

Cubicin® (Daptomycin)

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Cubicin® (Daptomycin): A new generation of antibiotics

- ▶ First-in-class cyclic natural lipopeptide
- ▶ Activity against major gram positive pathogens
- ▶ Concentration dependent killing
- ▶ Bactericidal
- ▶ Low resistance rate
- ▶ No cross resistance with other antibiotics
- ▶ Once-daily dosing
- ▶ Excreted primarily via kidneys



DAPTOMYCIN

Differential microbiology pattern

- No activity against Gram-negative pathogens
- Active *in vitro* against Gram-positive pathogens
 - *S. aureus*, coagulase-negative staphylococci (CoNS), *Enterococcus* spp.
 - β -haemolytic streptococci, *S. pneumoniae*, *S. viridans*
 - *Corynebacterium* spp., *Listeria monocytogenes*
 - *Clostridium difficile*, *Clostridium perfringens*
 - *Peptostreptococcus* spp., *Propionebacterium* spp.
- Active against MRSA, VRSA, VRE, PRSP...
- Low activity against some Gram-positive bacilli
 - *Lactobacillus* spp.



with permission from
Dr. Dirk Lammers, Bad Oeynhausen

DAPTOMYCIN: microbiology pattern

Antimicrobial agent	MIC ₉₀ (µg/ml)						
	<i>S. pneumoniae</i>	<i>S. aureus</i>	CoNS	<i>E. faecalis</i> VAN ^S	<i>E. faecalis</i> VAN ^R	<i>E. faecium</i> VAN ^S	<i>E. faecium</i> VAN ^R
Vancomycin	0.25-0.5	1-2	2	4	>128	2	128
Quinup./dalfop.	0.5-1	0.5	0.25-1	8	8	2	4
Linezolid	1-2	2-4	2-4	4	4	4	2
Tigecycline	0.06 -0.5	0.25 -0.5	0.5	0.25	0.5	0.25	0.12
Daptomycin*	0.12-0.25	0.5	0.5	1	2	2	4
Oritavancin	≤0.01	1-2	2	1	2	0.12	1
Dalbavancin	≤0.25	0.06 -0.25	0.06	0.12	>128 (VanA)	0.12	1(VanB)
Telavancin	0.01-0.06	0.5	0.5-1	1	4	0.5	4
Ceftobiprol	0.03 -0.06 (Pen ^S) 0.5 (Pen ^I) 1-2 (Pen ^R)	0.5-1(Met ^S) 2-4(Met ^R)	0.5-1(Met ^S) 2(Met ^R)	-	-	-	-

*Ca²⁺ supplemented media

DAPTOMYCIN: *in vitro* susceptibility testing

Recommendations

- Ca²⁺ supplemented media (mandatory!)
- Similar CLSI and EUCAST breakpoints
- Recommended methods:
 - Microdilution with MH broth + Ca²⁺ (50 µg/ml)
(including validated automatic systems)
 - Daptomycin-Ca²⁺ Etest (MH or Isosensitest)
- Non-recommended methods:
 - Agar dilution
 - Conventional disk diffusion

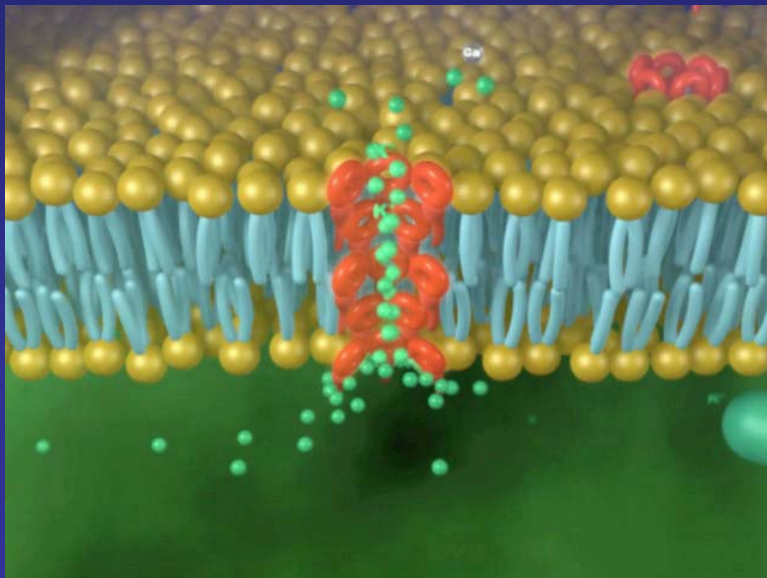
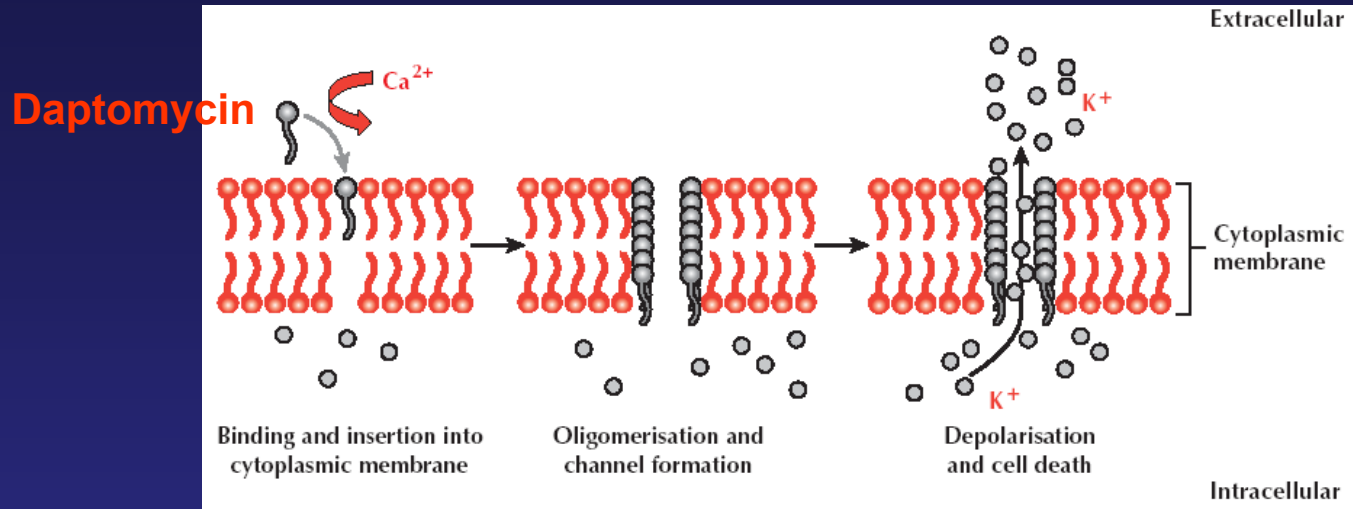
CLSI, M100-S16 2006

