SEICAV V congreso

Madrid, del 6 al 8 de octubre de 2016

Conferencia de Clausura

Madrid, 9 de Octubre del 2016

SEICAV

Sociedad Española de Infecciones Cardiovasculares

Endocarditis Infecciosa: áreas de investigación mirando al H2020

Dr. José M. Miró

Servicio de Enfermedades Infecciosas

Hospital Clínic – IDIBAPS

Universidad de Barcelona

Barcelona

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UNIVERSITAT DE BARCELONA

Potential conflict of interest

Dr. José M Miró has received honoraria for speaking or participating in Advisory Boards and/or research grants from the following Pharmaceutical Companies:

Abbvie
Boehringer-Ingelheim
Bristol-Myers Squibb
Chiron
Cubist
Merck
Novartis
Glaxo Smith Kline (GSK)
Gilead Sciences
Oxford Immunotec
Pfizer
Roche
Theravance
ViiV Healthcare

Looking to the Horizon H2020 Research in Infective Endocarditis

- Introduction
- Prevention
- Pathogenesis
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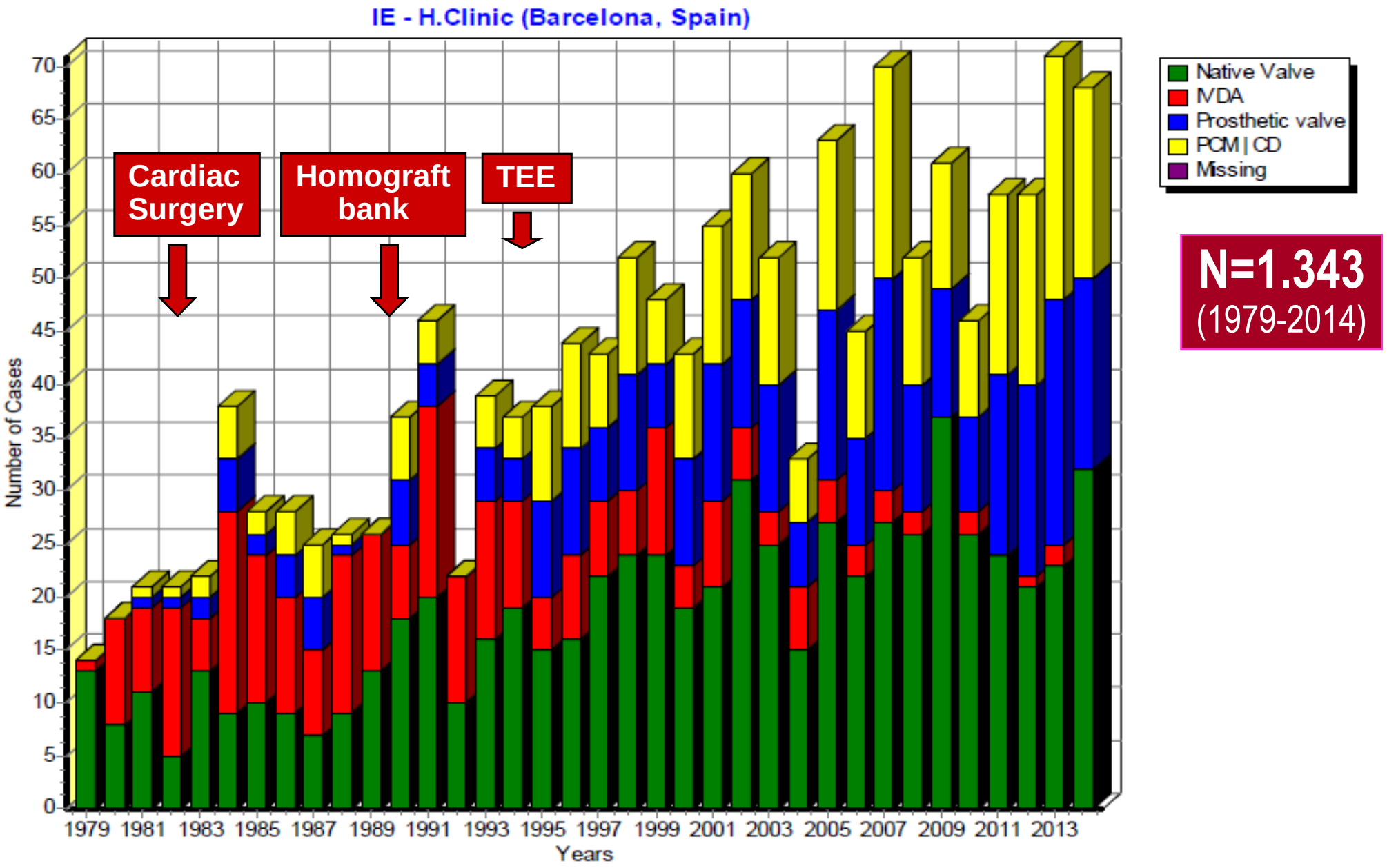
Surgery and Mortality Rates of Infective Endocarditis in the 21st Century

	Surgery	Mortality
IE in i.v. drug users	38%	10%
IE in general population	48%	17%
PV IE	49%	23%
Pacemaker/ICD IE	61%	10%
Overall	**≈50%**	**≈20%**

Murdoch R et al on behalf ICE investigators. Arch Intern Med. 2009;169:463-473.

IE at Hospital Clinic – Univ. of Barcelona (Spain)



N=1.343
(1979-2014)

CLÍNIC
BARCELONA
Hospital Universitari

SOCIETAT CATALANA DE MALALTIES INFECCIOSES I MICROBIOLOGIA CLÍNICA

Universitat de Barcelona

30º Aniversario del Grupo de Trabajo (GT) de Endocarditis Infecciosa (EI) del Hospital Clinic de Barcelona (1986-2016)

Barcelona - 11 de Marzo del 2016

Simposio "**ACTUALIZACIÓN DEL MANEJO DE LA ENDOCARDITIS INFECCIOSA. 30 AÑOS DE EXPERIENCIA**"

Fecha: Viernes, 11 de Marzo del 2016

Horario: 12.00 - 18.00 h

Localización: "Aula Magna" de la Facultad de Medicina de la Universidad de Barcelona (Campus Clinic, Casanovas, 143, 08036 Barcelona)

Experimental Endocarditis Model

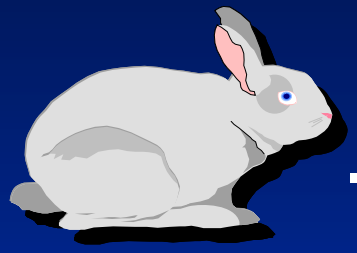
Day

0

1

2

5



- Aortic valve lesion - catheter (carotid artery)

⇦ ANTIBIOTIC PROPHYLAXIS

- I.V. microorganism challenge

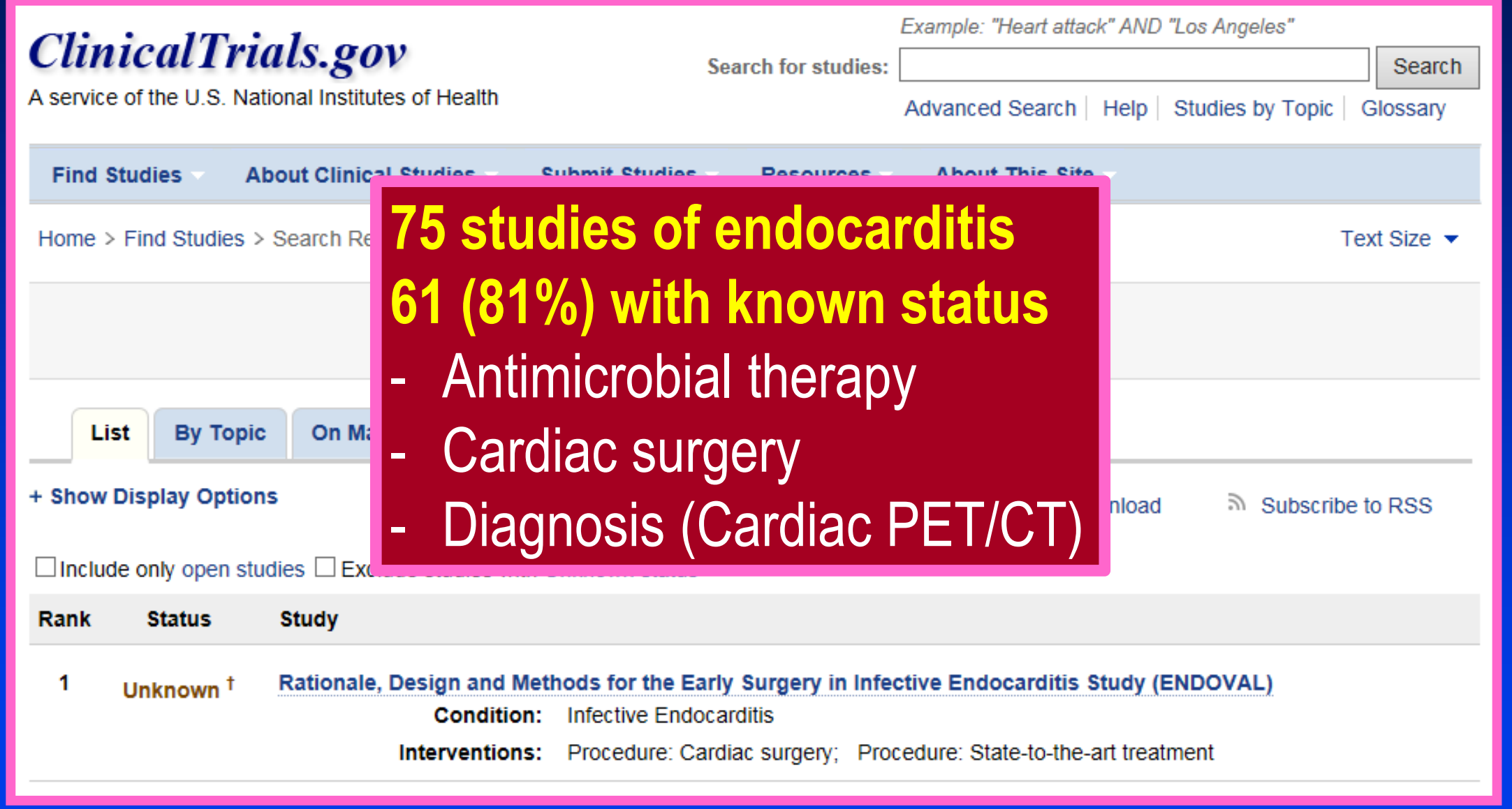
⇦ PATHOGENESIS

⇦ ANTIBIOTIC TREATMENT
ANTIBIOTIC DIFUSSION INTO VEGETATIONS

- Animal sacrifice. Qualitative & quantitative culture of aortic valve vegetations

Garrison & Freedman, 1970; Durack & Benson, 1972; Sande & Irwin, 1974.

