: UPGRADE, Lead Revision/Repositioning
- Device type: CRTD vs others
- High risk subgroups
- Potential for WRAP-IT SUBANALYSIS

TYRX : new Gold Standard in CIED Infection Prevention

- Individualized approach ?
- “NO EFFICACY” subgroups ?
- Economic impact to be analysed



The PADIT risk score

Risk factor	Points
1. Prior procedures	
None	0
One	1
Two	4
2. Age	
Younger than 60 years old	2
60-69 years old	1
At least 70 years old	0
3. Renal insufficiency	
Yes	1
No	0
4. Immunocompromised	
Yes	3
No	0
5. Type of procedure	
Pacemaker	0
Implantable cardioverter defibrillator	2
Cardiac resynchronization therapy device	4
Revision or upgrade	5

Minimum points = 0; maximum points = 15.

Hospitalization for Device infection

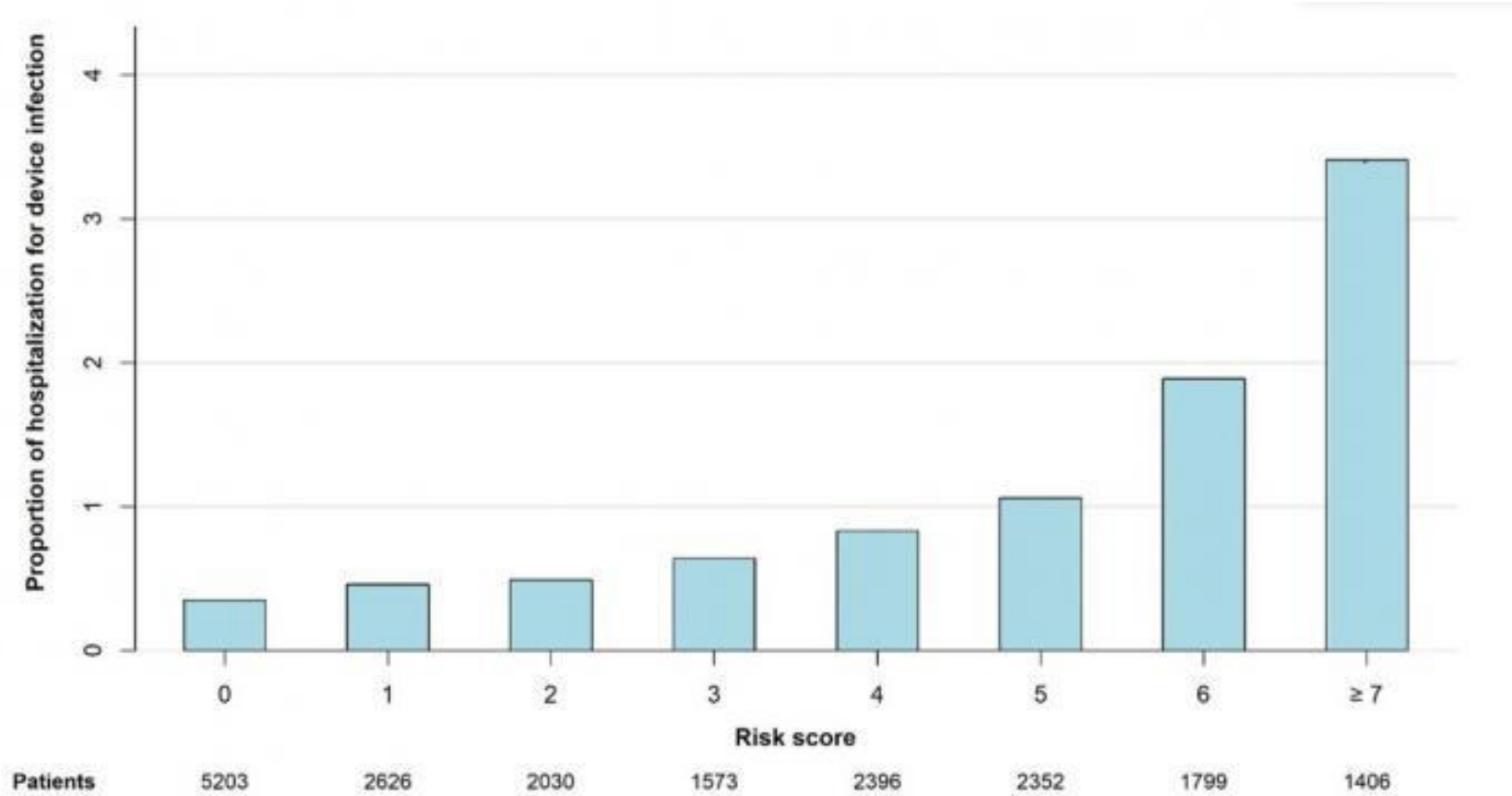


Figure: Rate of device infection stratified by PADIT infection risk score

High Risk situations : TYRX strongly recommended

Early pocket re-entry (<60 days)	**Lead dislodgement** **Hematoma** **Pocket revision**
Depressed Immune Defense	**Chronic inflammatory diseases on steroids** **Oncologic disease treated < 6 months** **Chronic infective process** **End-stage renal disease / Dialysis**