Cantón *et al.* 15th ECCMID 2006

Hanberger *et al.* Antimicrobial Agents Chemother 1991; 35: 710–6

Johnson *et al.* J Antimicrob Chemother 2004; 53: 860–2

Daptomycin: Unique mechanism of work



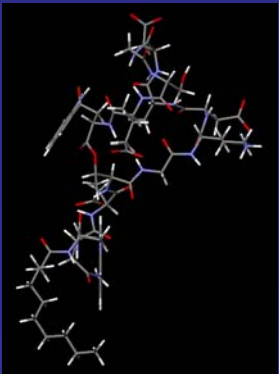
DAPTOMYCIN: mechanism of action

■ Interaction with cytoplasmic membrane

- Oligomerization and interaction of the lipid tail extension with the cell membrane without cytoplasm invasion
- Ca^{2+} -dependent insertion (formation of amphiphilic structure)

■ Multiple effects on cellular function

- Depolarization of membrane potential
- Interaction with ion efflux (K^+ , ...)
- Inhibition of synthesis pathways of:
 - Lipoteichoic acids (?) and peptidoglycan
 - Macromolecules (DNA, RNA, proteins)



Silverman *et al.* Antimicrob Agents Chemother 2003; 47: 2538–44

Jung *et al.* Chem Biol 2004; 11: 949–57

Steenbergen *et al.* J Antimicrob Chemother 2005; 55: 283–8

DAPTOMYCIN: bactericidal activity

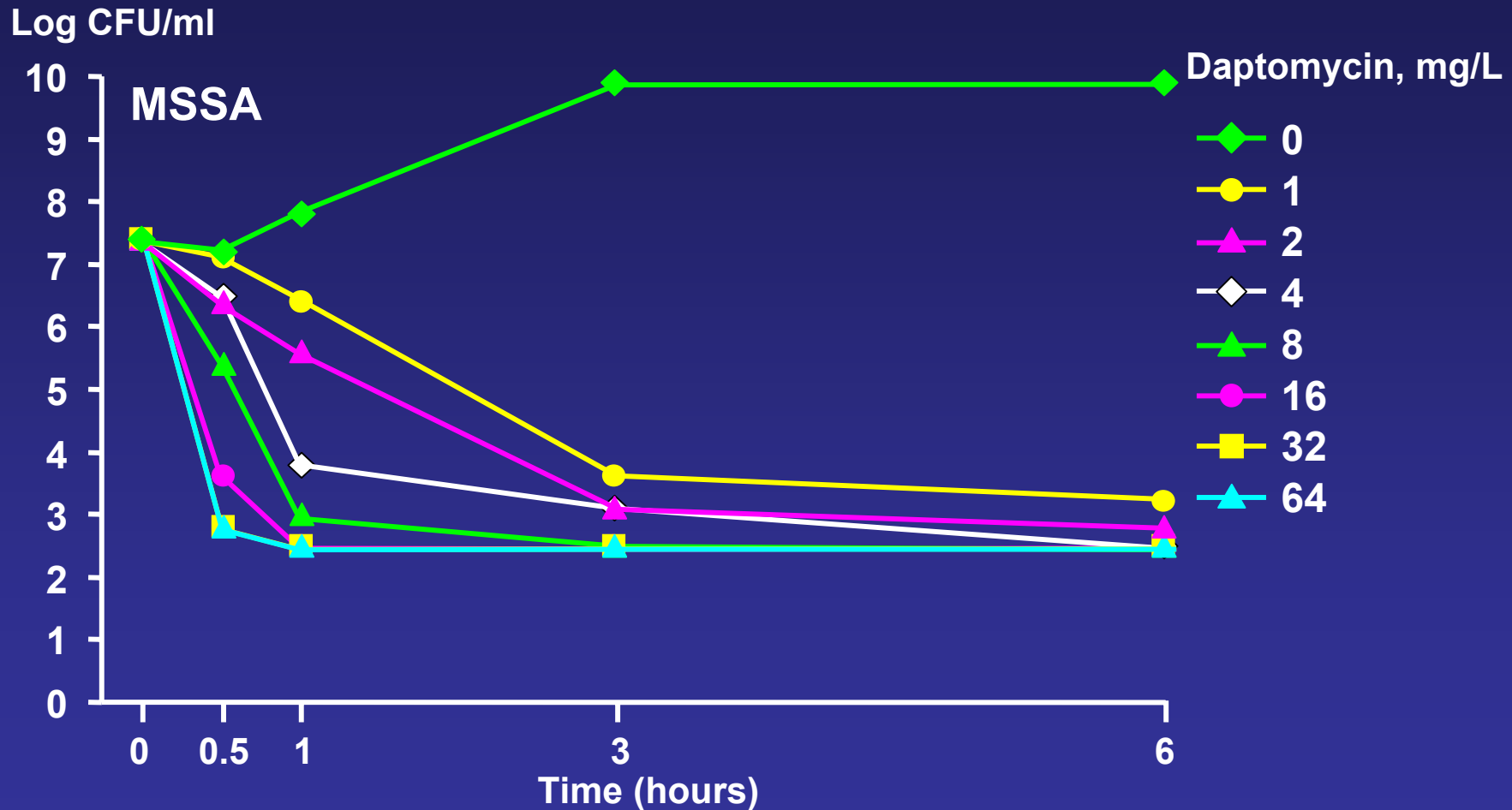
- Rapid (1–4 h) concentration-dependent bactericidal activity
 - Independent of bacterial inoculum
 - Both on exponential and stationary growth phases
- Mechanism of action does not require cell lysis



Wale *et al.* J Med Microbiol 1989; 30: 45–9

DAPTOMYCIN: bactericidal activity

Time killing studies against *S. aureus*



DAPTOMYCIN: pharmacokinetics & pharmacodynamics

- Absence of oral absorption, IV administration (4 mg/kg once daily)
- Linear PK:

4 mg/kg	→	58 µg/ml
6 mg/kg	→	99 µg/ml
8 mg/kg	→	133 µg/ml
- Prolonged $T_{1/2}$ (8–9 h)
- 92% protein binding: - reversible binding
- weaker than to cytoplasmic membrane
- Mainly distributed in plasma / interstitial liquid (\downarrow Vd, 0.1 L/Kg)
- Inhibition by pulmonary surfactant
- Elimination by urine (78%) (minimal excretion in faeces, 6%)
- PK/PD parameters defining efficacy: C_{max}/MIC , AUC/MIC

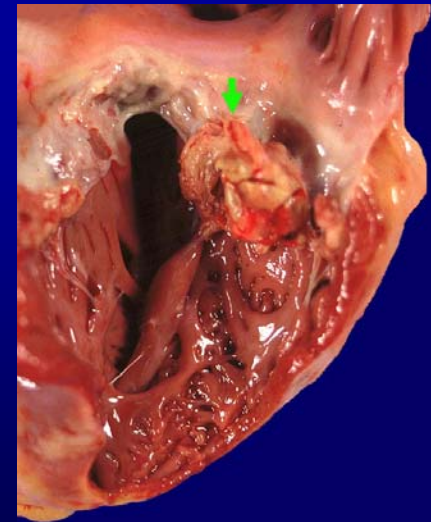
Dvorchik *et al.* Antimicrob Agents Chemother 2003; 47:1318–23

