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Daptomycin-containing regimens for treatment of Gram-positive endocarditis

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ABSTRACT

Purpose: Infective endocarditis (IE) is a severe infection, and a leading cause of mortality and morbidity. Due to its favourable microbiological and pharmacological characteristics, daptomycin is routinely used in clinical practice for treating IE.

Methods: A prospective study was conducted at a large tertiary-care hospital in Italy over an 8-year period (January 2010–January 2018) on all patients with native-valve endocarditis (NVE) or prosthetic-valve endocarditis (PVE) caused by Gram-positive bacteria. Patients with NVE and PVE treated with regimens that included daptomycin at different dosages (daptomycin-containing regimens, DCR) were compared with those treated with non-DCR. Primary endpoints of the study were 30-day mortality and clinical treatment failure.

Results: During the study period, 327 patients with Gram-positive NVE (n = 224, 68.8%) or PVE (n = 103, 31.2%) were analysed. Eighty-four (37.5%) NVE patients were treated with daptomycin, alone (59.9%) or with other antimicrobials. Most PVE patients (n = 61, 58%) were treated with a DCR, which always consisted of daptomycin plus other drugs. Among PVE patients, treatment with a DCR was associated with lower 30-day mortality than treatment with a non-DCR (6.5% vs. 38%, $P < 0.001$). Among NVE patients treated with DCRs, risk factors for 30-day mortality were streptococcal infections, persistent bacteraemia, and standard-dose (4–6 mg/kg) rather than high-dose daptomycin therapy. Overall, surgical treatment of IE and DCR were associated with clinical success and 30-day survival.

Conclusions: Compared with non-DCRs, using single-drug or multiple-drug DCRs is associated with lower 30-day mortality in PVE, but with higher 30-day mortality in NVE at approved doses and in a subgroup of streptococcal IE.

1. Introduction

Infective endocarditis (IE) is a life-threatening systemic infection involving cardiac valves. It is associated with substantial morbidity and high rates of mortality [1]. Gram-positive bacteria – including staphylococci, streptococci, and enterococci – are the predominant causes of IE [2], and the rates of antimicrobial resistance among these organisms have recently increased worldwide [3].

Daptomycin displays bactericidal activity against *Staphylococcus aureus* (including methicillin-resistant strains, MRSA), coagulase-negative staphylococci, and enterococci (including those that are vancomycin-resistant). It exerts intense activity in biofilm-associated infections and reaches adequate concentrations in endocardial vegetations [4,5]. It is therefore an attractive and widely used option for the management of IE [6]. Daptomycin is currently approved for the treatment of right-sided IE at a daily dose of 6 mg/kg [7]. However, in clinical practice the drug is also commonly prescribed to treat left-sided IE, but the dosage used in these cases is frequently higher (≥ 8 mg/kg/day) [8,9]. Studies that have been conducted to assess the efficacy and safety of these high-dose daptomycin regimens have revealed favourable outcomes, high rates of bacteraemia clearance, and acceptable safety profiles [10,11]. The efficacies of standard-dose and high-dose regimens in treating IE have not been compared in prospective studies. To address this gap, the current study prospectively analysed the clinical features and outcomes of over 300 cases of NVE or PVE treated with antimicrobial regimens containing daptomycin at various dosages, with or without other antimicrobials, and

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compared with single-drug or multidrug regimens that did not include daptomycin.

2. Patients and Methods

2.1. Patient Selection

A prospective observational study was conducted at a large tertiary-care hospital in Udine, Italy from January 2010 to January 2018. The study was preapproved by the local ethics committee and conducted in accordance with the principles of the Declaration of Helsinki. It consecutively enrolled all adult inpatients (age ≥ 18 years) with diagnoses of monomicrobial Gram-positive IE that satisfied the modified Duke criteria [12]. Patients were excluded from analysis if they did not complete > 50% of the antibiotic course recommended for IE by the American Heart Association [12].

2.2. Data collection and definitions

Patients' data from medical records, computerised hospital databases, and/or clinical charts were prospectively collected using a standard form. Data included: demographics, clinical and laboratory findings, baseline comorbidities, IE-affected valve(s), occurrence of IE relapse, microbiological data, the Charlson Comorbidity Index, date and type of previous cardiac surgery (if performed), immunosuppressive therapy, source of infection, date and results of transthoracic (TTE) or trans-oesophageal (TEE) echocardiography, any cardiac complications, peripheral embolism, peripheral septic thrombophlebitis, ischaemic stroke, persistent bacteraemia, worsening renal function, date of any surgical treatment for IE, Euroscore II and Logistic Euroscore [13,14], transfer to intensive care unit (ICU), development of septic shock, duration of hospital stay, duration of definitive antibiotic therapy, new hospital admission per IE complications, clinical treatment failure, and 30-day mortality.