Vulnerability to Surgical Site Infection	**Hospitalization within 30 days** **Index hospitalization longer than 7 days** **Previous CIED infection** **Chronic skin disease** **Pending skin issue by inside-out pressure**
Complex procedures	**Lead extraction and re-implantation** **Upgrade (one or more lead addition)** **Multiple (> 2) pocket entries**

Biffi M. *J Cardiovasc Electrophysiol* 2019; 30(8): 1191-1196

Prevention : general strategy + TYRX

- Adherence to a strict prevention protocol
- Prospective surveillance of the center performance, High operator volume (60/year)
- Comprehensive patients evaluation Before and During CIED surgery >> Individualized I.V. antibiotics
- Use TYRX in high risk settings

Patients Hospitalised > 6 days

Vancomycin 90-120 minutes before skin incision

Daptomycin 6 mg/kg 30 minutes before skin incision

ICU Patients

Vancomycin 90-120 minutes before skin incision

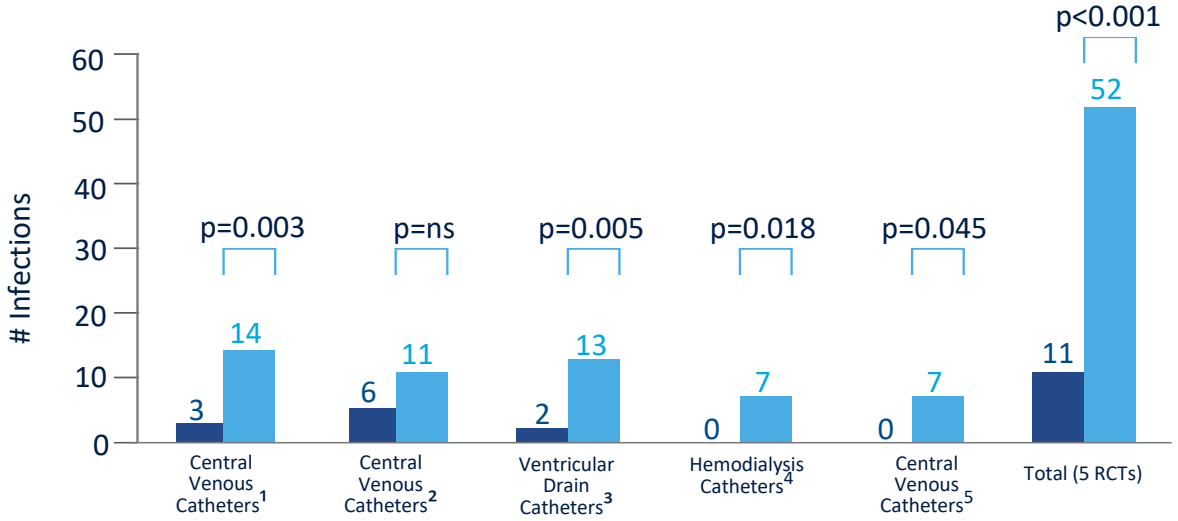
If intolerant, Daptomycin 6 mg/kg 30 minutes before skin incision