Silverman *et al.* J Infect Dis 2005; 191: 2149–52

Safdar *et al.* Antimicrob Agents Chemoter 2004; 48: 63–68

Overview

- **Daptomycin in clinical trials**
 - **Complicated skin and soft tissue infection (cSSTI) trials**
 - ***Staphylococcus aureus* bacteremia and infective endocarditis (IE) trial**



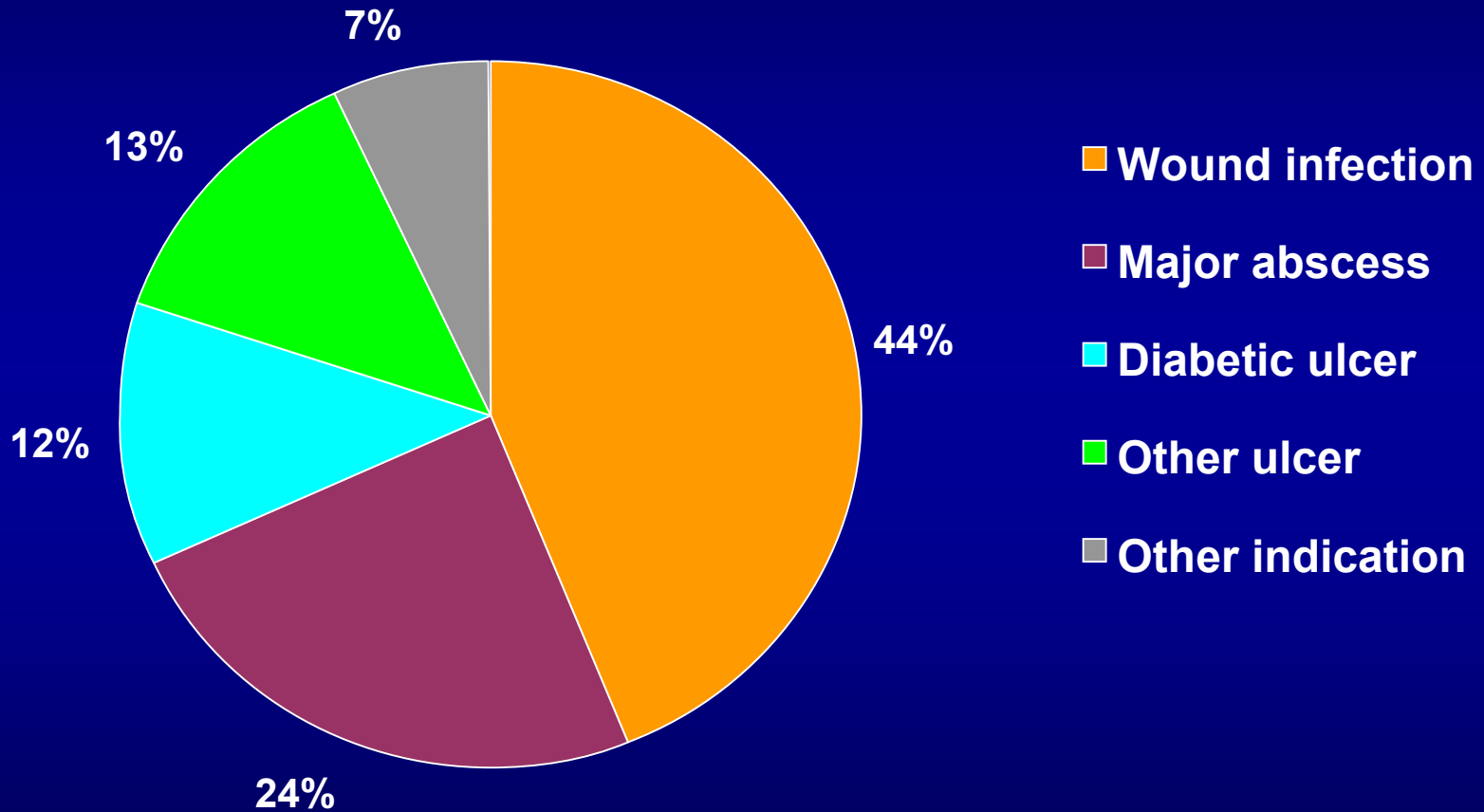
cSSTI trials

- Two randomized, evaluator-blinded studies
- Patients aged 18 to 85 years (ITT=1092)
- Daptomycin vs comparator for 7–14 days
 - Daptomycin 4 mg/kg once daily
 - Vancomycin 1 g twice daily or penicillinase-resistant penicillin* 4–12 g daily