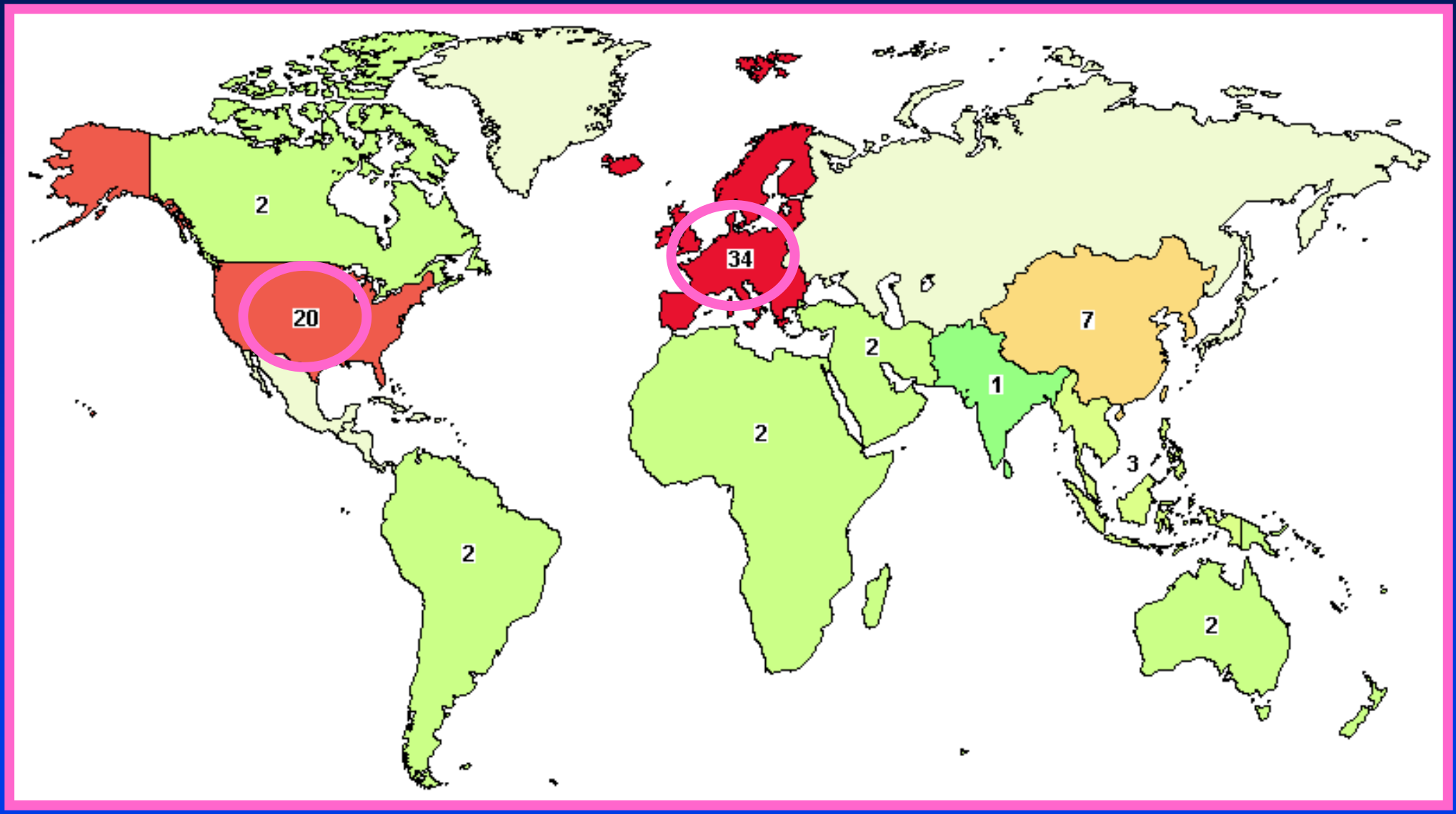
Research in Endocarditis



75 studies of endocarditis
61 (81%) with known status

- Antimicrobial therapy
- Cardiac surgery
- Diagnosis (Cardiac PET/CT)

Research in Endocarditis



Clinicaltrials.gov accessed in March 2016.

Looking to the Horizon H2020 Research in Infective Endocarditis

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Research in Prevention

- Antimicrobial prophylaxis: yes or no, that's the question!
- Prevention of Nosocomial and Non-Nosocomial HCA IE = Zero Bacteremia Protocols!
- Antibiotic prophylaxis in cardiac surgery and intracardiac devices (pacemaker and defibrillator)
- New devices with antibacterial properties
- Vaccines (*S. aureus*)

Randomized clinical (individual-based) trial

- Gold standard for evaluation of a medical intervention
- No trial conducted so far for antibiotic prophylaxis of IE
- **No such trial likely to be conducted in the future**
  - Too many patients to be enrolled
  - By far too much expensive
  - Unsolved medical-legal and ethical issues, even in the UK
  - May not be feasible even if money was not an issue
    - Dentists' adherence
    - Patients' adherence
    - Endpoint definition

What about a randomized registry-based trial?

- **It has already been done and (well) published**
  - Screening and Prostate-Cancer Mortality in a Randomized European Study (N Engl J Med 2009;360:1320-8)
  - Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (N Engl J Med 2013;369:1587-97)

- **What is a registry-based randomized trial?**
  - A registry-based trial is a RCT conducted within or with the help of a registry (the registry is used to identify patients and/or to replace the CRF and/or to carry out the follow-up)

  - <u>Numerous advantages</u>
    - A rigorous randomized experiment that can test a causal link between a treatment and an outcome
    - Because inexpensive, investigators can enroll large numbers of patients
    - Realworld population created from existing consecutively registry-enrolled patients, which makes it possible to assess effectiveness in addition to efficacy

How could a registry-based randomized trial be implemented for antibiotic prophylaxis of IE?

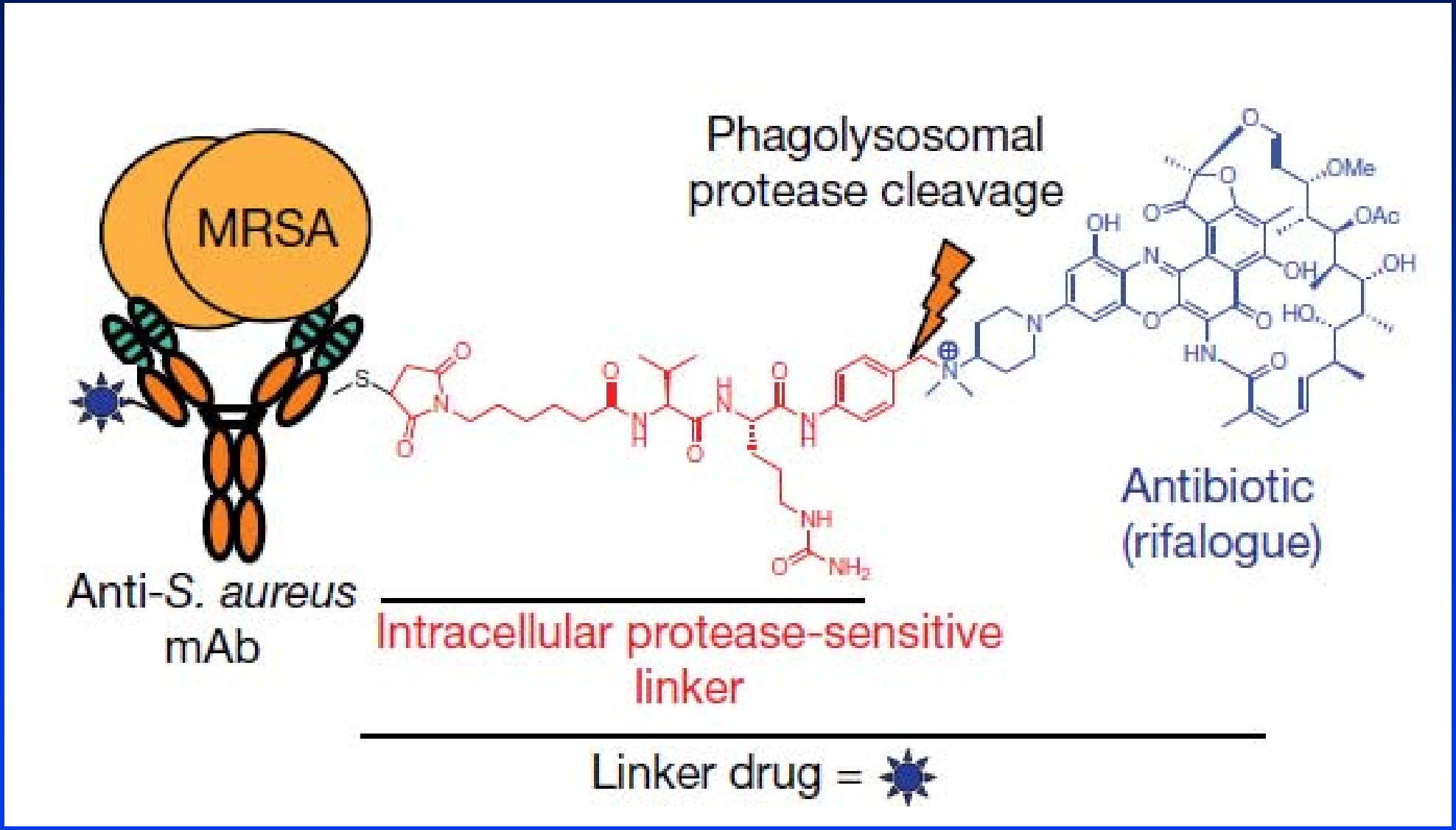
- **Population (registry-based)**
  - Registries make it possible to identify (all) people with high-risk conditions (prosthetic valve, other cardiac conditions …)
- **Randomization (not registry-based but cluster-based)**
  - Geographic area
  - Dentist's patients
- **Follow-up and Endpoint (registry-based)**
  - National hospital discharge diagnosis database
  - Advantage
    - Virtually all IE cases are diagnosed and treated in hospitals
  - Drawbacks
    - Diagnosis of IE would not be expert-validated
    - Causative microorganism may not be reported