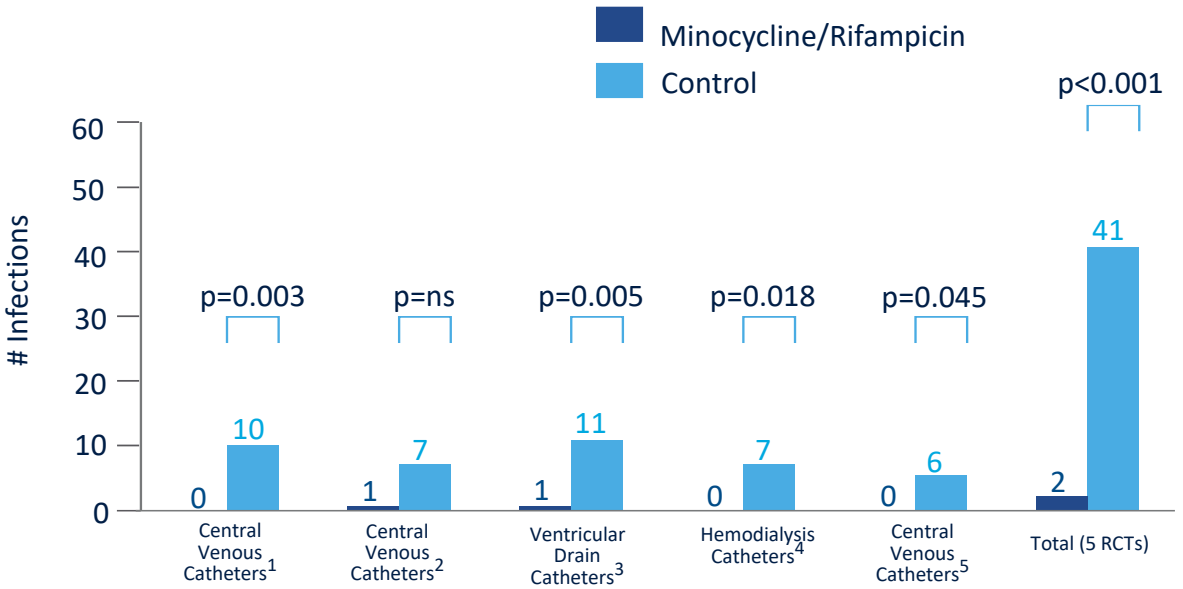
Oxacillin resistance according to site of acquisition in CIED Infection: The Mayo Clinic Experience

Am J Cardiol 2012;110:1143–1149

Minocycline/Rifampicin Coating Significantly Reduce Infections

5 RANDOMIZED CONTROLLED TRIALS (RCTS)[1-5]





- Combination of Minocycline and Rifampicin reduces the risk of infection by a factor of **4.8** (relative risk = 0.2)

- Combination of Minocycline and Rifampicin reduces the risk of infection caused by the two most common pathogens (coagulase (-) *Staphylococcus* and *S aureus*) associated with CIED Infections by a factor of **20.6** (relative risk = 0.05)

1. Hanna H et al. *J Clin Oncol.* 2004;22(15):3163-3171. **2.** Leon C et al. *Intensive Care Med.* 2004;30(10):1891-1899. **3.** Zambramski JM et al. *J Neurosurg.* 2003;98(4):725-730. **4.** Chatzinikolaou I et al. *Amer J Med.* 2003;115(5):352-357. **5.** Raad I et al. *Ann Intern Med.* 1997;127(4):267-274.