*Cloxacillin, flucloxacillin, oxacillin, or nafcillin

cSSTI trials: baseline diagnosis

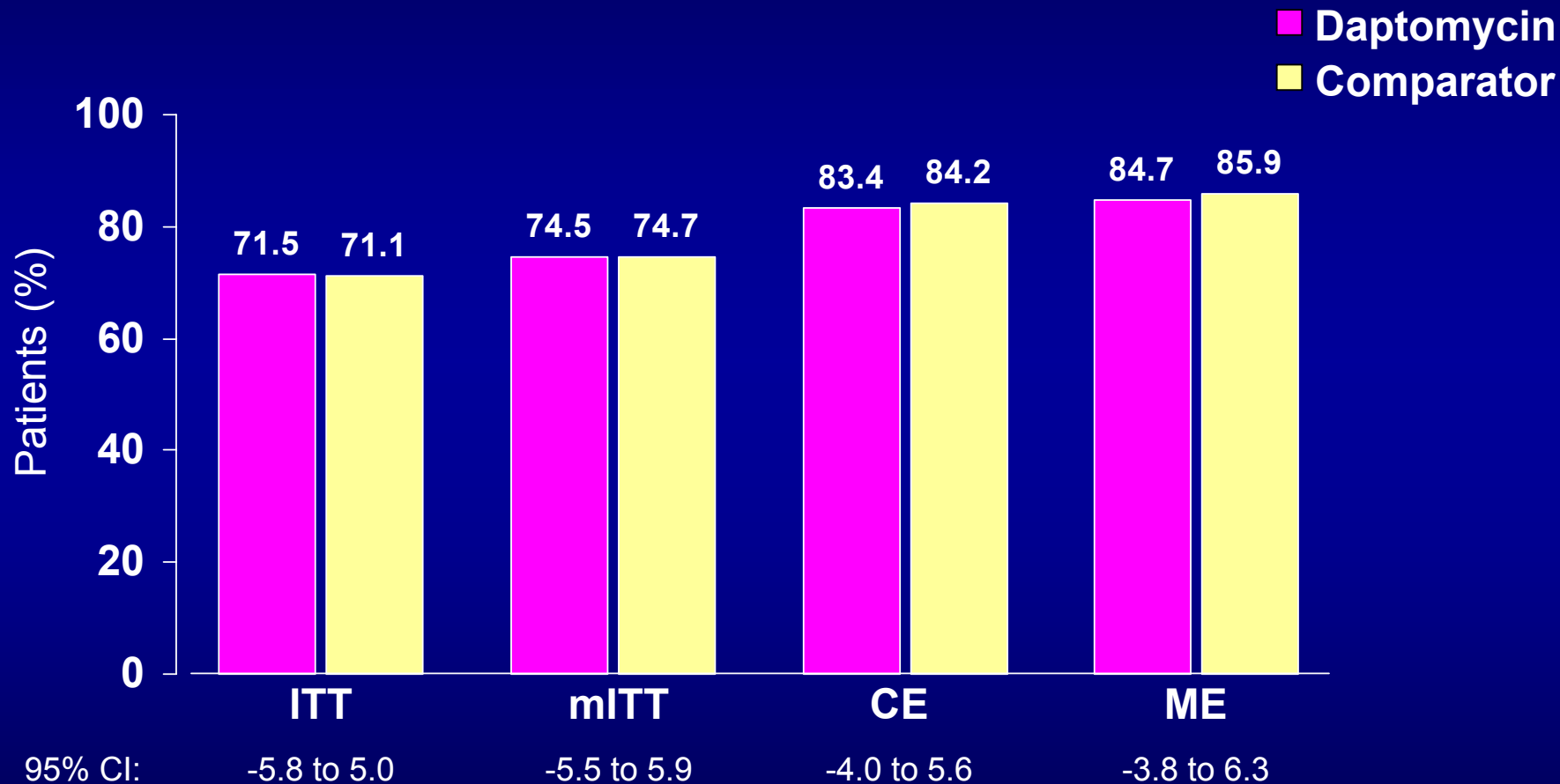


cSSTI trials: Gram-positive pathogens cultured from primary site of infection

Pathogen*	Daptomycin (n=428)		Comparator (n=506)	
	n	%	n	%
<i>Staphylococcus aureus</i> (MSSA)	231	54	239	50.7
<i>Staphylococcus aureus</i> (MRSA)	40	9.3	47	10
<i>Streptococcus pyogenes</i>	92	21.5	103	21.9
<i>Streptococcus agalactiae</i>	30	7	41	8.7
<i>Streptococcus dysgalactiae equismilis</i>	12	2.8	15	3.2
<i>Enterococcus faecalis</i>	45	10.5	61	13

*Patients may be infected with multiple Gram-positive pathogens at the primary site of infection

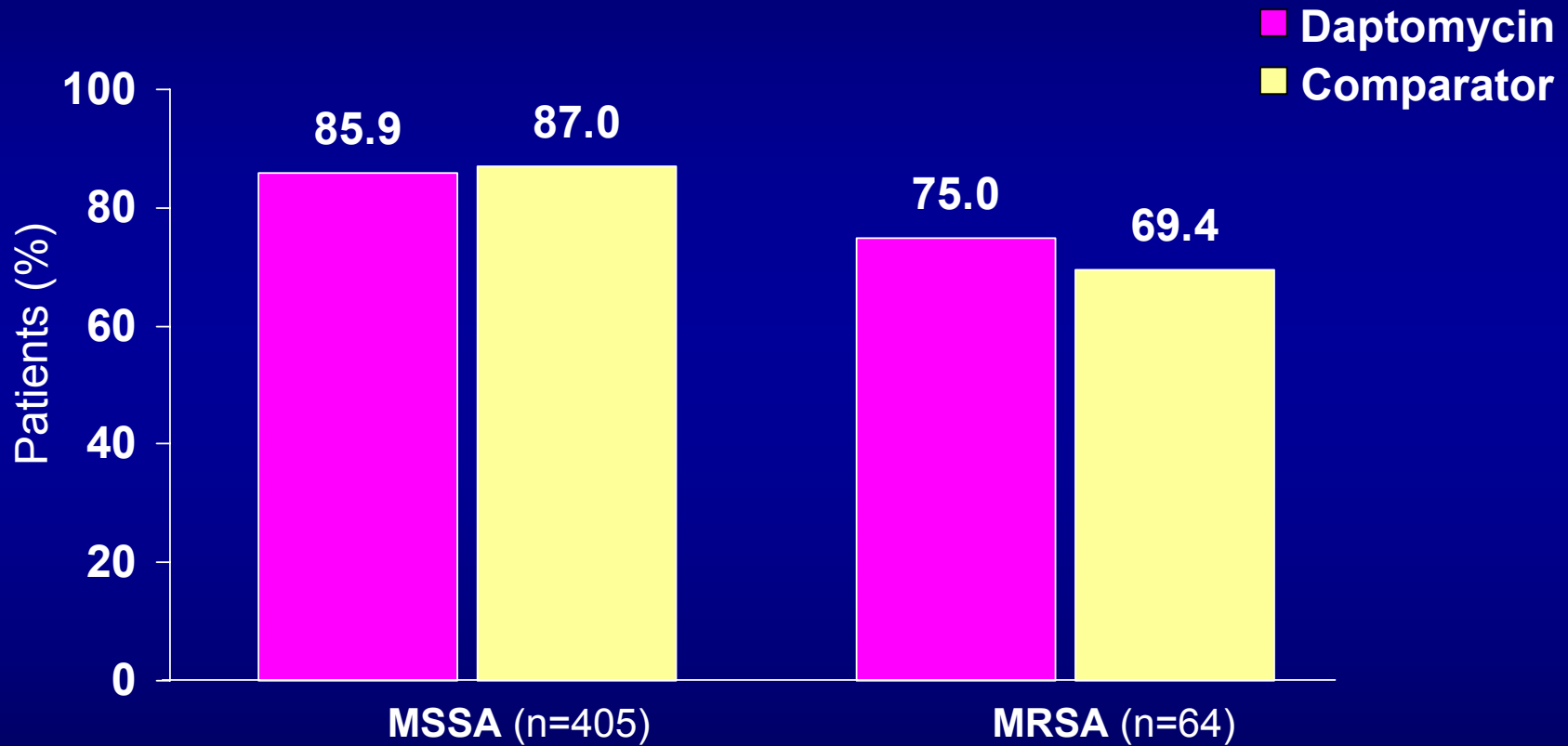
cSSTI trials: clinical success* of daptomycin vs comparators



ITT, intent-to-treat; mITT, modified intent-to-treat;
CE, clinically evaluable; ME, microbiologically evaluable

*Cure or improvement sufficient
to stop antibiotic treatment

cSSTI trials: clinical success* in *S. aureus* infected patients (ME)



95% CI:

-5.6 to 7.8

-28.5 to 17.4

ME, microbiologically evaluable

*Cure or improvement sufficient to stop antibiotic treatment

cSSTI trials: duration of effective IV therapy*

Duration of IV therapy	Daptomycin	Comparator
4 to 7 days	63%**	33%**
≥8 days	37%	67%