New Approaches for Treating CRB

- **Dalbavancin**, a new lipoglycopeptide with a half-life of 14 days. Dosage: IV 1000 mg dose followed 1 week later by a 500 mg dose.
- New antimicrobial strategies: **Antibody–Antibiotic Conjugates (AAC)**

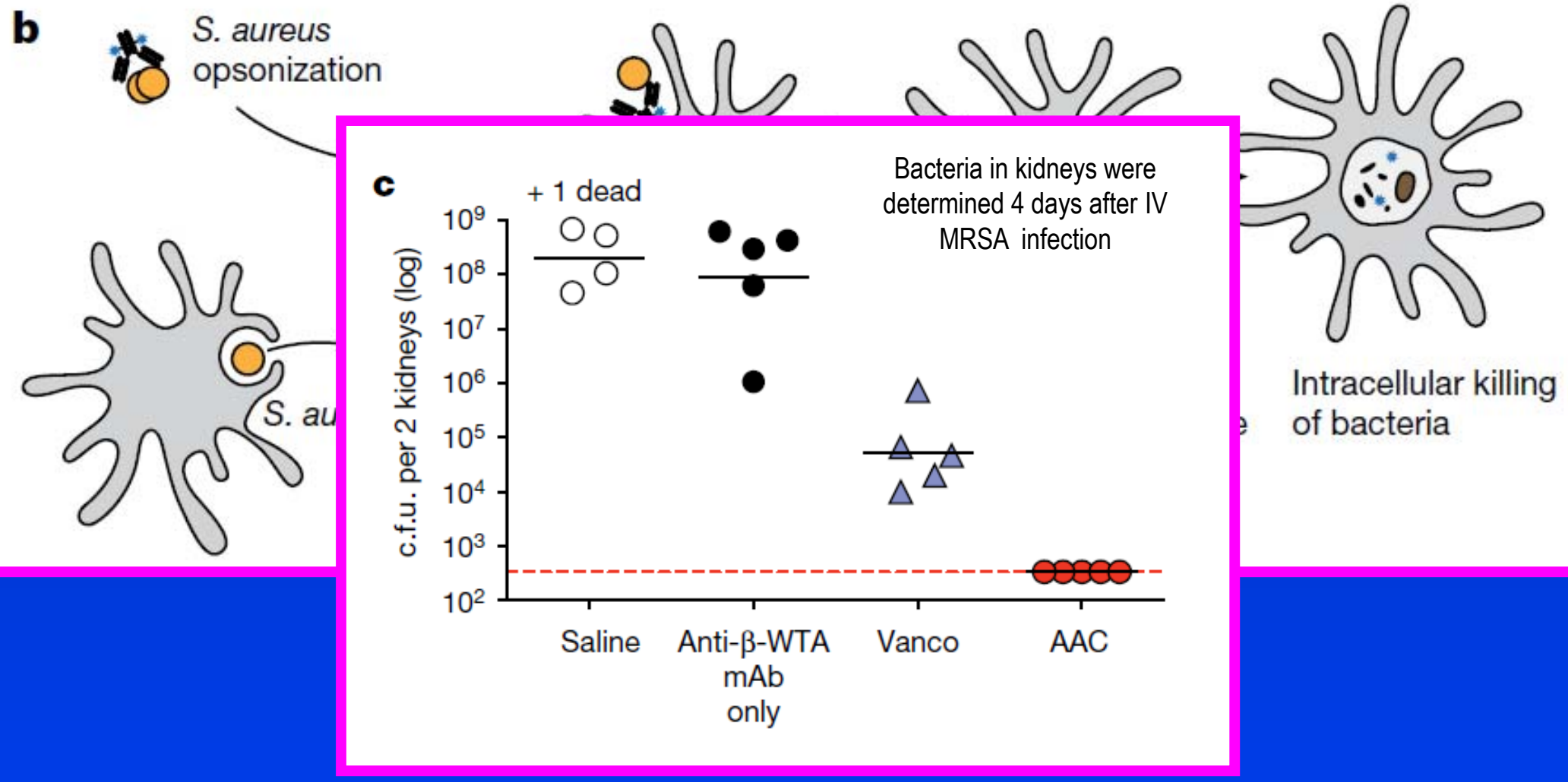
→ Preventing Complications of SA-CRB: **Dalbavancin plus Immunotherapy**

Antibody–Antibiotic Conjugate (AAC) Design



Lehar Sm et al. Nature. 2015 Nov 19;527(7578):323-8

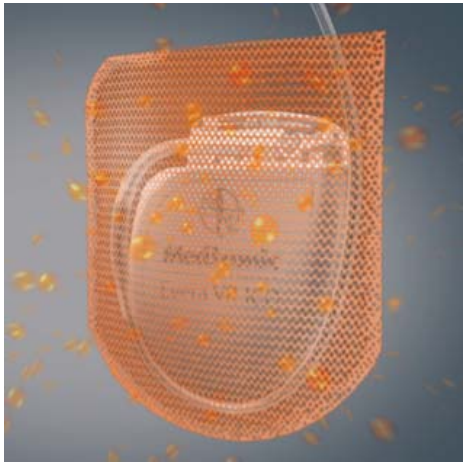
Antibody–Antibiotic Conjugate Design



Lehar Sm et al. Nature. 2015 Nov 19;527(7578):323-8

THE TYRX™ ABSORBABLE ANTIBACTERIAL ENVELOPE

TIME SEQUENCE SIMULATION OF ELUTION & ABSORPTION



Envelope after implantation[1]

- Absorbable Envelope is eluting **Minocycline & Rifampin**

Envelope at 4 weeks[2]

- Absorbable Envelope is dissolving into fragments

Envelope at ~9 weeks[3]

- Mesh has no physical presence and is fully absorbed

1. Huntingdon Life Sciences Study TR-2013-001. **2.** Data on File, 093013-1. **3.** Huntingdon Life Sciences Study TR-2011-054.

Medtronic

Looking to the Horizon H2020 Research in Infective Endocarditis

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Research in Pathogenesis

- Human genome markers for IE susceptibility
- Microbial markers for persistent bacteremia
- Microbial factors that foster resistance to host defenses and innate immunity
- Molecular basis of initial adhesion of bacteria to intracardiac devices
- Anti-biofilms agents
- Antimicrobial resistance mechanisms (e.g. HLDR *S. mitis*)
- Impact of virulence genes (e.g. *agr*) and *S. aureus* antimicrobial resistance on outcome (e.g. Vancomycin MIC)

Looking to the Horizon H2020 Research in Infective Endocarditis

- Introduction
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- Pathogenesis
- **Diagnosis & Management**
- Antimicrobial therapy
- Surgery

Research in Diagnosis & Management

- Differentiating bacteremia from IE.
- Role of biomarkers for IE diagnosis and response to therapy
- Diagnosis of culture-negative IE
- Early diagnosis of IE
- Role of FDG PET/CT for diagnosis of early PVE (<2 mo.), TAVI-IE, ICED infections and extra-cardiac septic foci
- Role of FDG PET/CT for PVE/ICED management
- Management of embolic strokes

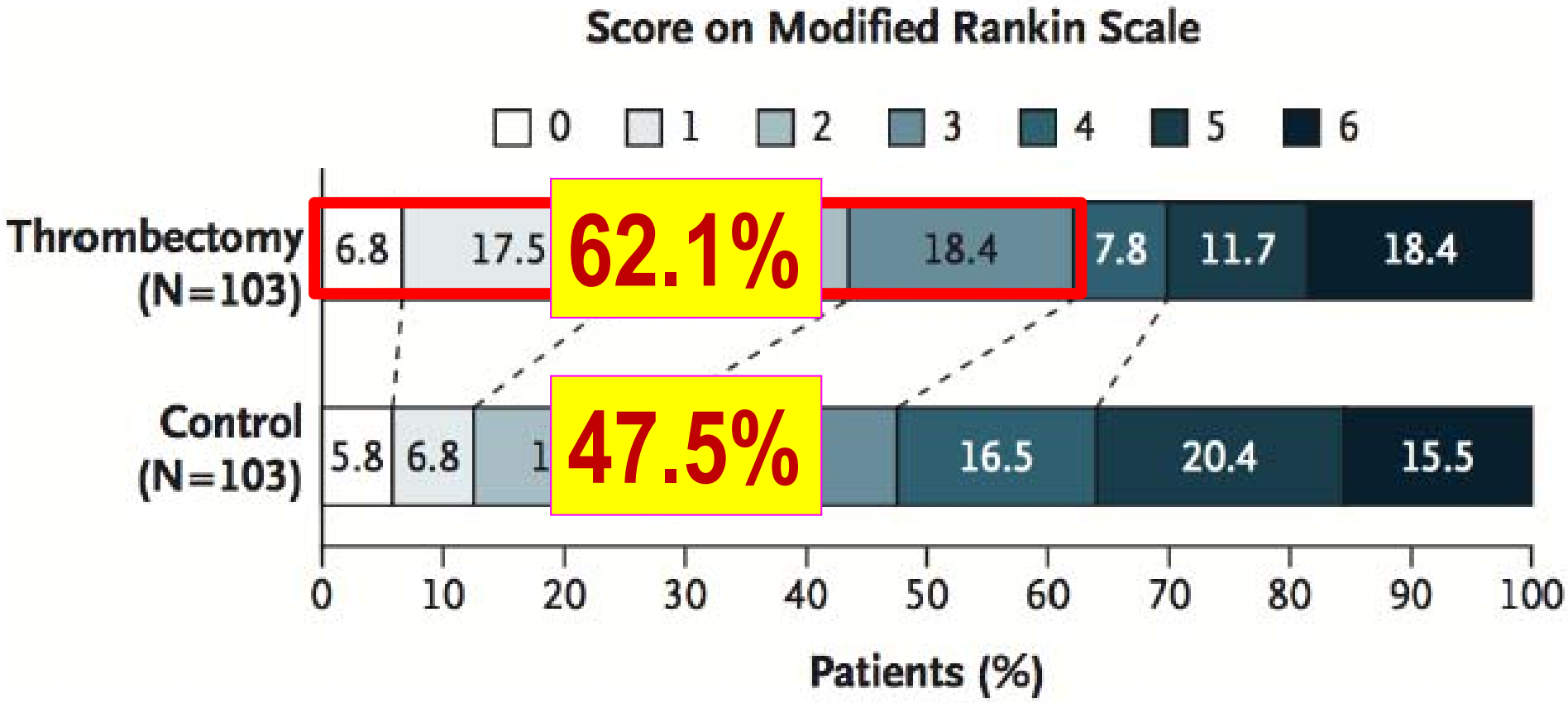
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

T.G. Jovin, A. Chamorro, E. Cobo, M.A. de Miquel, C.A. Molina, A. Rovira, L. San Román, J. Serena, S. Abilleira, M. Ribó, M. Millán, X. Urra, P. Cardona, E. López-Cancio, A. Tomasello, C. Castaño, J. Blasco, L. Aja, L. Dorado, H. Quesada, M. Rubiera, M. Hernández-Pérez, M. Goyal, A.M. Demchuk, R. von Kummer, M. Gallofré, and A. Dávalos, for the REVASCAT Trial Investigators*

Jovin TG et al. NEJM 2015; DOI: 10.1056/NEJMoa1503780



Jovin TG et al. NEJM. 2015.

