P0900

Real-world use of daptomycin across a wide range of geographical regions: A pooled analysis from the CORE and EU-CORE registries

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INTRODUCTION AND PURPOSE

- Infections caused by resistant Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), are difficult-to-treat and often associated with increased morbidity, mortality and healthcare expenditures in hospitalised patients[1,2]
- Daptomycin, a cyclic lipopeptide antibiotic with rapid bactericidal activity against wide range of Gram-positive pathogens including MRSA and VRE, is approved for the treatment of complicated skin and soft tissue infection (cSSTI; 4 mg/kg/day), right-sided infective endocarditis (RIE) due to *S. aureus*, and bacteraemia associated with cSSTI and RIE (6 mg/kg/day)[3]
- Cubicin® Outcome Registry and Experience (CORE) and European Cubicin® Outcomes Registry and Experience (EU-CORE) are two multicentre, retrospective, non-interventional registries, designed to collect real-world data on clinical outcomes of daptomycin treatment in patients with Gram-positive infections
- The data from both registries (conducted between 2004 and 2012) were pooled and analysed to understand the trend of prescribing patterns, duration of treatment, effectiveness and safety of daptomycin in a large number of patients across a wide geographical region

METHODS

- CORE included data from approximately 164 sites in the United States of America (USA)[4,5,6] and EU-CORE included data from 310 sites across 18 countries in Europe (12), Latin America (5) and Asia (1)[7]
- Data from both registries were collected for patients treated with at least one dose of daptomycin between 2004 and 2012 with ≥30 days of safety follow-up using standardised case report forms
- Post-treatment follow-up data for up to 2 years were collected for a subset of patients (CORE: osteomyelitis/orthopaedic foreign body device infections; EU-CORE: endocarditis, intracardiac/intra-vascular device infections and osteomyelitis/orthopaedic device infections)
- In both registries, the overlapping data collection period was from 2007 to 2009
- Patients who had received daptomycin as part of a controlled clinical trial were excluded
- The clinical outcome was assessed as success (cured or improved), failure or non-evaluable, both at the end of daptomycin treatment and at follow-up (**Table 1**)

Table 1. Definitions of clinical outcomes

Response*		
Success (cured or improved)	**Cured** • Clinical signs and symptoms resolved (and/or) • No additional antibiotic therapy necessary (or) • Negative culture at the end of therapy	**Improved** • Partial resolution of clinical signs and symptoms (and/or) • Additional antibiotic therapy warranted
Failure	• Inadequate response to daptomycin therapy • Worsening or new/recurrent signs and symptoms • Need for a change in antibiotic therapy (or) • Positive culture reported at the end of therapy	
Non-evaluable	• Unable to determine response due to insufficient information	

*Assessed by the investigator

- All reports of adverse events (AEs) and serious AEs (SAEs) were recorded, regardless of their relationship to daptomycin therapy

RESULTS

- A total of 11557 patients (CORE, 5482; EU-CORE, 6075) treated with daptomycin were included in the analysis. Demographics and baseline characteristics are presented in **Table 2**
- The majority of patients (89%) had significant underlying diseases (**Table 2**)

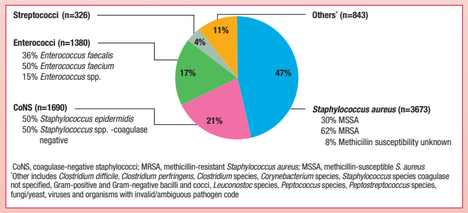
Table 2. Patient demographics and baseline characteristics

Parameters	N=11557 n (%)*
Gender, male	6587 (57)
Age† (years), median (range)	62 (1–103)
<65 years	7111 (62)
≥65 years	4441 (38)
≥75 years	1732 (15)
Body weight (kg), median (range)	78 (6–275)
Race, Caucasian	7191 (62)
Significant underlying diseases (>10% patients)	10255 (89)
Cardiovascular disease	6321 (55)
Diabetes mellitus	3234 (28)
Gastrointestinal disease	1579 (14)
Oncologic disease	1931 (17)
Pulmonary disease	1791 (16)
Renal disease	1923 (17)

*Unless otherwise indicated
†Data missing for five patients

- The most commonly isolated pathogen was *S. aureus* (**Figure 1**)
- The most common primary infections were cSSTIs (31%) and bacteraemia (22%) (**Table 3**)

Figure 1. Primary infecting pathogens



CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*
*Other includes *Clostridium difficile*, *Clostridium perfringens*, *Clostridium* species, *Corynebacterium* species, *Staphylococcus* species coagulase not specified, Gram-positive and Gram-negative bacilli and cocci, *Leuconostoc* species, *Peptococcus* species, *Peptostreptococcus* species, fungi/yeast, viruses and organisms with invalid/ambiguous pathogen code

Table 3. Primary infections

Infections	N=11557 n (%)
Complicated skin and soft tissue infection	3607 (31)
Bacteraemia	2522 (22)
Endocarditis	798 (7)
Foreign body/prosthetic infection	988 (9)
Osteomyelitis (non-prosthetic and prosthetic device-related)	994 (9)
Uncomplicated skin and soft tissue infection	1510 (13)
Other*	1138 (10)

*Other includes septic arthritis, urinary tract infections/pyelonephritis, central nervous system infections, metastatic abscess, antibiotic prophylaxis (surgical and nonsurgical), neutropenic fever, necrotizing fasciitis, necrotizing infections, unknown or not otherwise specified infections, and missing data