*Patients who were successfully treated with IV therapy alone (89.8% of total)

**p<0.001

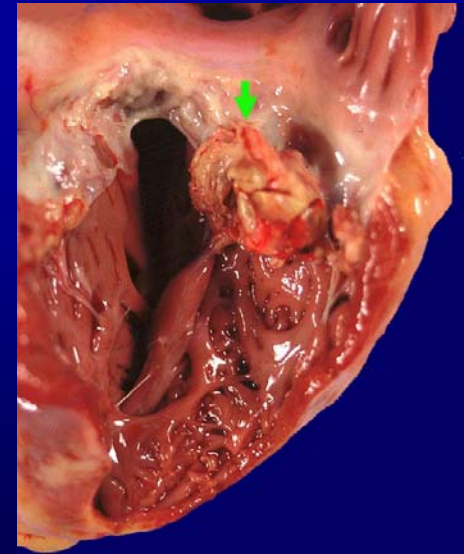
cSSTI trials: incidence (%) of adverse events occurring in $\geq 3\%$ of patients

Adverse event	Daptomycin (%, n=534)	Comparator (%, n=558)
Constipation	6.2	6.8
Nausea	5.8	9.5
Injection site reaction	5.8	7.7
Headache	5.4	5.4
Diarrhea	5.2	4.3
Insomnia	4.5	5.4
Rash	4.3	3.8
Vomiting	3.2	3.8
Abnormal liver function test results	3.0	1.6
Pruritus	2.8	3.8
Fungal infection	2.6	3.2

Elevated serum creatine phosphokinase (CPK) levels: 2.8% (daptomycin) & 1.8% (comparator)

***S. aureus* bacteremia and IE trial: background**

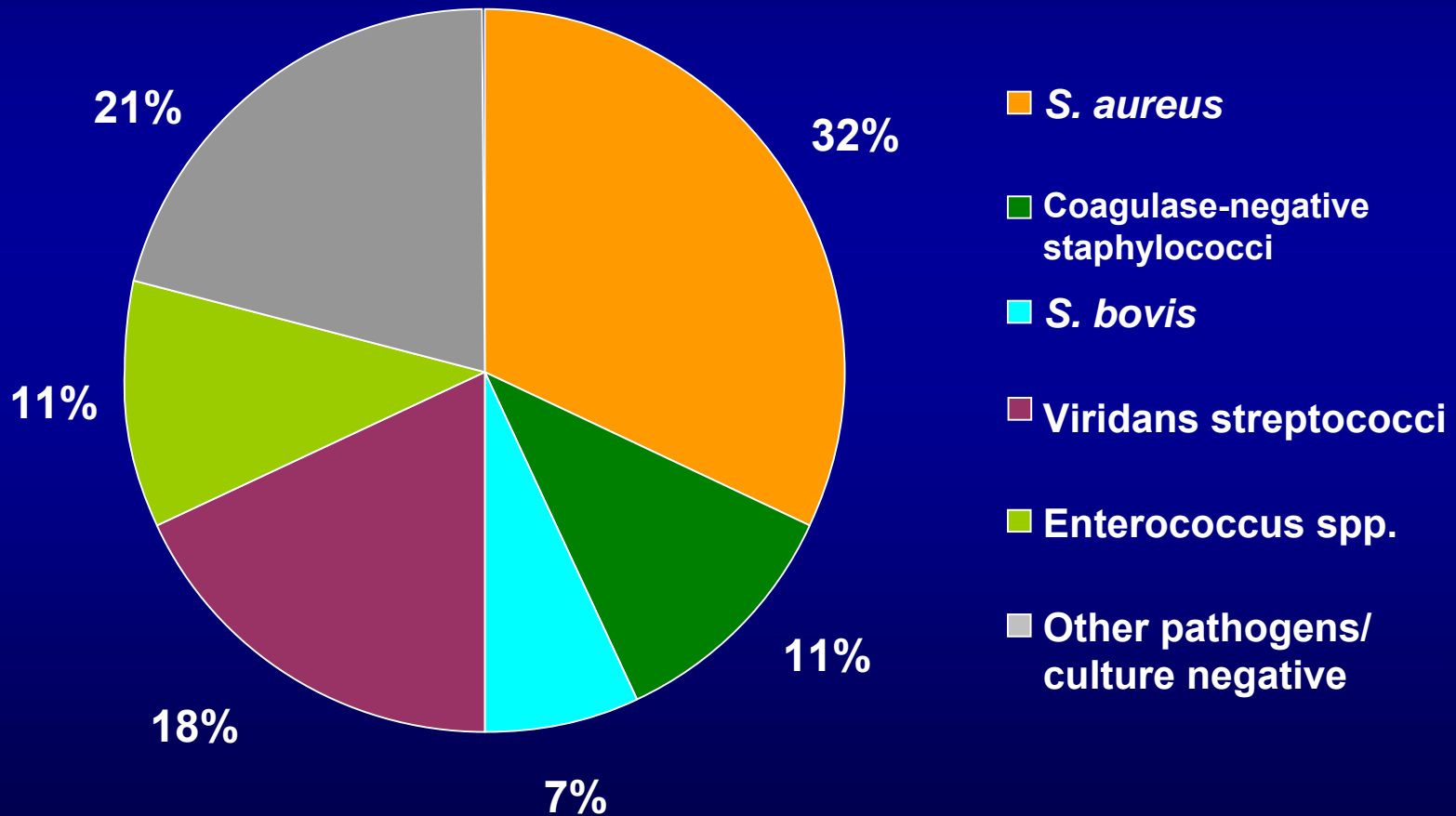
- **>150,000 patients treated with daptomycin since registration**
 - No new toxicities
- **Supportive data for dosing at ≥ 6 mg/kg from 15 other trials**
 - 414 subjects and patients



Frequency of *S. aureus* in infective endocarditis

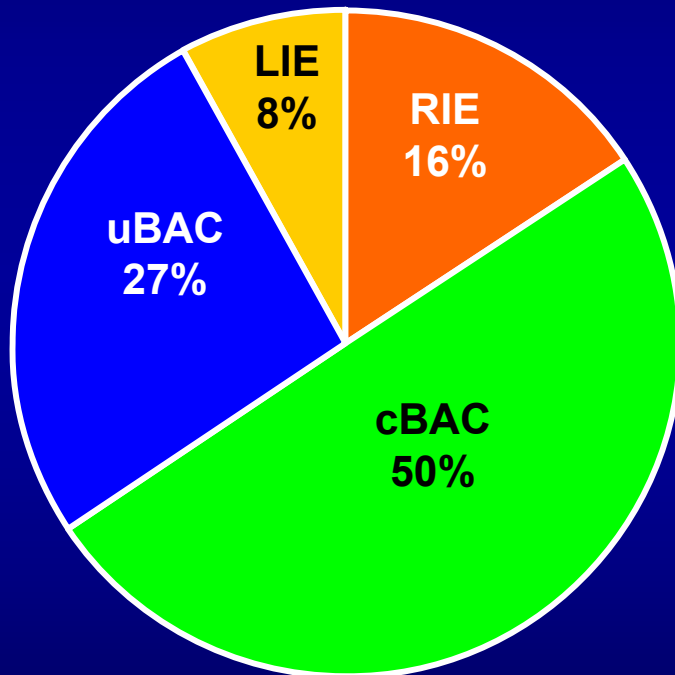
- International Collaboration on Endocarditis (ICE)