Looking to the Horizon H2020 Research in Infective Endocarditis

- Introduction
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- Diagnosis & Management
- **Antimicrobial therapy**
- Surgery

AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD; Vance G. Fowler, Jr, MD, MHS; Imad M. Tleyjeh, MD, MSc; Michael J. Rybak, PharmD, MPH; Bruno Barsic, MD, PhD; Peter B. Lockhart, DDS; Michael H. Gewitz, MD, FAHA; Matthew E. Levison, MD; Ann F. Bolger, MD, FAHA; James M. Steckelberg, MD; Robert S. Baltimore, MD; Anne M. Fink, PhD, RN; Patrick O'Gara, MD, FAHA; Kathryn A. Taubert, PhD, FAHA; on behalf of the American Heart

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

2015

Circulation. 2015; On line.

www.americanheart.org

European Heart Journal
doi:10.1093/eurheartj/ehv319

ESC GUIDELINES

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM)

EUROPEAN SOCIETY OF CARDIOLOGY

2015

Eur Heart J. 2015; On line.

www.secardiologia.es

Research in Antimicrobial Therapy

- ~~No gentamicin for MSSA NA IE~~ … but daptomycin?
- Role of rifampin – The ARREST Trial
- Better therapies for susceptible GP cocci
- Better therapies for MDR GP cocci
- New strategies: IV – Oral De-escalation
- Role of new antibiotics: Dalbavancin for OPAT, Tedizolid for oral therapy.
- Optimal treatment for HACEK, Fungal, Whipple, Q fever and Bartonella IE

Thwaites *et al. Trials* 2012, **13**:241
http://www.trialsjournal.com/content/13/1/241

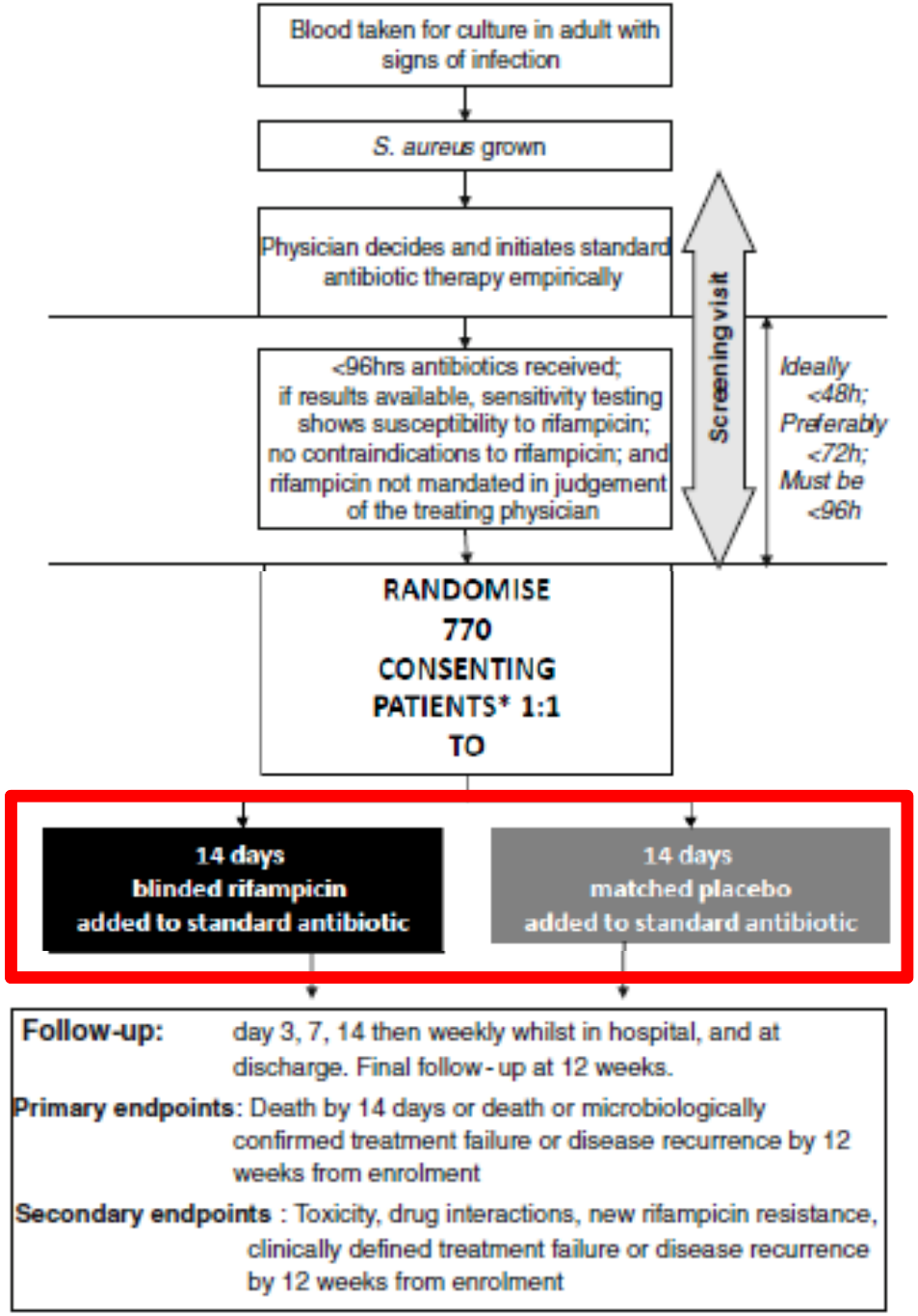
TRIALS

STUDY PROTOCOL Open Access

Adjunctive rifampicin to reduce early mortality from *Staphylococcus aureus* bacteraemia (ARREST): study protocol for a randomised controlled trial

Guy Thwaites[1*], Cressida Auckland[2], Gavin Barlow[3], Richard Cunningham[4], Gerry Davies[5,6], Jonathan Edgeworth[1], Julia Greig[7], Susan Hopkins[8], Dakshika Jeyaratnam[9], Neil Jenkins[10], Martin Llewelyn[11], Sarah Meisner[12], Emmanuel Nsutebu[6], Tim Planche[13], Robert C Read[14], Matthew Scarborough[15], Marta Soares[16], Robert Tilley[4], M Estée Török[17], John Williams[18], Peter Wilson[19], Sarah Wyllie[20], A Sarah Walker[21,22] and on behalf of the United Kingdom Clinical Infection Research Group

There are randomized 670 patients to date, from 30 sites in the UK. The trial opened in December 2012. The sample size is 770 patients. We should have completed recruitment by July 2016; and we aim to report in early 2017


Blood taken for culture in adult with signs of infection
S. aureus grown
Physician decides and initiates standard antibiotic therapy empirically
<96hrs antibiotics received; if results available, sensitivity testing shows susceptibility to rifampicin; no contraindications to rifampicin; and rifampicin not mandated in judgement of the treating physician
Screening visit
Ideally <48h; Preferably <72h; Must be <96h
RANDOMISE 770 CONSENTING PATIENTS* 1:1 TO
14 days blinded rifampicin added to standard antibiotic
14 days matched placebo added to standard antibiotic
Follow-up: day 3, 7, 14 then weekly whilst in hospital, and at discharge. Final follow-up at 12 weeks.
Primary endpoints: Death by 14 days or death or microbiologically confirmed treatment failure or disease recurrence by 12 weeks from enrolment
Secondary endpoints : Toxicity, drug interactions, new rifampicin resistance, clinically defined treatment failure or disease recurrence by 12 weeks from enrolment

Cloxacillin plus Gentamicin *vs.* Cloxacillin plus Daptomycin for the Treatment of MSSA EE

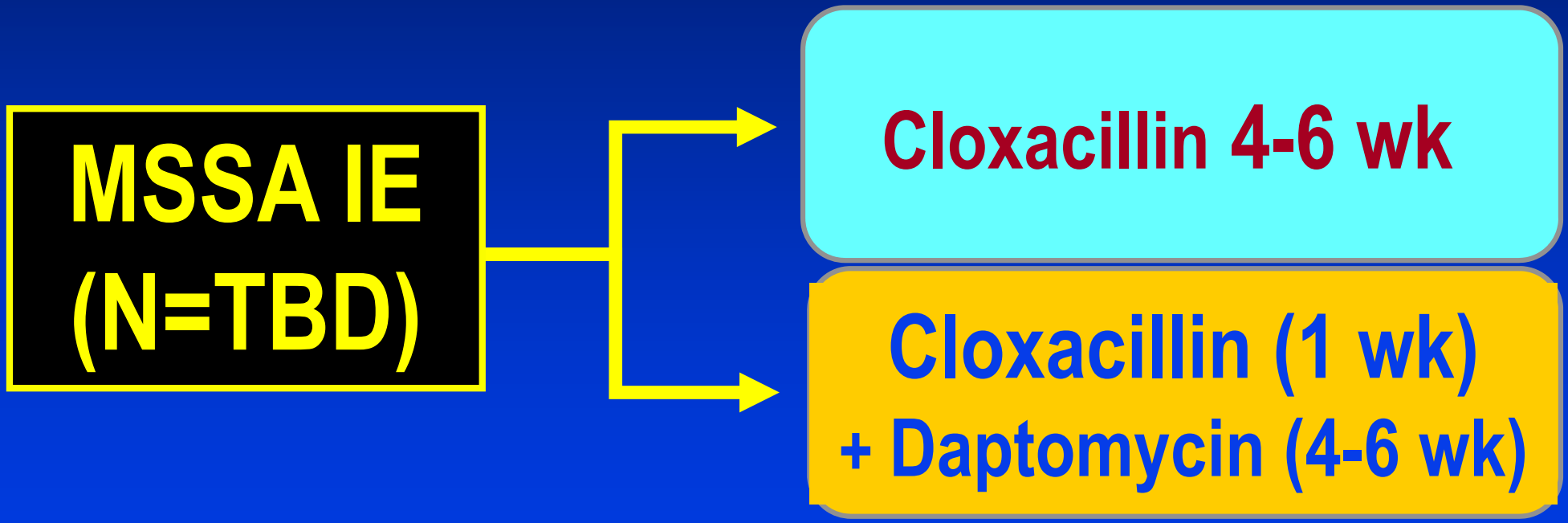
Garcia de la Maria C et al. ECCMID, Amsterdam, NL, April 2016