Definitive IE was defined according to modified Duke criteria [12], and septic shock was defined according to the criteria of the Surviving Sepsis Campaign [15]. The following definitions were established prior to data analysis: IE relapse – a new diagnosis of IE caused by the same organism after clinical and microbiological resolution of a previous episode of treated IE; TTE or TEE positivity – findings that revealed evidence of vegetation, fistula, abscess, peri-prosthetic leakage or dehiscence, pseudo-aneurysm, perforation, or valve aneurysm; time to surgery – the number of days that elapsed between diagnosis of IE and surgical treatment of the infection (when performed); persistent bacteraemia – blood culture positivity after 72 h of organism-specific targeted antibacterial treatment [16]; single-drug vs. multiple-drug treatment regimens – regimens that included one vs. more than one antimicrobial (with in vitro activity against the isolate); daptomycin-containing regimen (DCR) – any antimicrobial regimen that included daptomycin, alone or with one or more other antimicrobials (with in vitro activity against the isolate); standard vs. high daptomycin dosages – daily dosages of 4–6 mg/kg vs. ≥ 8 mg/kg, respectively; clinical treatment failure – lack of response to the definitive antimicrobial regimen, as reflected by the presence of any of the following after ≥ 45 days of therapy: ongoing fever, leucocytosis, or other clinical signs of infection that could not be attributed to causes other than IE; 30-day mortality – death from any cause within the 30 days following diagnosis of IE.

Synchronous or metastatic foci of infection were identified by means of clinical and imaging examinations. When present, fluid collections and abscesses were drained and the fluid was cultured. Coagulase-negative staphylococci (CoNS) and other skin commensals were considered aetiologically irrelevant unless they were isolated from two or more sets of blood cultures and their causative role was consistent with clinical data.

2.3. Statistical Analysis

Between-group differences were assessed with the χ^2 test or Fisher exact test (for categorical variables) and the two-tailed *t* test or Mann-Whitney test (for continuous variables), as appropriate. Univariate and multivariate analysis using a Cox regression model were used to determine the effects of different variables on 30-day mortality and clinical treatment failure rates in the cohort as a whole and subgroups thereof (NVE patients, PVE patients, patients treated with DCR). Wald confidence intervals and hazard ratios were computed based on estimated standard errors. Possible confounding factors and interactions were weighted during analyses. *P*-values of ≤ 0.05 were considered significant, and all reported *P*-values were two-tailed. All analyses were performed with the SPSS software package (version 20.0, SPSS Inc., Chicago, Illinois).

3. Results

The study cohort comprised 327 adults with Gram-positive IE (NVE in 224 (68.8%) cases, PVE in 103 (31.2%)) (Table 1). The mean ages of the NVE and PVE subgroups were similar (67.4 and 68.3 years, respectively). In both groups, the aortic valve was most frequently affected (51.7% of the NVE cases, 81.5% of those involving PVE). Infective endocarditis relapses occurred in 22 (21.3%) patients with PVE. Eighty-nine (86.4%) of the PVE patients and 111 with NVE (49.5%) underwent surgery for IE. The PVE group had higher mean Euroscores than the NVE group (Euroscore II: 11.8 ± 3.9 vs. 7.1 ± 3.1; logistic Euroscore: 33.8 ± 23.5 vs. 24.5 ± 7.2). Thirty-day mortality rates were similar in the two groups (22.3% in NVE, 19.4% in PVE), as were the rates of clinical treatment failure (4.4% in the NVE group vs. 5.8% in patients with PVE).

As for the aetiologies of the IE, staphylococcal species were the most commonly identified causes of NVE and PVE (Table 1). As shown in Fig. 1, most of the staphylococcal isolates recovered from NVE or PVE patients were *Staphylococcus aureus*, but the proportion of these isolates that were methicillin-resistant (MRSA) was far higher in the PVE group (43.7% vs. 13.5% of those in the NVE group). In both sub cohorts, less than 5% of the infections were attributed to CoNS. Streptococcal isolates were more than twice as common in the NVE group (n = 68, 30.3% vs. n = 15, 14.5% in the PVE group). The percentages of PVE and NVE cases attributed to enterococcal species were similar (13.5% of PVE cases vs. 12.9% of those in the NVE group) (Table 1), and in both subgroups, *Enterococcus faecalis* (Fig. 1) was the most commonly isolated species.