- ~1700 prospective infective endocarditis cases from 16 countries

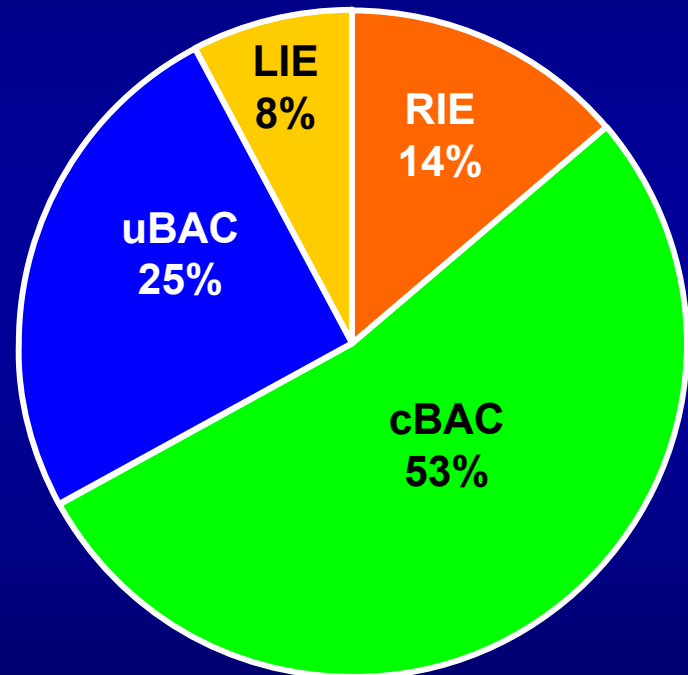


S. aureus bacteremia and IE trial: final diagnosis (mITT)

**Daptomycin group
N=120**

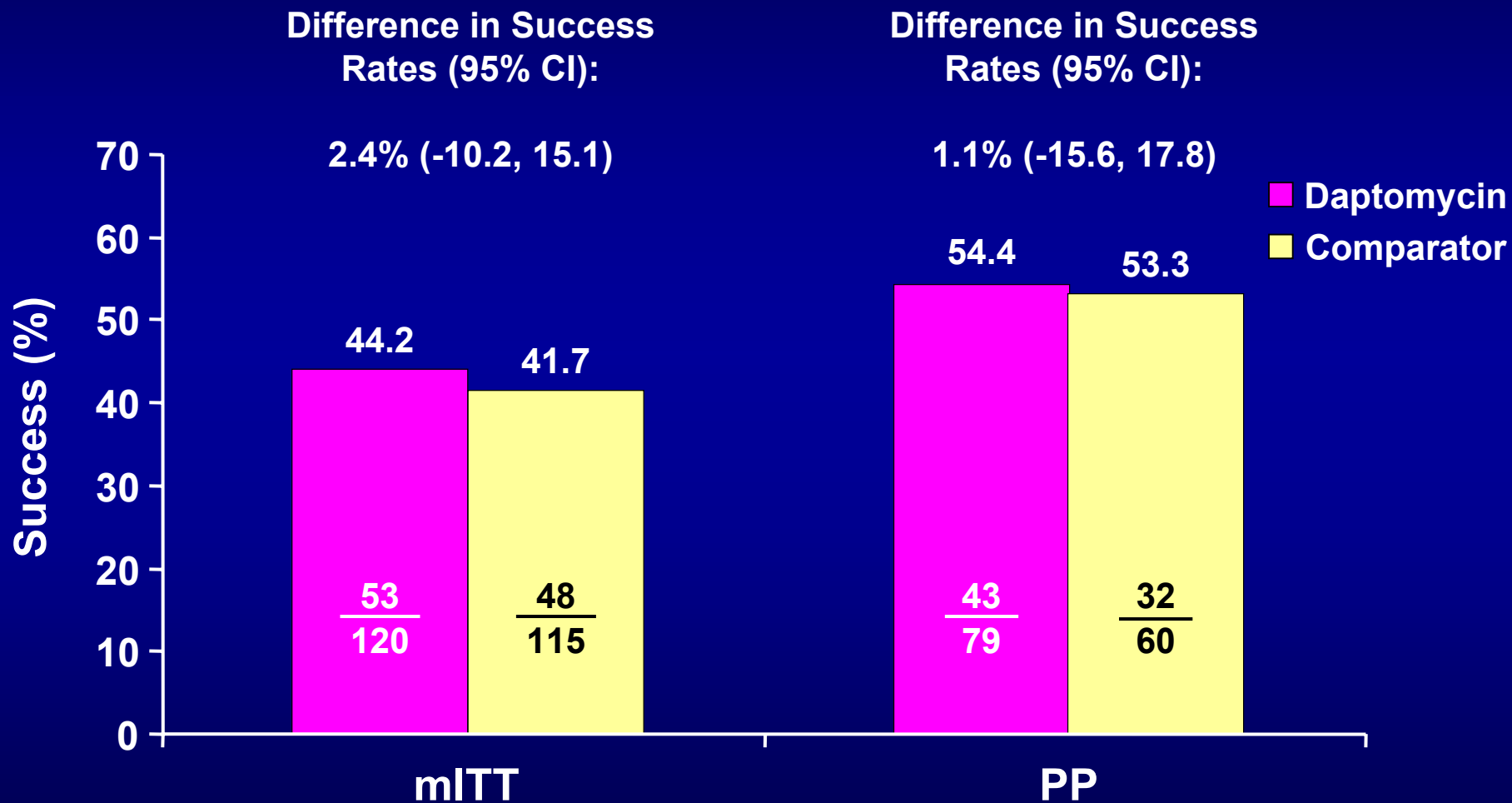


**Comparator group
N=115**