Treatment group	Animals with sterile vegetations/total (%)	Median log_{10} cfu/g of vegetation (IQR)
Control	0/10 (0)	9 (8.1-9.3)
Daptomycin (6 mg/kg/24h)	0/11 (0)[a,b]	2 (2-3.3)[c,d]
Cloxacillin (2g/4h)	0/10 (0)	3 (2-4.5)[e]
Cloxacillin (2 g/4h) + gentamicin (1 mg/kg/8h)	3/10 (30)[f,g]	2 (0.5-2)[e,h,i]
Daptomycin (6 mg/kg/24h) + cloxacillin (2 g/4h)	8/11 (73)[a,f]	0 (0-1)[c,h]
Daptomycin (6 mg/kg/24h) + fosfomycin (2 g/6h)	10/11 (91)[b,g]	0 (0-0)[d,i]

[a]*P*= .001; [b]*P*< .001; [c]*P*= .001; [d]*P*< .001; [e]*P*= .026; [f]*P*= .086; [g]*P*= .008; [h]*P*= .080; [i]*P*= .005

RCT of the Efficacy and Safety of Cloxacillin *vs.* Cloxacillin plus Daptomycin for the Treatment of MSSA IE

Multicenter, Randomized (1:1) Open-label Clinical Trial



- Recruitment: 2 yr. Europe
- Only MSSA IE
- End points: TOC 12 weeks after finishing Rx, Toxicity, Relapses, Resistance, Surgery and Mortality.

What is the best empiric antibiotic therapy against MSSA and MRSA Bacteremia/IE?

- ß-Lactam [e.g. cloxacillin] (MSSA)
- Vancomycin (MSSA/MRSA)
- Vancomycin plus ß-Lactams (MRSA/MSSA)
- Daptomycin alone (MSSA/MRSA)
- Daptomycin plus ß-Lactam/Fosfomycin (MRSA/MSSA)

What is the best empiric antibiotic therapy against MSSA and MRSA Endocarditis?

- ß-Lactam [e.g. cloxacillin] (MSSA)
- Vancomycin (MSSA/MRSA)
- Vancomycin plus ß-Lactams (MRSA/MSSA)
- Daptomycin alone (MSSA/MRSA)
- Daptomycin plus ß-Lactam/Fosfomycin (MRSA/MSSA)

What are the problems when we are treating MRSA IE with Vancomycin?

- Poor bactericidal activity
- Poor diffusion within the vegetations
- Vancomycin MIC (AUC/MIC PD target)
- hVISA strains
- Tolerance

→ High rate of failures

Activity of Cloxacillin (CLO) plus Vancomycin (VAN) against MRSA-277 EE

Strain	Sterile veg/Total (%)	Median(IQR) Log_{10} CFU/g veg
Control	0/15(0)	9 (8.6-9.5)
VAN (1 g/6h)	8/16 (50)[a,b]	1 (0-2.2)[d]
DAP (6 mg/Kg/d)	13/18 (72)[b,c]	0 (0-1.5)
CLO+VAN	**13/15 (87)[a,c]**	**0 (0-0)[d]**

[a]$p=0.05$, [b]$p=0.29$, [c]$p=0.6$ [d]$p=0.09$

Castañeda X et al. 52nd ICAAC, San Francisco, USA, 2012. Abstract B-648.

Pilot RCT: Combination of Vancomycin and β-lactam (BL) therapy for MRSA Bacteremia (CAMERA)

	Standard therapy Van	Combination therapy Van+BL	Relative Risk (95% CI)	P value
Intention to treat population	***N=29***	***N=31***		
Hospital mortality	5 (17%)	5 (16%)	0.96 (0.48,1.90)	0.91
28 day mortality	5 (17%)	5 (16%)	0.96 (0.48,1.90)	0.91
90 day mortality	6 (21%)	5 (16%)	0.86 (0.46,1.59)	0.65
Duration of bacteremia >3 days	8 (28%)	4 (13%)	0.47 (0.16,1.39)	0.16
Duration of bacteremia >7 days	4 (14%)	1 (3%)	0.23 (0.03,1.97)	0.14
Relapsed bacteremia	1 (3%)	0 (0%)	0	0.30

Davis JS et al. CID 2016.

Daptomycin plus Fosfomycin *vs.* Daptomycin plus Cloxacillin for the Treatment of MRSA EE with a Van MIC of 2 mg/L

Miro JM et al. ECCMID, Barcelona 2014 & Garcia de la María et al. SEICAV. Madrid. 2016

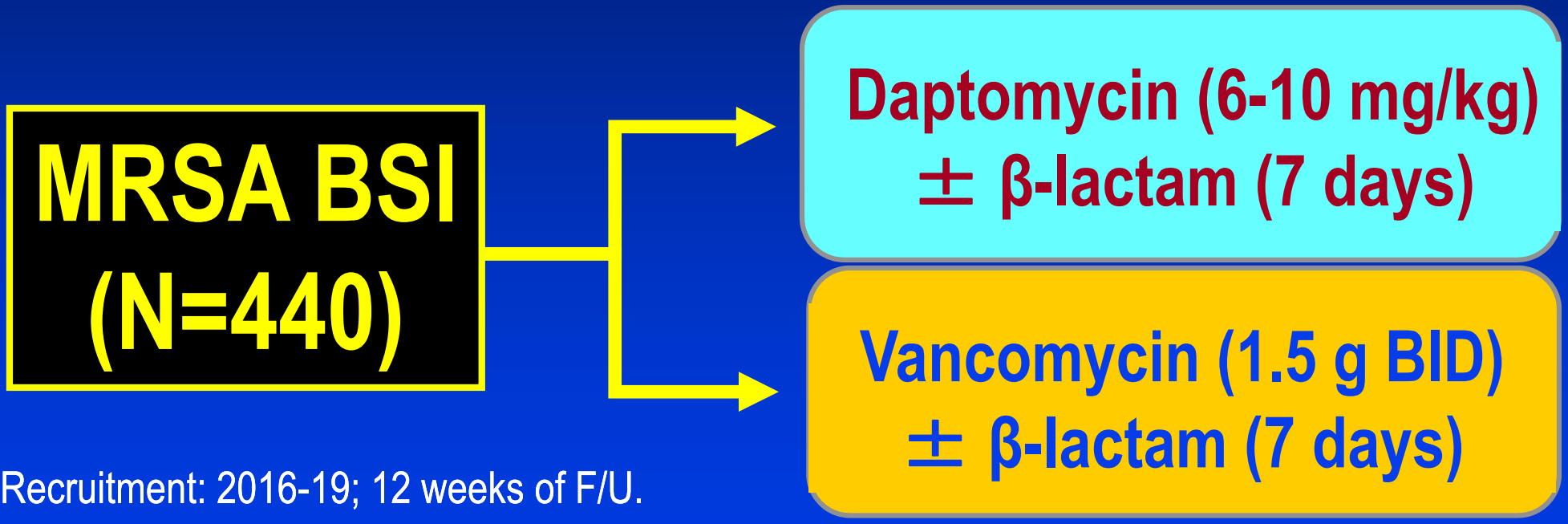
Treatment group	Animals with sterile vegetations/total (%)	Median log_{10} cfu/g of vegetation (IQR)
Control	0/12 (0)	10 (9.8–10)
Daptomycin (6 mg/kg/24 h)	13/18 (72)[a]	0 (0–1.5)[b]
Daptomycin (6 mg/kg/24 h) + cloxacillin (2 g/4 h)	14/16 (88)	0 (0–0)
Daptomycin (6 mg/kg/24 h) + fosfomycin (2 g/6 h)	16/16 (100)[a]	0 (0–0)[b]
Daptomycin (10 mg/kg/24 h)	14/15 (93)	0 (0–0)
Vancomycin 1g/6 h + Cloxacillin 2g/4 h	13/15 (87)	0 (0-0)

[a] $P = .046$
[b] $P = .025$

RCT Efficacy and Safety of β-lactam plus Daptomycin vs. Vancomycin for MRSA BSI – CAMERA2