Reasons for daptomycin use among NVE and PVE patients are reported in Fig. 2. Daptomycin was used as first-line therapy for 26.2% of NVE and 41% of PVE; use of daptomycin for failure of previous therapy was recorded in 53.6% of patients with NVE and 41% with PVE; resistance to previous therapy was the reason for daptomycin use for 20.2% of NVE and 18% of PVE.

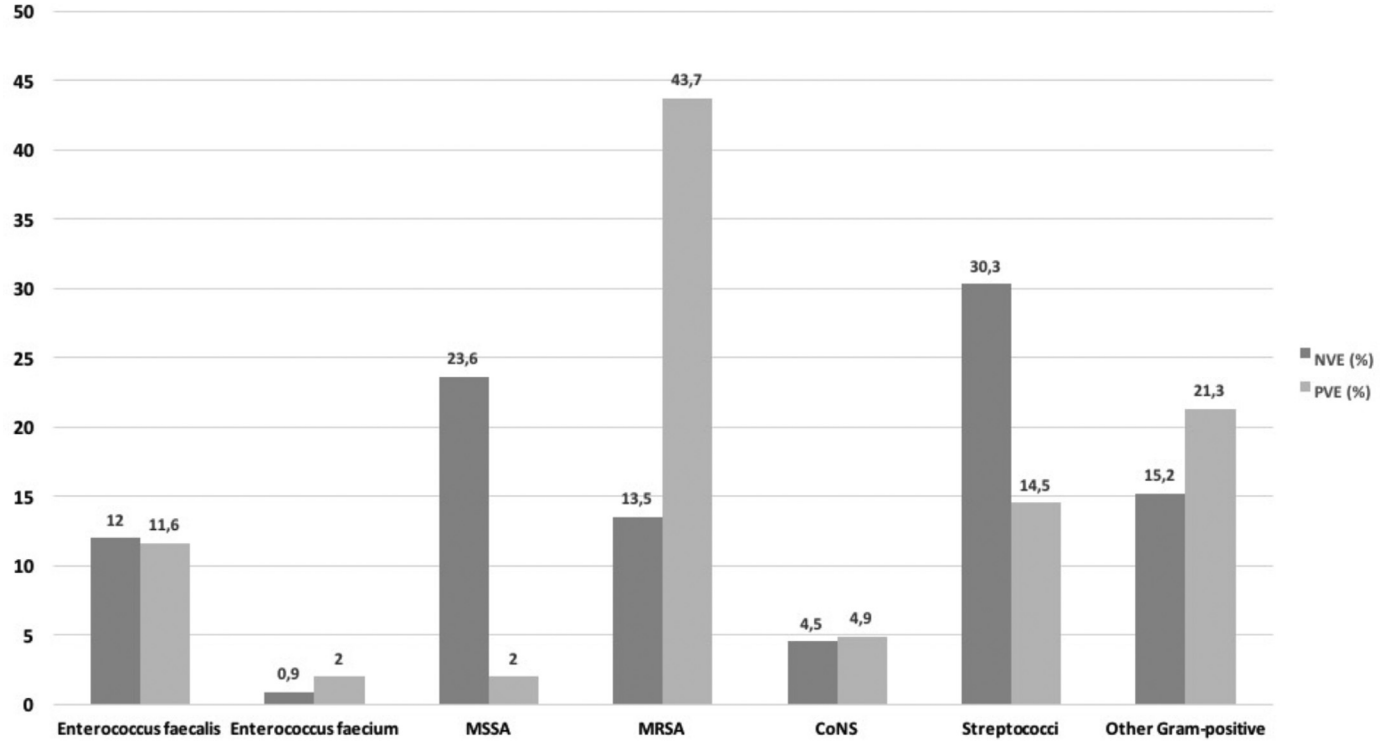
Fig. 3 shows the characteristics of the DCRs used to treat patients with NVE and PVE. In the NVE subgroup, well over half the DCRs consisted of daptomycin alone (59.5%); the multiple-drug DCRs used in this group mainly combined daptomycin with a ß-lactam (13.1%) or cephalosporin (13.1%). In the PVE group, DCRs always included one (83.6%) or two (16.4%) other antimicrobials, in most cases an aminoglycoside (62.4%) or rifampin (16.4%).