Localized Delivery of Synergistic, Broad-Spectrum Antibiotics

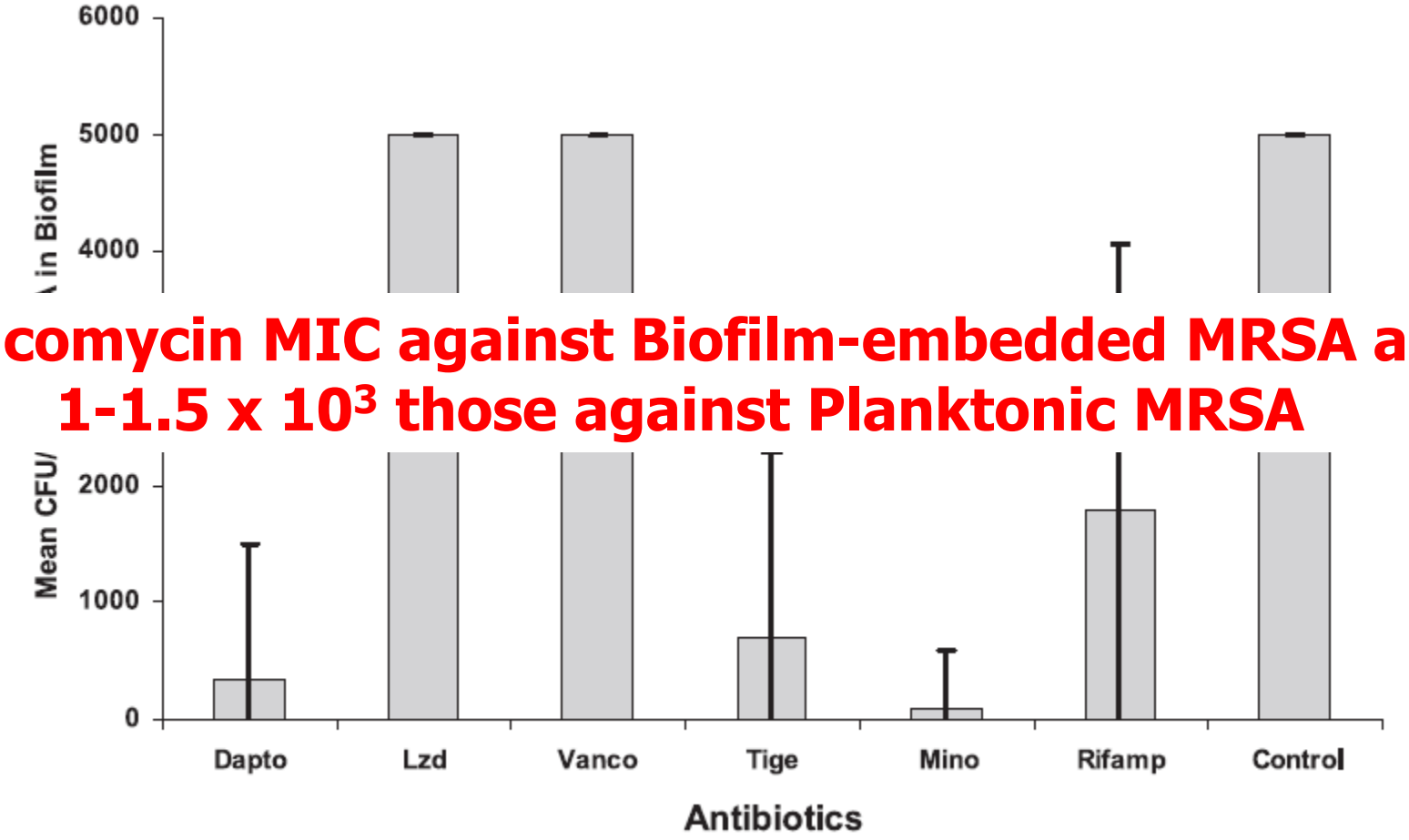
MINOCYCLINE activity against CIED infection pathogens[1]	
GRAM (+) BACTERIA	GRAM (-) BACTERIA
S aureus *S pneumoniae*	*E coli* *M catarrhalis*
MECHANISM OF ACTION Bacteriostatic; inhibits protein synthesis	