Australasian Society of Infectious Diseases Clinical Research Network

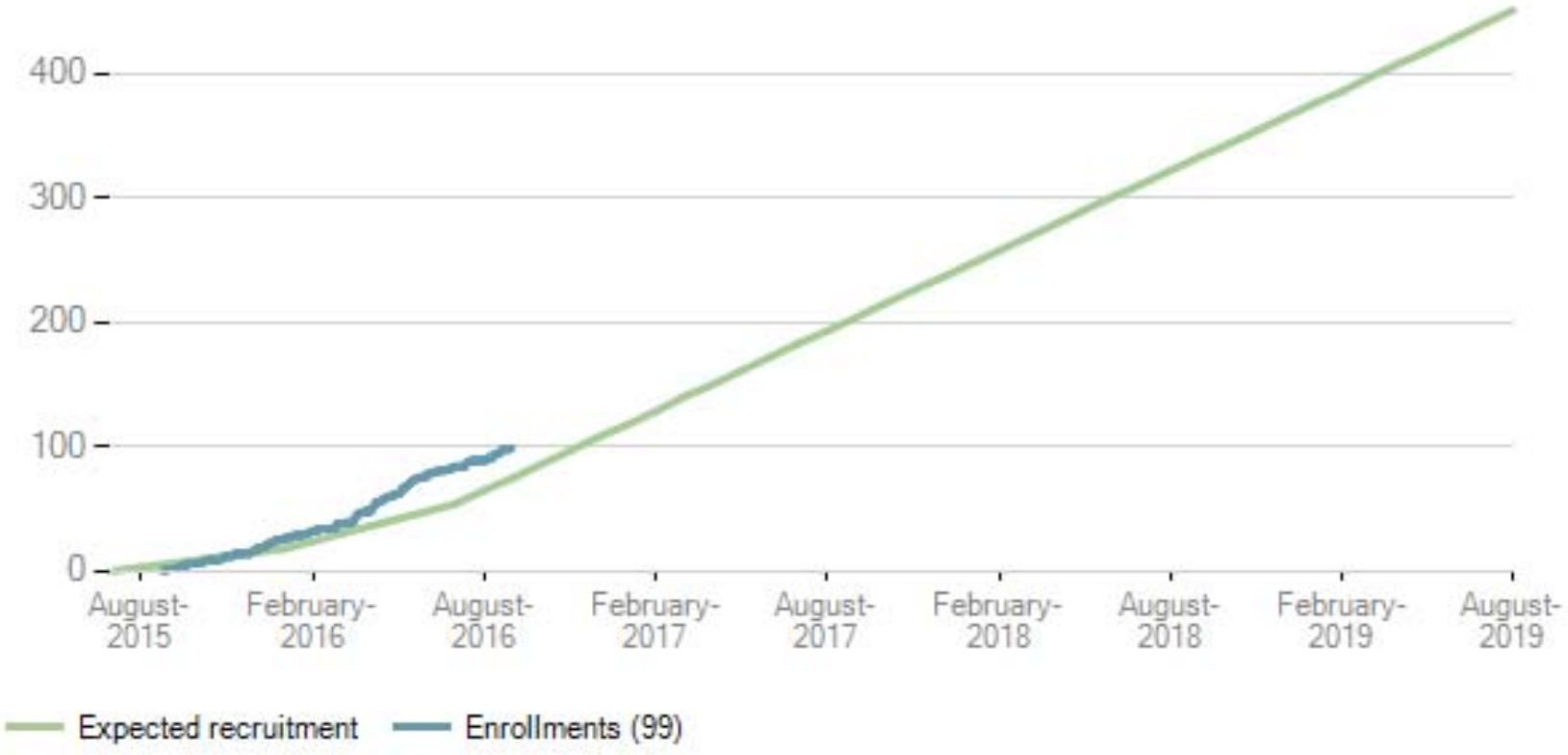
Multicenter, Randomized Open-label Clinical Trial



- Recruitment: 2016-19; 12 weeks of F/U.
- Drugs adjusted to renal failure
- β-lactams: flucloxacillin, cloxacillin, or cefazolin
- Primary Endpoint (composite outcome at 90-d): Mortality, BC+ 5 days, Relapse, Rx failure.

Tong et al. Trials. 2016; 17:170

CAMERA 2 Progress

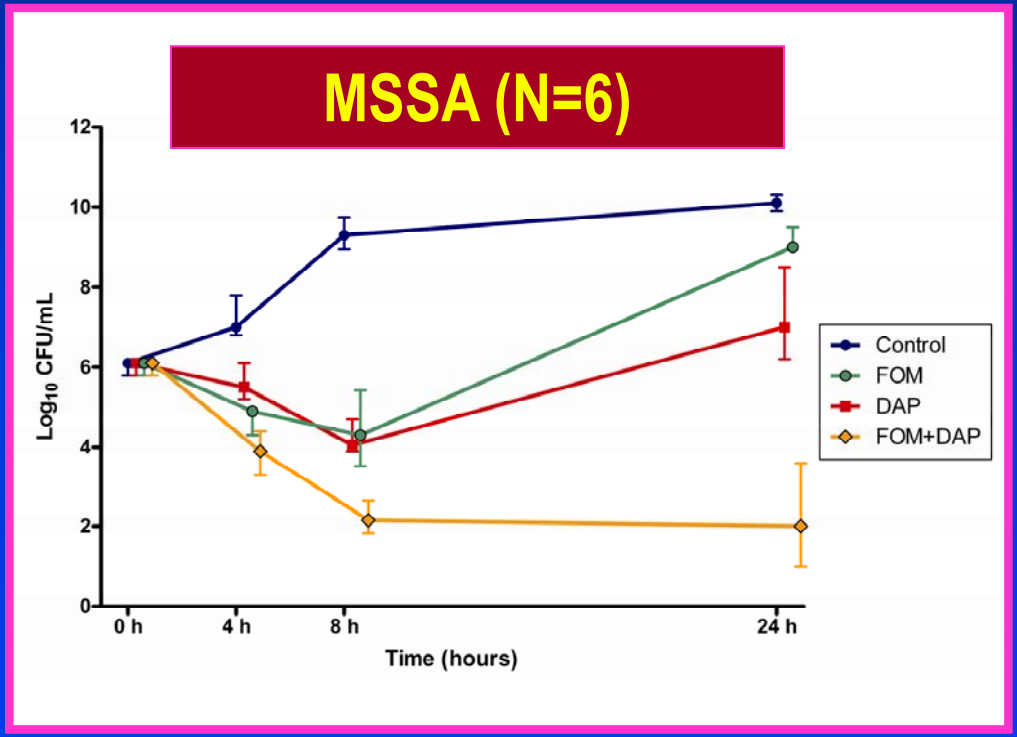


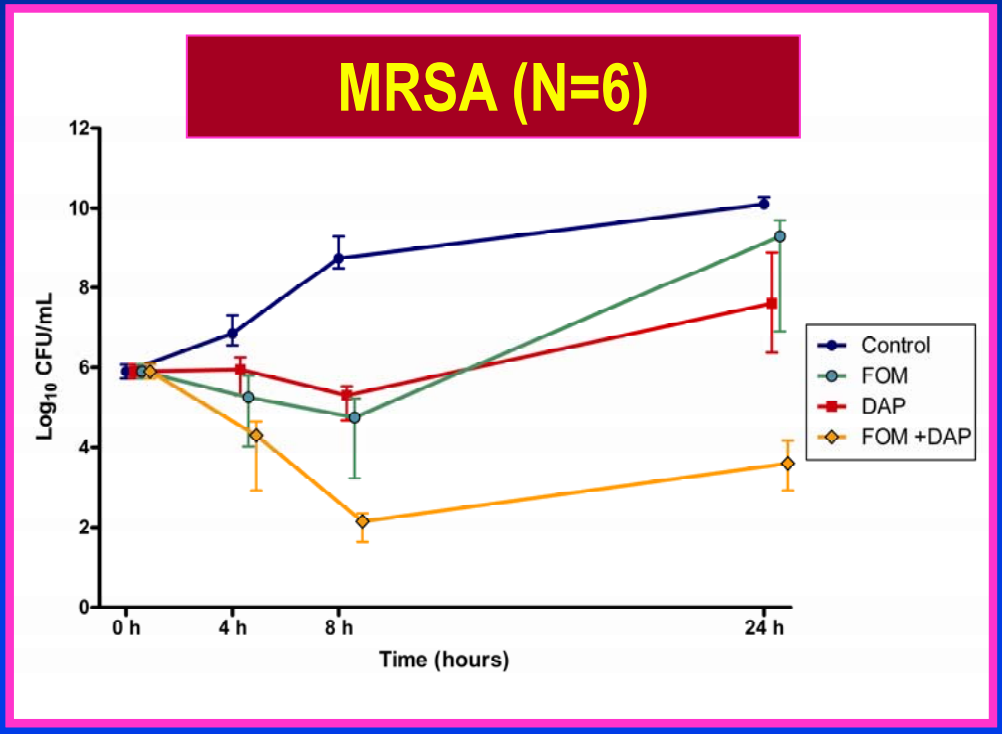
Doherty Institute

Daptomycin (DAP) plus Fosfomycin (FOM) is Synergistic against Methicillin-susceptible (MSSA) and Methicillin-resistant *Staphylococcus aureus* (MRSA) Strains

Miro JM et al. Antimicrob Agents Chemother. 2012; 56:4511-5

Two patients with complicated MRSA NV IE and one patient with MSSA PVE were succesfully treated with the combination of daptomycin plus fosfomycin.





Daptomycin plus Fosfomycin *vs.* Daptomycin plus Cloxacillin for the Treatment of MRSA EE with a Van MIC of 2 mg/L

Miro JM et al. ECCMID, Barcelona May 2014

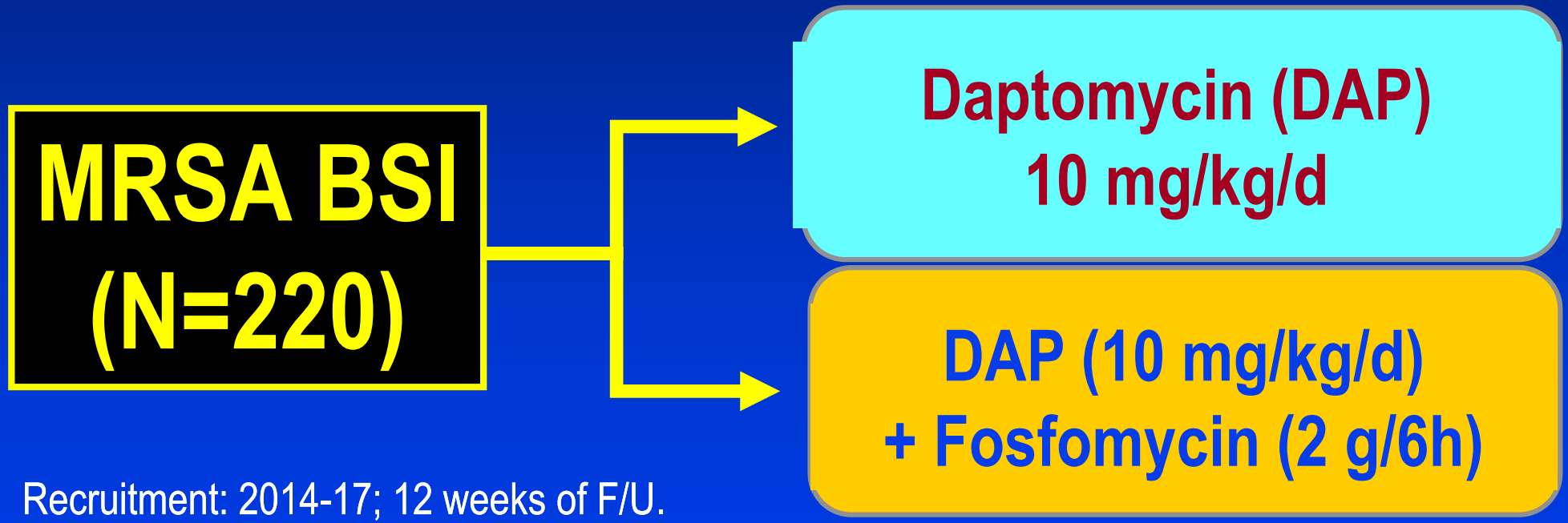
Treatment group	Animals with sterile vegetations/total (%)	Median log_{10} cfu/g of vegetation (IQR)
Control	0/12 (0)	10 (9.8–10)
Daptomycin (6 mg/kg/24 h)	13/18 (72)[a]	0 (0–1.5)[b]
Daptomycin (6 mg/kg/24 h) + cloxacillin (2 g/4 h)	14/16 (88)	0 (0–0)
Daptomycin (6 mg/kg/24 h) + fosfomycin (2 g/6 h)	16/16 (100)[a]	0 (0–0)[b]
Daptomycin (10 mg/kg/24 h)	14/15 (93)	0 (0–0)

[a] $P = .046$
[b] $P = .025$

Evaluation of the efficacy and safety of Daptomycin ± Fosfomycin for the treatment of MRSA BSI in Spain

PI 12/01907 - Dr. Miquel Pujol (H. Bellvitge)

Multicenter, Randomized (1:1) Open-label Clinical Trial



- Recruitment: 2014-17; 12 weeks of F/U.
- Drugs adjusted to renal failure
- Susceptible to study drugs
- End points: TOC 12 weeks after finishing Rx, Toxicity, Resistance and Mortality.