Univariate analysis of survivors compared with non-survivors at 30 days in NVE and PVE patients are reported in Table 2 and Table 3, respectively. In Table 2, chronic renal disease (60% vs. 24.7%, $P < 0.001$), transfer to ICU (40% vs. 14.9%, $P < 0.001$), septic shock (64% vs. 12.1%, $P < 0.001$), and clinical treatment

Table 1
Characteristics of patients with NVE or PVE.

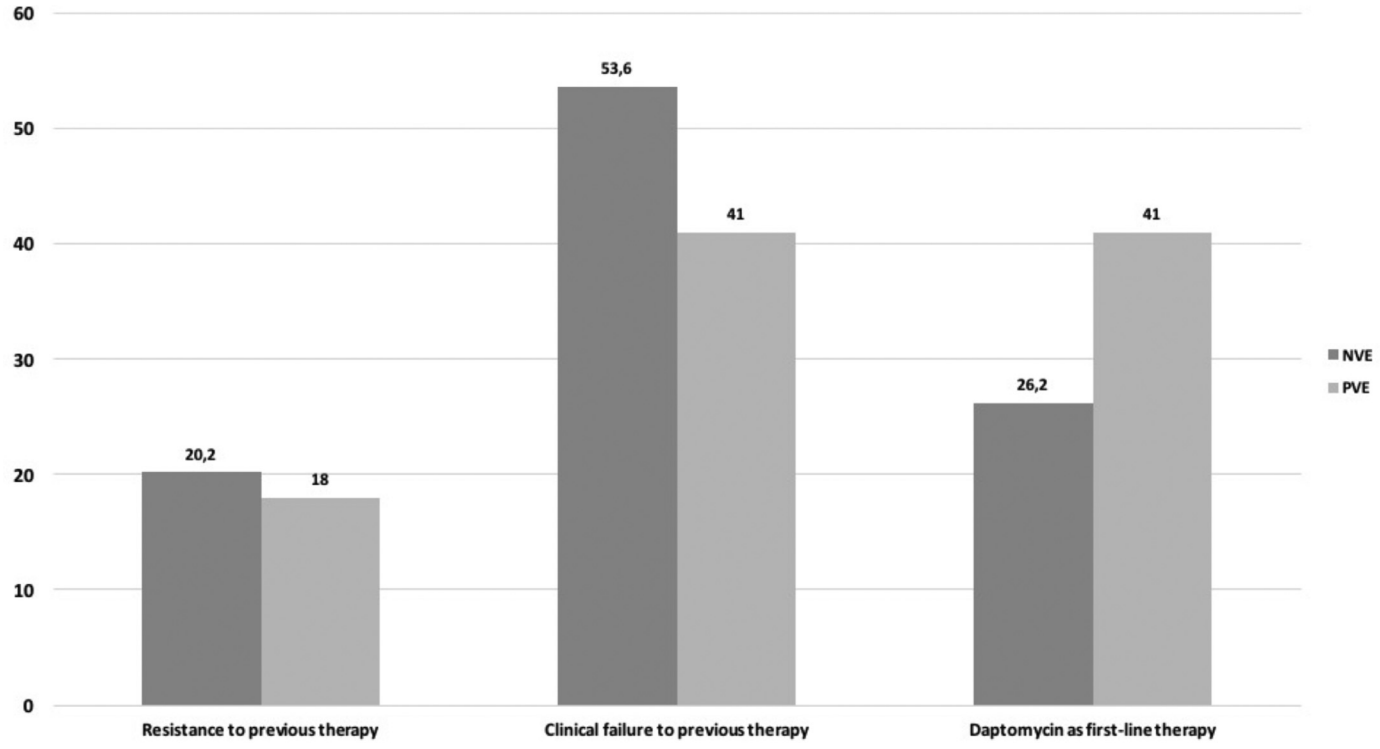
Variables	NVE N = 224 (%)	PVE N = 103 (%)
Age in years (mean ± SD)	67.4 ± 16.3	68.3 ± 17.1
Male sex	145 (64.7)	76 (73.7)
Comorbidities		
COPD	22 (9.8)	10 (9.7)
Coronary artery disease	33 (14.7)	42 (40.7)
Heart failure	32 (14.2)	20 (19.4)
Diabetes	63 (28.1)	24 (23.3)
Neurological disease	20 (8.9)	20 (19.4)
Cancer	23 (10.2)	6 (5.8)
Chronic renal disease	73 (32.5)	44 (42.7)
Dialysis	12 (5.3)	1 (0.9)
Chronic liver disease	16 (7.1)	6 (5.8)
SOT/HSCT	3 (1.3)	3 (2.9)
Active intravenous drug abuse	5 (2.2)	4 (3.8)
Charlson Comorbidity Index (mean ± SD)	4.1 ± 2.9	5 ± 2.4
Duke classification		
Definite IE	197 (87.9)	80 (77.6)
Possible IE	27 (12.0)	23 (22.3)
Affected valve(s)		
Mitral	110 (49.1)	25 (24.2)
Aortic	116 (51.7)	84 (81.5)
Tricuspid	12 (5.3)	2 (1.9)
Pulmonary	2 (0.9)	0
Two or more valves	16 (7.1)	8 (7.7)
Aetiology		
Enterococcal species	29 (12.9)	14 (13.5)
Streptococcal species	68 (30.3)	15 (14.5)
Staphylococcal species	93 (41.5)	52 (50.4)
Other Gram-positive species	34 (15.1)	22 (21.3)
Previous cardiac surgery	19 (8.4)	103 (100.0)
Immunosuppressive therapy	5 (2.2)	3 (2.9)
Source of IE		
Dental procedure	9 (4.0)	4 (3.8)
Urinary tract infection	8 (3.5)	0
SSTI	34 (15.1)	9 (8.7)
Intra-abdominal infection	15 (6.6)	10 (9.7)
Previous invasive procedure	26 (11.6)	19 (18.4)
Positive echocardiogram		
TTE	187 (83.4)	78 (75.7)
TEE	184 (82.1)	83 (80.5)