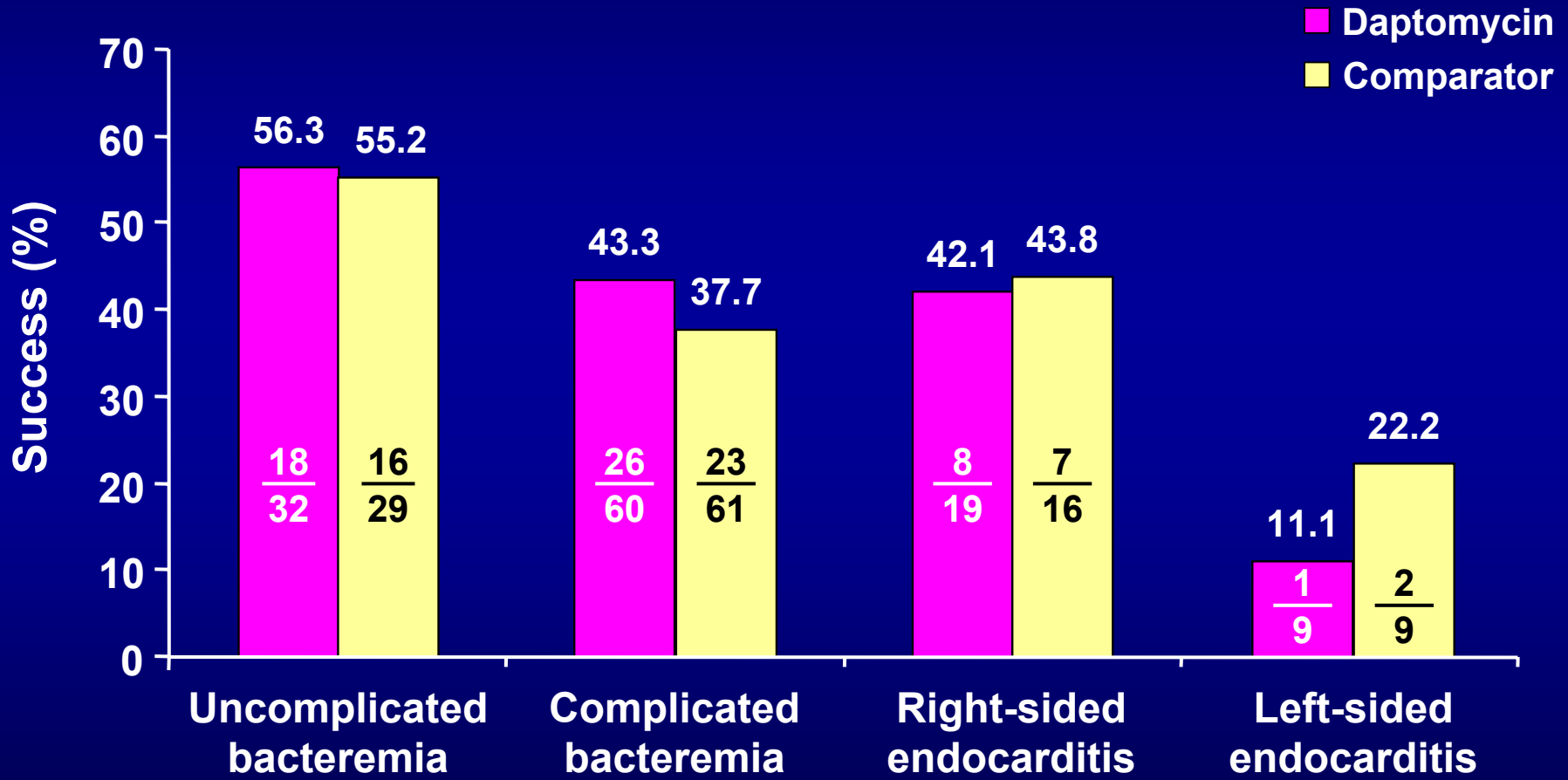


cBAC, complicated bacteremia; uBAC; uncomplicated bacteremia;
LIE, left-sided infective endocarditis; RIE, right-sided infective endocarditis

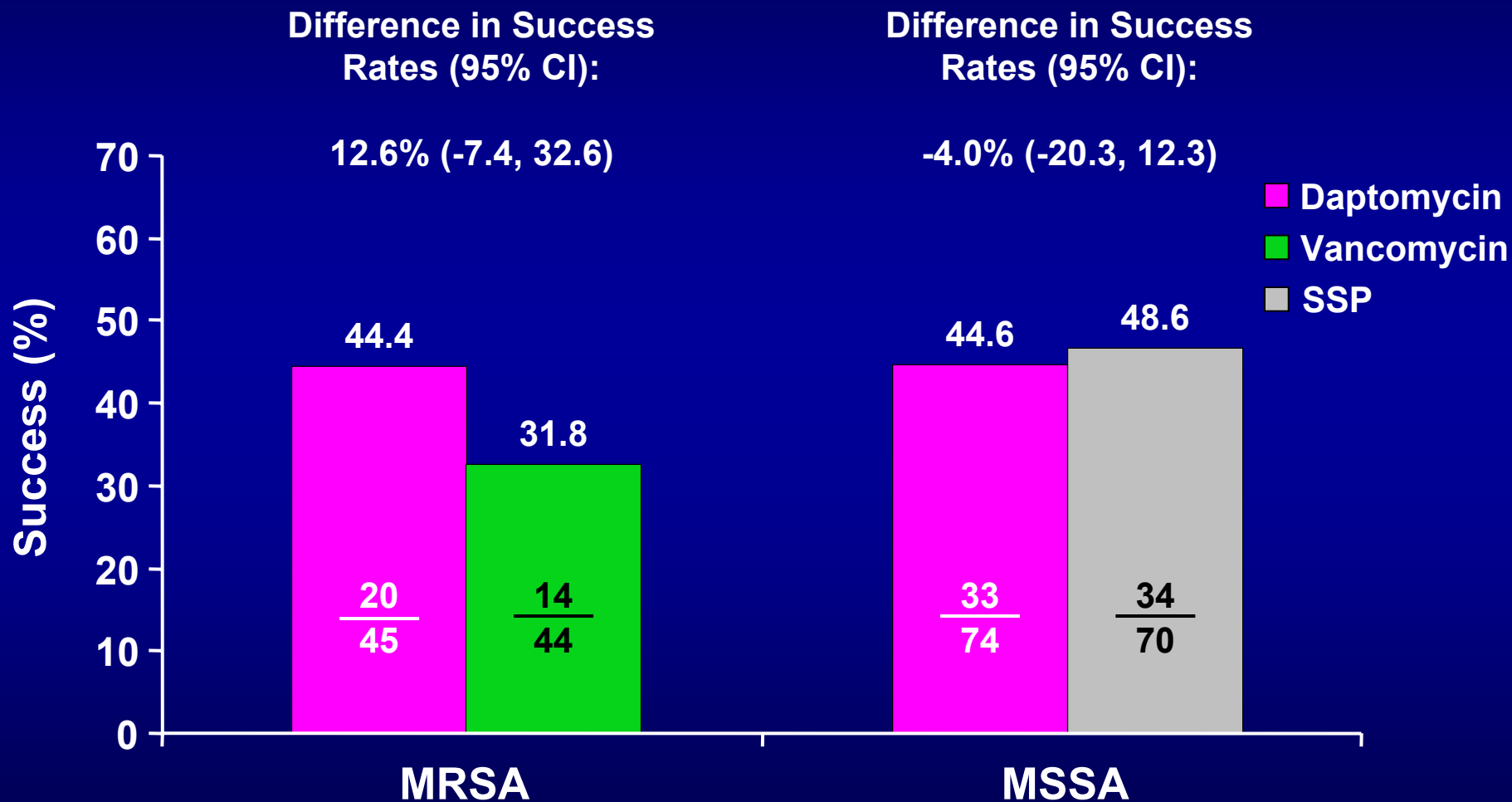
S. aureus bacteremia and IE trial: primary endpoint – success at TOC (mITT/PP)