What would be the antibiotic combinations to treat Daptomycin-Non Suseptible (DNS) MRSA IE?

- **Daptomycin + β-lactams***

- Vancomycin + β-lactams
- Daptomycin + Trimethoprim-Sulfamethoxazole**
- Daptomycin + Fosfomycin
- Fosfomycin + Imipenem
- Other antibiotic combinations***

* Ceftaroline, cloxacillin/nafcillin.

*** Trimethoprim-Sulfamethoxazole + Clindamycin; Linezolid + Carbapenems.

** Steed ME et al. AAC. 2010; 54:5187–5192; Claeys KC et al. AAC. 2015 59: 1969-1976.

Daptomycin in the treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus epidermidis* (MRSE)

García-de-la-Maria C *et al. Antimicrob Agents Chemother* 2010; 54:2781-6.

Treatment groups	Doses	Sterile vegetations/ #total (%)	Median (IQR) log10 cfu/g veg
Control	-/-	0/15 (0)	7.4 (6; 8.3)
Vancomycin-SD	1 g/12 h	3/16 (19) [a]	2 (2; 2)
Vancomycin-HD	1 g/6 h	5/15 (33) [b]	2 (0; 2)
Daptomycin - 6	6 mg/kg 24 h	9/15 (60) [a]	0 (0; 4)
Daptomycin - 10	10 mg/kg 24 h	11/15 (73) [b]	0 (0; 1)

[a]*P*=0.02; [b]*P*=0.03.

Vancomycin and Daptomycin MIC/MBCs were 2/4 and 0.5/1 mg/L respectively.

Daptomycin, simulating 6 mg/kg and 10 q 24 h i.v.; Vancomycin, simulating 30 mg/kg/24 h. divided in 2 doses i.v. and 60 mg/kg/24 h divided in 4 doses achieving AUC/MIC = 400.

New Therapies for Prosthetic Valve Endocarditis Caused by Methicillin-Resistant CoNS

Regimen	Dosage and route	Duration (weeks)*
Daptomycin*	10 mg/kg/24 h. IV	≥ 6
+ Rifampin (PVE)	+ 300 mg/8 h. PO/IV	≥ 6
+ Gentamicin (PVE)	+ 3 mg/kg/24h. IV/IM (in 2-3 doses)	2

Alternatives

- Ceftaroline	600 mg/kg/8h IV	≥6
- Linezolid	600 mg/12 h. PO/IV	≥6
- Other antibiotics*		

***MRSE NV IE** = Daptomycin plus Beta-lactams or Fosfomycin; Fosfomycin plus Imipenem; Televancin, Dalbavancin; Oritavancin, Tedizolid and other active antibiotics against MRSE

Ampicillin-Ceftriaxone *vs.* Ampicillin-Gentamicin for the Treatment of *E. faecalis* IE

Fernandez-Hidalgo N et al., Clin Infect Dis. 2013; 56:1261-8. .

	Type of Treatment		
	A+C* N=159	A+G** N=87	*P* value
- AE leading Rx D/C	1%	25%***	<0.001
- Died on Rx	22%	21%	0.91
- Died after Rx (3 months)	8%	7%	0.72
- Surgery	33%	40%	0.39
- Rx failure	1%	2%	0.54
- Relapses (survivors)	3%	4%	0.67

* Ampicillin 2 g/4 h plus ceftriaxone 2 g/12 h during 6 weeks; **51 (32%) cases had HLAR strains.**

** Ampicillin plus gentamicin following AHA Guidelines; *** Renal failure in most cases (23% vs. 0%, P<0.001).

Ampicillin plus Short *vs.* Standard Gentamicin Course for the Treatment of *E. faecalis* IE*

Dahl A et al., Circulation. 2013;127:1810-7.

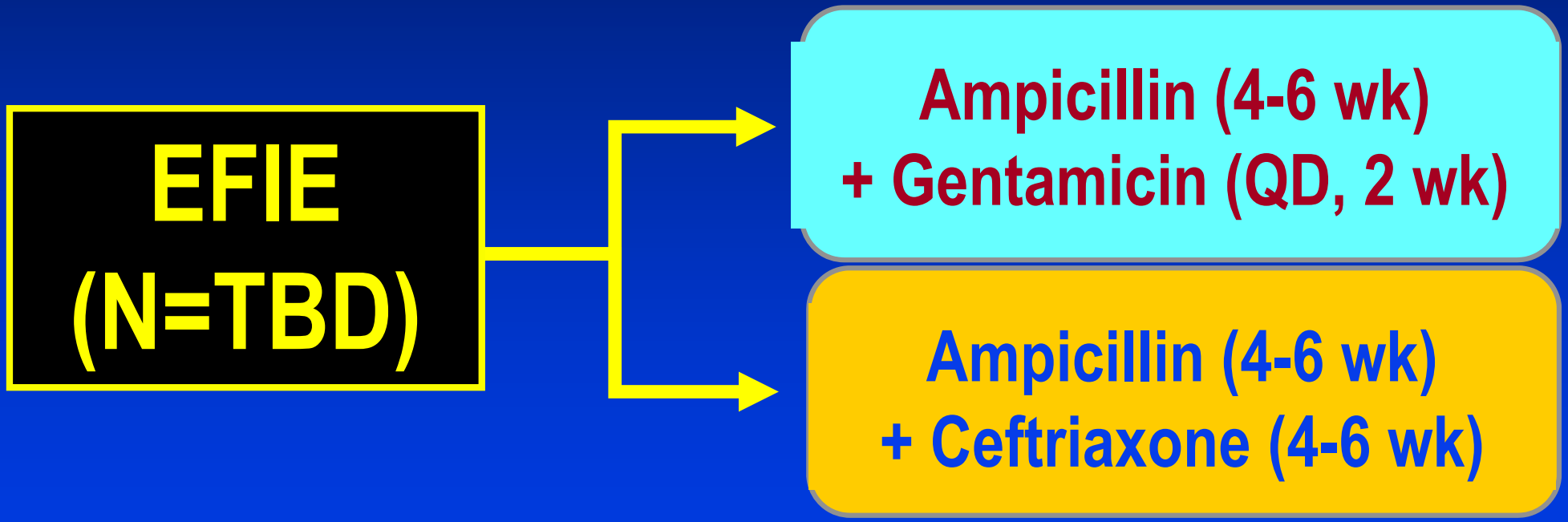
	Study Periods		
	2002-06 N=41	2007-11 N=42	*P* value
- Duration of Gentamicin	28 (18-42)	14 (7-15)	<0.001
- Gentamicin QD dosing	80%	93%	0.049
- Δ eGFR (discharge–baseline)**	-11	-1	0.009
- Died on Rx	4%	2%	0.43
- 1-yr event free survival***	66%	69%	0.75
- Surgery	37%	33%	0.70
- Relapses (survivors)	7%	5%	0.67

* There were no cases with HLAR. Treatment duration following AHA Guidelines; ** in ml/min.

*** 1-year event free survival = No relapse, no death.

Evaluation of the Efficacy and Safety of Ampicillin plus Ceftriaxone vs. Gentamicin for the Treatment of EFIE

Multicenter, Randomized (1:1) Open-label Clinical Trial



- Recruitment: 2 yr. Europe
- Only *E. faecalis* IE without HLAR
- End points: TOC 24 weeks after finishing Rx, Toxicity, Relapses, Surgery and Mortality.

Miro JM et al., Circulation. 2013; 127:1763-6

What would be the antibiotic combinations to treat Vancomycin-Resistant *E. faecium* (VRE) IE?

- **Daptomycin + Beta-lactams***
- Daptomycin + Tigecycline (+ Gentamicin)
- Daptomycin + Fosfomycin
- Oritavancin (+Gentamicin)
- Tigecycline + Gentamicin

* Ceftaroline, ertapenem or ampicillin.
Smith JR et al. JAC 2015; on line.

Munita JM et al. Curr Infect Dis Rep (2012) 14:339–349
Pericas JM et al. Future Microbiol. 2015; in press.