Cardiac complications		
Perforation or rupture	13 (5.8)	1 (0.9)
Aneurysm	2 (0.9)	1 (0.9)
Abscess	24 (10.7)	42 (40.7)
Fistula	7 (3.1)	13 (12.6)
Prosthesis dislocation	–	41 (39.8)
New valvular failure	30 (13.3)	23 (22.3)
Others complications		
Peripheral embolism	110 (49.1)	34 (33.0)
Peripheral septic thrombophlebitis	1 (0.4)	2 (1.9)
Ischaemic stroke	83 (37.0)	46 (44.6)
Persistent bacteraemia	4 (1.7)	3 (2.9)
Septic shock	53 (23.6)	19 (18.4)
Worsening renal function	34 (15.1)	12 (11.6)
Treatment		
Surgery for IE	111 (49.5)	89 (86.4)
Time to surgery (days), (mean ± SD)	33.1 ± 23.2	25.8 ± 18.9
Euroscore II (mean ± SD)	7.1 ± 3.1	11.8 ± 3.9
Logistic Euroscore (mean ± SD)	24.5 ± 7.2	33-8 ± 23.5
Time to definitive therapy (days), (mean ± SD)	6.4 ± 3.5	8.1 ± 5.2
Duration of definitive antibiotic therapy (days), (mean ± SD)	52.2 ± 41.5	59.3 ± 27.1
DCR	84 (37.5)	61 (59.2)
Outcomes		
Clinical treatment failure	10 (4.4)	6 (5.8)
30-day mortality	50 (22.3)	20 (19.4)
New hospital admission for IE complications	16 (7.1)	8 (7.7)

NVE, native-valve endocarditis; PVE, prosthetic-valve endocarditis; SD, standard deviation; COPD, chronic obstructive pulmonary disease; SOT/HSCT, solid organ transplant/haematopoietic stem cell transplant; IE, infective endocarditis; SSTI, skin and soft-tissue infection; TTE, transthoracic echocardiogram; TEE, transoesophageal echocardiogram; ICU, intensive care unit; DCR, daptomycin-containing regimen



Abbreviations. NVE: native-valve endocarditis; PVE: prosthetic-valve endocarditis; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; CoNS, coagulase-negative staphylococci

Fig. 1. Isolates responsible for the 327 cases of monomicrobial Gram-positive native-valve endocarditis (NVE) and prosthetic-valve endocarditis (PVE).