S. aureus bacteremia and IE trial: final diagnosis – success at TOC (mITT)



S. aureus bacteremia and IE trial: MRSA and MSSA success at TOC – pathogen specific therapy (mITT)



***S. aureus* bacteremia and IE trial: all reasons for failure at TOC (mITT)**

	Daptomycin N=120 n (%)	Comparator N=115 n (%)
Overall failure	67 (55.8)	67 (58.3)
<i>Reason for failure (more than one reason may be indicated for each patient)</i>		
Persisting or relapsing <i>S. aureus</i> infection	19 (15.8)	11 (9.6)
Death	13 (10.8)	13 (11.3)
Clinical failure without persisting/relapsing <i>S. aureus</i>	4 (3.3)	4 (3.5)
Treatment-limiting adverse events	8 (6.7)	17 (14.8)
Non-study antibiotics	20 (16.7)	16 (13.9)
No blood culture	9 (7.5)	12 (10.4)
Non-evaluable (e.g. withdrew consent, left hospital against medical advice)	9 (7.5)	14 (12.2)

***S. aureus* bacteremia and IE trial: reasons for failure (mITT)**

	n (%)	
	Daptomycin N=120	Comparator N=115
Patient could not be evaluated (e.g. withdrew consent, completed <4 days of therapy)	9 (7.5)	14 (12.1)
Lack of efficacy*	27 (22.5)	22 (19.1)
Treatment-limiting AE	7 (5.8)	12 (10.4)
Potentially effective non-study antibiotic	15 (12.5)	9 (7.8)
No blood culture	7 (5.8)	9 (7.8)
d/c for other reasons	2 (1.7)	1 (0.9)
Total	67 (55.8)	67 (58.3)

***S. aureus* bacteremia and IE trial: failure due to persisting/relapsing *S. aureus* – emergence of reduced susceptibility to daptomycin**

Patient ID	Final Diagnosis	Baseline Pathogen	Duration of Therapy (days)	Baseline MIC (µg/mL)	Highest MIC (µg/mL)	Clinical Summary
037	LIE	MRSA	7	0.25	2	Mitral/aortic IE
183	LIE	MRSA	8	0.5	2	Mitral IE, stroke
152	RIE	MSSA	20	0.25	4	Tricuspid IE, large pulmonary emboli, tunnel infection
212	cBAC	MRSA	14	0.25	2	IV port infection
105	cBAC	MRSA	23	0.25	2	Septic arthritis
136	cBAC	MRSA	35	0.5	2	Undiagnosed retroperitoneal abscess

***S. aureus* bacteremia and IE trial: vancomycin patients with increased vancomycin MICs**

Pt ID	Final Dx	Baseline Pathogen	Duration of Tx (days)	Baseline MIC (µg/mL)	Highest MIC (µg/mL)	Clinical summary
043	LIE	MRSA	27	0.5	≤2 (local)	Mitral IE, stroke, intramural abscess and death
038	cBAC	MRSA	26	0.5–1	2 (central) 2 (local)	Enterocutaneous fistulae, inadequately drained subphrenic abscess, septic thrombophlebitis
169	cBAC	MRSA	15	0.5–1	8 (local)	Psoas and scrotal abscesses, MRSA pneumonia
206	cBAC	MRSA	13	0.5–1	2 (local)	Cutaneous T-cell lymphoma, infected ulcers
237	cBAC	MRSA	35	0.5	2 (local)	Sternal osteomyelitis
113	uBAC	MRSA	19	0.5	2 (local)	Abdominal wound/mesh, skin graft, graft failure

S. aureus bacteremia and IE trial: safety data

Overview of adverse events (AEs)	Daptomycin N=120 %	Comparator N=116 %
Any drug-related AE	35.0	42.2
Any serious AE (SAE)	51.7	44.8
Any drug-related SAE	2.5	5.2
Deaths	15.0	16.4
Study drug d/c due to drug-related AE	8.3	11.2
Most Common ($\geq 10\%$) AEs		
Anemia	12.5	15.5
Diarrhea	11.7	18.1
Vomiting	11.7	12.9
Constipation	10.8	12.1
Nausea	10.0	19.8
Hypokalemia	9.2	12.9
Renal impairment	6.7	18.1
Headache	6.7	10.3
Peripheral edema	6.7	13.8
Arthralgia	3.3	11.2

d/c, discontinuation

***S. aureus* bacteremia and IE trial: maximum CPK in patients with CPK elevation on treatment**

Safety Population

	Daptomycin N=120 n (%)	Comparator N=116 n (%)
Number of patients with CPK > 500	11 (9.2)	2 (1.7)
Maximum CPK (U/L)		
> 500–1000	4 (3.3)	1 (<1.0)
> 1000–2000	3 (2.5)	0
> 2000–3000	1 (<1.0)	1 (<1.0)
> 3000–4000	2 (1.7)	0
> 4000–5000	0	0
> 5000*	1 (<1.0)	0

*Maximum post-baseline CPK 5548 U/L

Fowler *et al.* *New Engl J Med* 2006; 355: 653–65
Vigliani. AIDAC meeting, March 2006; www.fda.gov

S. aureus* bacteremia and IE trial: clinically significant decrease in renal function*

Safety Population

	Daptomycin N=118 n (%)	Comparator N=114 n (%)	P-value*
Clinically significant decrease in renal function**			
Through end of study	13 (11.0)	30 (26.3)	0.004

***Fisher's exact test**

****Renal failure: treatment-emergent CrCl <50 mL/min (if baseline \geq 50 mL/min)
or a decrease of \geq 10 mL/min (if baseline <50 mL/min)**

Summary (1)

- **cSSTI trials**

- **Daptomycin equally as effective as comparators in treating a wide range of cSSTIs**
- **At least as effective as comparators in treating cSSTIs caused by MRSA**
- **Effective in patients with serious infections**
- **Safety and tolerability profile similar to those of comparators**

Summary (2)

- ***S. aureus* bacteremia and IE trial**
 - Primary efficacy endpoint met in ITT and PP populations
 - Daptomycin response higher than vancomycin response in MRSA
 - Efficacy results robust and consistent
 - Across pre-specified subgroups
 - Per adjudication committee and investigator
 - Well tolerated for extended treatment durations
 - Less nephrotoxic than standard-of-care agents
 - Daptomycin (6 mg/kg IV once daily) effective in the treatment of patients with *S. aureus* bacteremia including those with known or suspected endocarditis