The POET Trial: IV to Oral De-escalation Trial

Iversen K et al. Am Heart J 2013;165:116-22

Partial oral treatment of endocarditis

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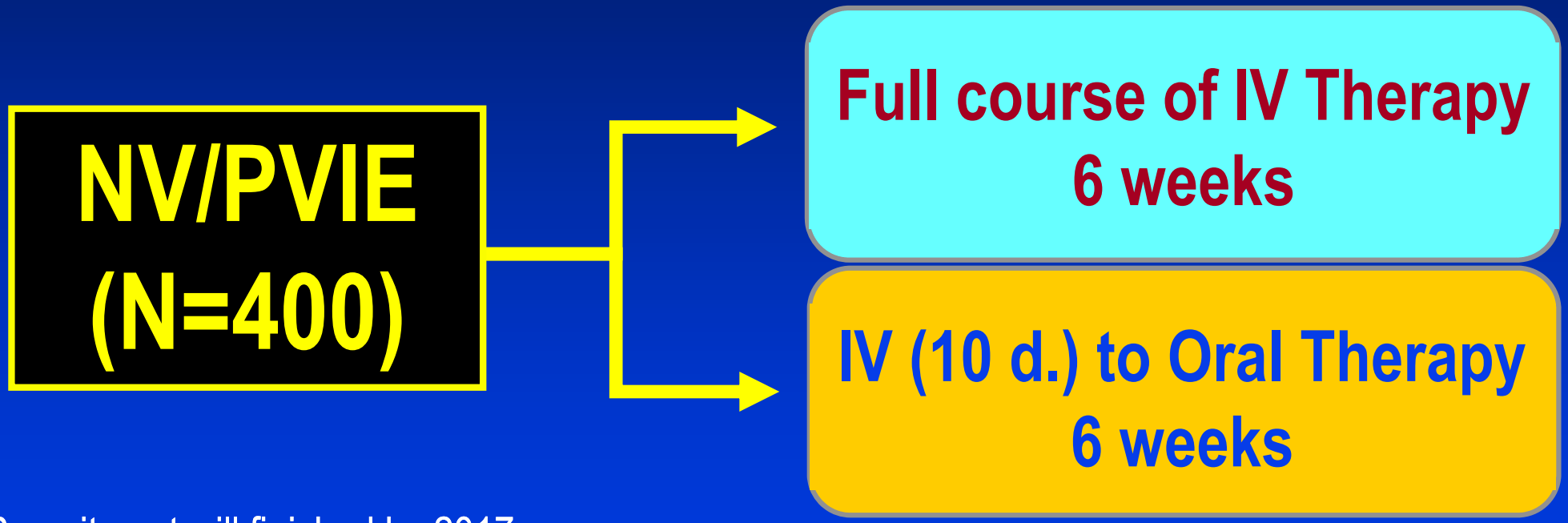
Background Guidelines for the treatment of left-sided infective endocarditis (IE) recommend 4 to 6 weeks of intravenous antibiotics. Conversion from intravenous to oral antibiotics in clinically stabilized patients could reduce the side effects associated with intravenous treatment and shorten the length of hospital stay. Evidence supporting partial oral therapy as an alternative to the routinely recommended continued parenteral therapy is scarce, although observational data suggest that this strategy may be safe and effective.

Study Design This is a noninferiority, multicenter, prospective, randomized, open-label study of partial oral treatment with antibiotics compared with full parenteral treatment in left-sided IE. Stable patients (n = 400) with streptococci, staphylococci, or enterococci infecting the mitral valve or the aortic valve will be included. After a minimum of 10 days of parenteral treatment, stable patients are randomized to oral therapy or unchanged parenteral therapy. Recommendations for oral treatment have been developed based on minimum inhibitory concentrations and pharmacokinetic calculations. Patients will be followed up for 6 months after completion of antibiotic therapy. The primary end point is a composition of all-cause mortality, unplanned cardiac surgery, embolic events, and relapse of positive blood cultures with the primary pathogen.

The POET Trial: IV to Oral De-escalation Trial

Iversen K et al. Am Heart J 2013;165:116-22

Multicenter, Randomized (1:1) Open-label Clinical Trial in Denmark



- Recruitment will finished by 2017.
- All cases of streptococcal, staphylococcal, or enterococcal left sided NV/PV IE will be included.
- Susceptible to study drugs & PK studies
- The primary end point is a composition of all-cause mortality, unplanned cardiac surgery, embolic events, and relapse.

The POET Trial: IV to Oral De-escalation Trial

Iversen K et al. Am Heart J 2013;165:116-22

Inclusion criteria
- Left-sided endocarditis based on the Duke criteria
- Infected with one of the following microorganisms:
  - Streptococci
  - *E faecalis*
  - *S aureus*
  - Coagulase-negative staphylococci
- >18 y
- ≥10 d of appropriate parenteral antibiotic treatment overall and at least 1 wk of appropriate parenteral treatment after valve surgery
- T <38.0°C >2 d
- C-reactive protein dropped to <25% of peak value or <20 mg/L, and white blood cell count $<15 \times 10^9$/L during antibiotic treatment
- No sign of abscess formation revealed by echocardiography
- Transthoracic and transesophageal echocardiography performed within 48 h of randomization

Exclusion criteria
- Body mass index >40
- Concomitant infection requiring intravenous antibiotic therapy
- Inability to give informed consent to participation
- Suspicion of reduced absorption of oral treatment due to abdominal disorder
- Reduced compliance

- **Patients randomized to IV treatment**: Treated according to guidelines from Danish Cardiac Society (ESC)
- **Patients randomized to oral treatment**: Treated according to new study guidelines.
- **OPAT program was not considered in this trial.**

The POET Trial: Current Status

Iversen K et al. Am Heart J 2013;165:116-22

- Eight departments are actively recruiting
- <300 patients included as of today (planned 400). Inclusion slower than anticipated. **Recruitment will finish by end 2017**.
- **All categories of IE are included**; NVE, PVE, medically treated, surgically treated including single or double valves, reconstruction after extensive surgery
- 2015 Data Safety Monitoring Board (DSMB) reports; *"No safety concerns, keep enrolling as planned"*
- Authors hope to develop a new more lenient treatment (a new paradigm!)

The RODEO study

'**R**elais **O**ral **D**ans les **E**ndocardites à staphyl**O**coques multi-sensibles'

Objectives

- *'To evaluate safety & efficacy of partial oral treatment for **left-sided multi-susceptible staphylococcal IE**, compared with full-length parenteral treatment'*

Design

- Multicenter, nationwide (France)
- Randomized 1:1, open-label
- Funding (550 k€): French Ministry of Health (PHRC)

L. Bernard, C. Pulcini, P. Tattevin

The RODEO Trial: IV to Oral De-escalation Trial

Iversen K et al. Am Heart J 2013;165:116-22

Multicenter, Randomized (1:1) Open-label Clinical Trial in France

***S. aureus* & CoNS IE (N=324)**

→ **Full course of IV Therapy 6 weeks (2015 ESC)**

→ **IV (14 d.) to Oral Therapy LEV+RIF 4 weeks**

- Approved in October 2014.
- Recruitment started on March 2016.
- Only staphylococcal left sided NV/PV IE will be included. Susceptible to study drugs (MSSA, MSSE)
- The primary end point is a composition (M3) of all-cause mortality, unplanned cardiac surgery and relapse.

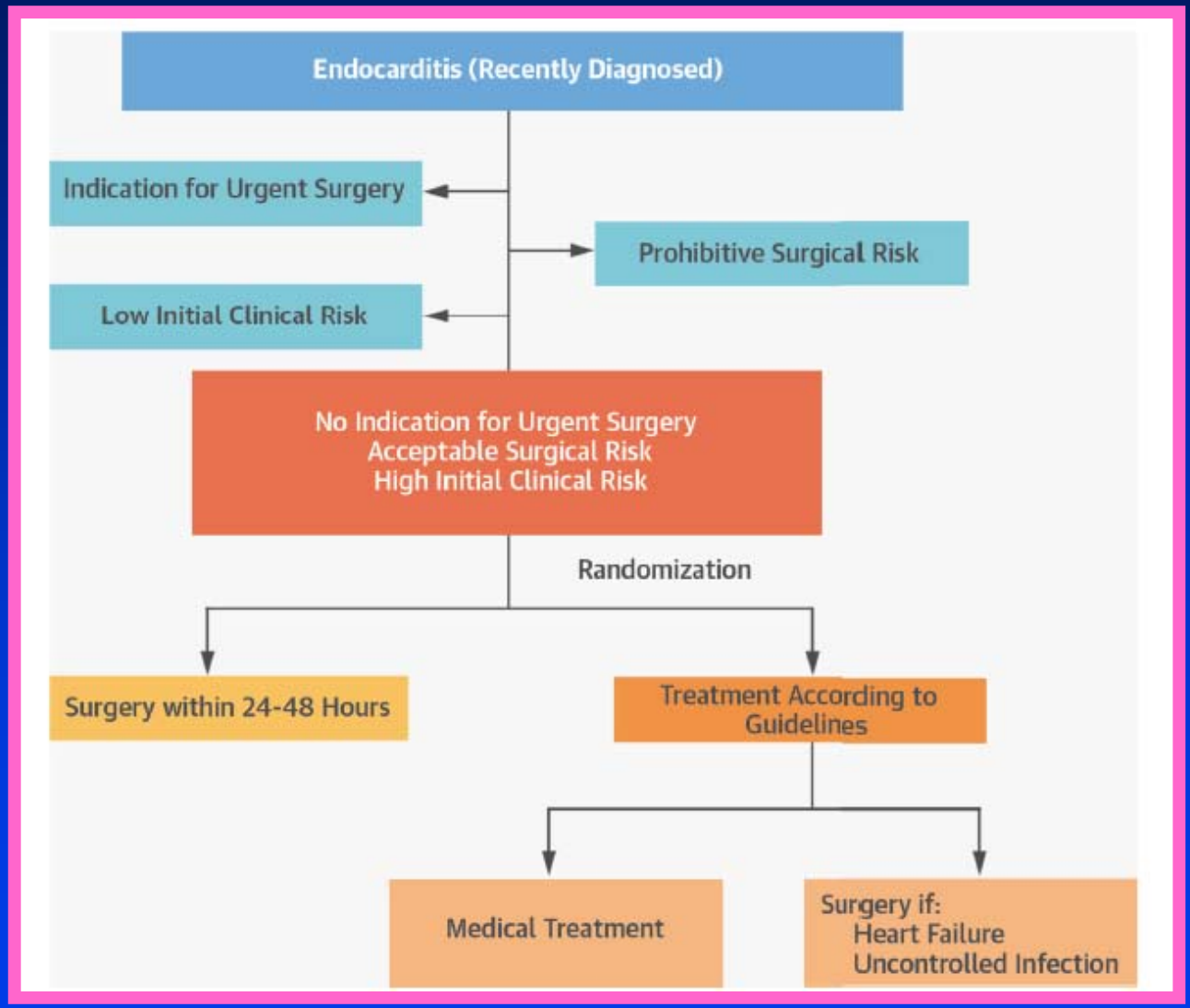
Looking to the Horizon H2020 Research in Infective Endocarditis

- Introduction
- Prevention
- Pathogenesis
- Diagnosis & Management
- Antimicrobial therapy
- **Surgery**

Research in Surgery

- To find a more accurate “IE Prognosis Score” (e.g. new “EuroScore” for IE)
- Optimal timing of cardiac surgery in patients with intermediate risk: we need a RCT!
- Surgery for big vegetations in non-VGS IE
- How and when perform surgery in SAIE. Surgery for uncontrolled infection
- Surgery in special patients (e.g. TAVI-IE, cirrhosis)
- Optimal timing for reimplantation of PCM & DF

Proposal of a Randomized Clinical Trial to Test Early Surgery in Intermediate/High Risk Left-Sided IE



San Román, J.A. et al. JACC. 2015; 66:1068–76.

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...

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