Abbreviations: NVE: native-valve endocarditis; PVE: prosthetic-valve endocarditis.

Fig. 2. Reasons for daptomycin use among native-valve endocarditis (NVE) and prosthetic-valve endocarditis (PVE) patients.

Table 2
Univariate analysis of survivors compared with non-survivors at 30 days in NVE patients.

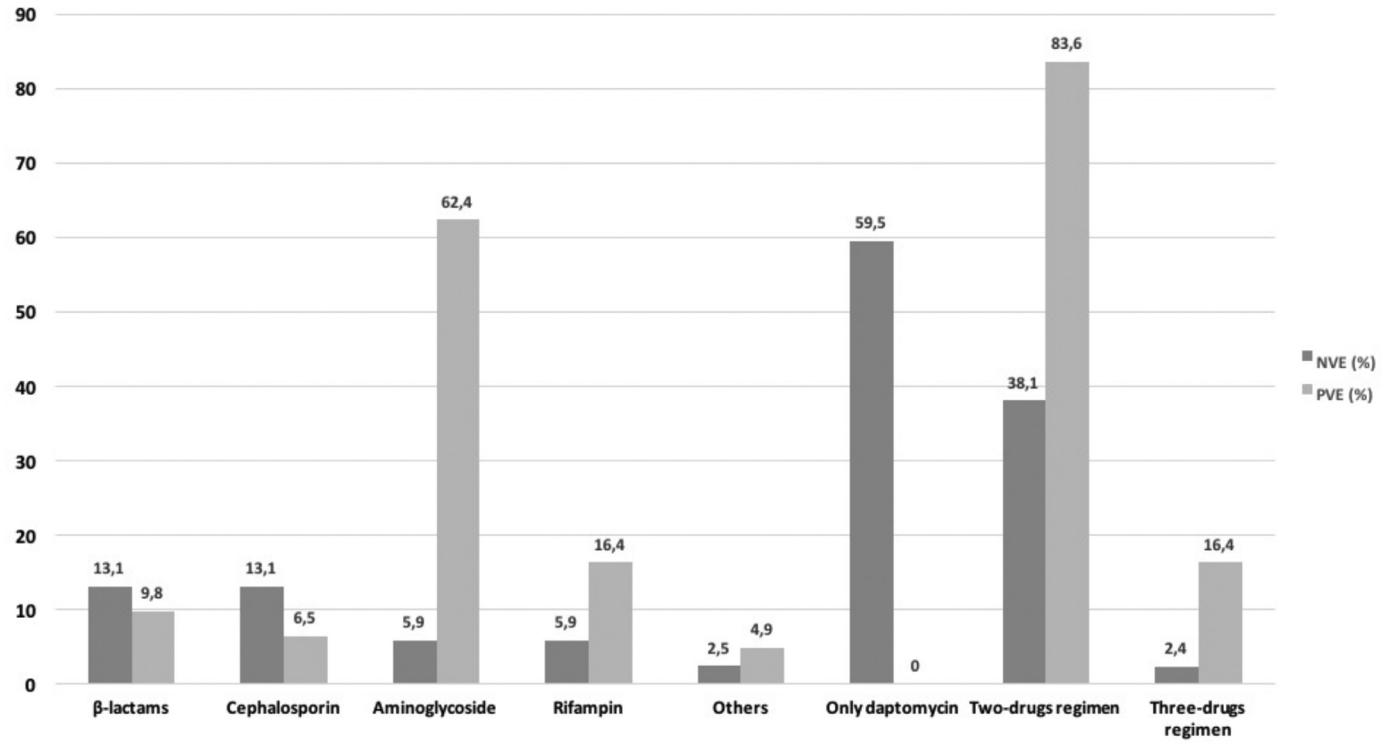
Variables	Survivors N = 174 (%)	Non-survivors N = 50 (%)	*P*
Age, mean ± SD (years)	66.8 ± 15.7	67.9 ± 16.2	0.37
Male sex	111 (63.8)	34 (68)	0.61
Comorbidities			
COPD	21 (12.1)	1 (2)	**0.02**
Coronary artery disease	24 (13.8)	9 (18)	0.1
Heart failure	23 (13.2)	9 (18)	0.1
Diabetes	47 (27.0)	16 (32)	0.16
Neurological disease	14 (8.0)	6 (12)	0.2
Cancer	17 (9.8)	6 (12)	0.3
Chronic renal disease	43 (24.7)	30 (60)	**< 0.001**
Dialysis	5 (2.9)	6 (12)	**0.01**
Chronic liver disease	9 (5.2)	7 (14)	0.05
SOT/HSCT	2 (1.1)	1 (2)	0.53
Active intravenous drug abuse	5 (2.9)	0	0.58
Affected valve(s)			
Mitral	89 (51.1)	21 (42)	0.26
Aortic	87 (50.0)	29 (58)	0.33
Tricuspid	11 (6.3)	1 (2)	0.3
Pulmonary	2 (1.1)	0	1.0
Two or more valves	11 (6.3)	5 (10)	0.41
Relapse of IE	6 (3.4)	2 (4)	1.0
Duke classification			
Definite	151 (86.7)	46 (92)	0.07
Possible	23 (13.2)	4 (8)	0.07
Aetiology			
Enterococcal species	21 (12.1)	8 (16)	0.47
Streptococcal species	59 (33.9)	9 (18)	**0.003**
Staphylococcal species	69 (39.7)	24 (48)	0.33
Other Gram-positive species	26 (14.9)	8 (16)	0.83
Charlson Comorbidity Index, mean ± SD	3.8 ± 3.1	4.4 ± 2.5	0.06
Previous cardiac surgery	16 (9.2)	3 (6)	0.57
Immunosuppressive therapy	4 (2.3)	1 (2)	1.0
Source of IE			
Dental procedure	9 (5.2)	0	0.1
Urinary tract	4 (2.2)	4 (8)	0.08
SSTI	23 (13.2)	11 (22)	0.06
Intra-abdominal infection	14 (8.0)	1 (2)	0.08
Previous invasive procedure	17 (9.8)	9 (18)	**0.04**