RIFAMPIN activity against CIED infection pathogens[1]	
GRAM (+) BACTERIA	GRAM (-) BACTERIA
S aureus (including MRSA) *S epidermidis* *C jeikeium* *S pneumoniae*	*H influenzae* *M catarrhalis*
MECHANISM OF ACTION Bacteriocidal; inhibits DNA-dependent RNA polymerase activity	

- Minimum inhibitory concentration reached within 2 hours of implant, maintained for 7 days
- Uses <5% of recommended oral daily dosage, non-systemic[1,2]
  - Medium size Envelope: 8.0 mg rifampin, 5.1 mg minocycline
  - Large size Envelope: 11.9 mg rifampin, 7.6 mg minocycline

1. Gilbert DN et al. *The Sanford Guide to Antimicrobial Therapy.* 39th ed. 2012: Antimicrobial Therapy Inc.; Hyde Park, VT. **2.** Huntingdon Life Sciences Study TR-2013-001.

Antibiotic sensitivity of MRSA embedded in biofilm



Vancomycin MIC against Biofilm-embedded MRSA are 1-1.5 x 10^3 those against Planktonic MRSA

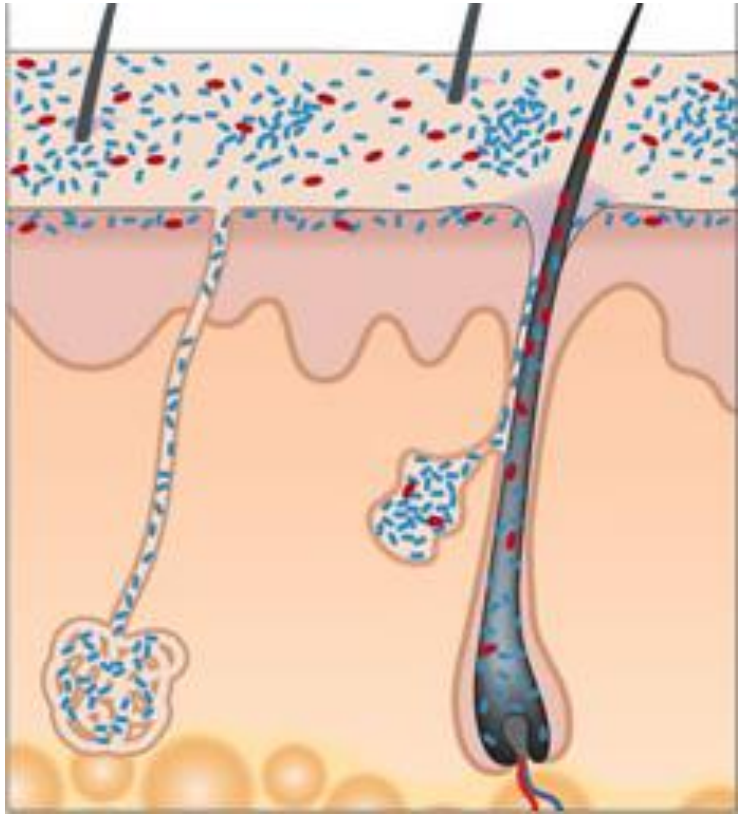
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2007, 1656–1660

STAPHYLOCOCCI in the SKIN

80% of skin bugs reside on the corneal layer

20% is embedded in biofilms within hair follicles and glands

Recolonization occurs very soon after antiseptic use



Marcia A. Ryder et al. 2005 Advanced Practice Nursing eJournal