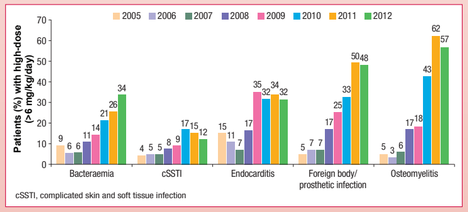
Prior and concomitant antibiotic therapy

- In total, 71% patients received antibiotics prior to daptomycin treatment
- Daptomycin was used concomitantly with other antibiotics in 57% inpatients; the frequently administered antibiotics were carbapenems (18%), penicillins (12%), fluoroquinolones (11%) and cephalosporins (10%)

Dosage and duration of daptomycin therapy

- The most commonly prescribed dose of daptomycin was 6 mg/kg/day in 4968 (43%) patients; 1564 (13.5%) patients received higher doses (>6 mg/kg/day)
- The median (range) overall duration of daptomycin treatment was 12 (1–370) days; 8 (1–246) days for inpatients and 16 (1–358) days for outpatients
- An increasing trend towards prescription of high-dose daptomycin (>6 mg/kg/day) was observed over time: mainly for bacteraemia, osteomyelitis and foreign body/prosthetic infections (**Figure 2**)

Figure 2. Prescribing pattern of high-dose daptomycin over time

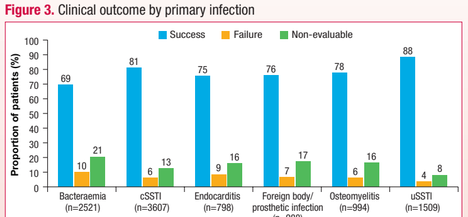


cSSTI, complicated skin and soft tissue infection

Treatment outcomes

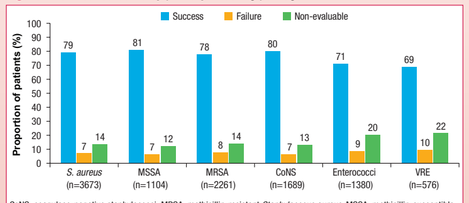
- Overall, a clinical success rate of 77% was reported with daptomycin treatment. Clinical outcomes by the most frequent primary infections and by primary infecting pathogens are presented in **Figure 3** and **Figure 4**, respectively

Figure 3. Clinical outcome by primary infection



cSSTI, complicated skin and soft tissue infection; uSSTI, uncomplicated skin and soft tissue infection

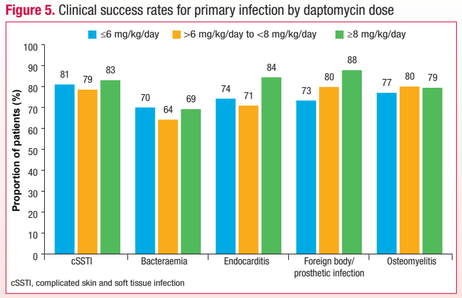
Figure 4. Clinical outcome by primary infecting pathogen



CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; VRE, vancomycin-resistant enterococci

- During the overlapping period (2007–2009) both CORE and EU-CORE recorded similar clinical success rates (72% and 78%, respectively)
- Clinical success rate was higher (80%) when daptomycin was used as first-line therapy than that when used as second-line therapy (76%)
- Higher daptomycin doses were associated with greater clinical success rates for some infections, particularly for endocarditis and foreign body/prosthetic infections (**Figure 5**)

Figure 5. Clinical success rates for primary infection by daptomycin dose



cSSTI, complicated skin and soft tissue infection

Safety and tolerability

- Overall AEs and SAEs, regardless of their relationship to daptomycin treatment, were reported in 1879 (16.3%) and 1050 (9.1%) patients, respectively
- AEs possibly related to daptomycin treatment were reported in 628 (5.4%) patients (**Table 4**)
- Elevation in blood creatine phosphokinase levels as an AE possibly related to daptomycin treatment was reported in 175 (1.5%) patients
- SAEs possibly related to daptomycin treatment were reported in 133 (1.2%) patients
- Study drug discontinuation occurred in 519 (4.5%) patients due to AEs regardless of their relationship to daptomycin treatment

Table 4. AEs possibly related to daptomycin

	N=11557 n (%)
AEs by preferred term (>0.1% patients)	
Blood creatine phosphokinase increased	175 (1.5)
Diarrhoea	52 (0.4)
Nausea	44 (0.4)
Rash	50 (0.4)
Blood creatinine increased	18 (0.2)
Myalgia	21 (0.2)

AE, adverse event

CONCLUSIONS

- The present analysis re-affirms the real-world safety and effectiveness of daptomycin across wide geographical regions including the USA and Europe
- The real-world data suggests that daptomycin is effective and well tolerated for management of difficult-to-treat infections caused by various Gram-positive pathogens, including those caused by resistant strains (MRSA and VRE)

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Disclosures
CORE was funded by Cubist Pharmaceuticals and EU-CORE by Novartis Pharma AG.
Acknowledgements: All authors participated in the development of this poster and approved the final poster for presentation. The authors acknowledge the work of the CORE and EU-CORE investigators, Kenneth Lamp (previous medical director, CORE) and Uwe Trostmann (previous clinical scientist, EUCORE). The authors thank Rohita Gattoju (Novartis) for medical writing support and Anand Durgam (Novartis) for design support.

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