Positive echocardiogram			
TTE	152 (87.3)	35 (70)	**0.02**
TEE	148 (85.1)	36 (72)	0.06
Cardiac complications			
Perforation or rupture	10 (5.7)	3 (6)	1.0
Aneurysm	2 (1.1)	0	1.0
Abscess	17 (9.8)	7 (14)	0.2
Fistula	7 (4.0)	0	0.19
New valvular failure	21 (12.1)	9 (18)	0.06
Other complications			
Peripheral embolism	83 (47.7)	27 (54)	0.91
Peripheral septic thrombophlebitis	1 (0.5)	0	0.71
Ischaemic stroke	69 (39.7)	14 (28)	0.2
Persistent bacteraemia	0	4 (8)	**0.03**
Worsening renal function	16 (9.2)	18 (36)	**< 0.001**
Transfer to ICU	26 (14.9)	20 (40)	**< 0.001**
Septic shock	21 (12.1)	32 (64)	**< 0.001**
Treatment			
DCR	61 (35.1)	23 (46)	0.18
Surgery for IE	100 (57.4)	11 (22)	**< 0.001**
Time to surgery (days), mean ± SD	24.1 ± 15.8	38.9 ± 28.1	**0.01**
Euroscore II, mean ± SD	6.5 ± 3.6	8.9 ± 3.2	**< 0.001**
Logistic Euroscore, mean ± SD	12.6 ± 10.4	38.3 ± 1.9	**< 0.001**
Duration of definitive antibiotic therapy (days), mean ± SD (days)	65.6 ± 42.1	55.1 ± 44.5	0.06
Time to definitive therapy (days), mean ± SD	6.1 ± 3.0	7.3 ± 3.1	0.07
High-dose daptomycin (≥ 8 mg/kg)	40 (22.9)	8 (9.5)	**0.02**
Outcomes			
New hospital admission for IE complications	7 (4.0)	9 (18)	**0.001**
Clinical treatment failure	3 (1.7)	7 (14)	**0.01**

NVE, native-valve endocarditis; SD, standard deviation; COPD, chronic obstructive pulmonary disease; SOT/HSCT, solid organ transplant/haematopoietic stem cell transplant; IE, infective endocarditis; SSTI, skin and soft-tissue infection; TTE, transthoracic echocardiogram; TEE, transoesophageal echocardiogram; ICU, intensive care unit; DCR, daptomycin-containing regimen

Table 3
Univariate analysis of survivors compared with non-survivors at 30 days in PVE patients.

Variables	Survivors N = 83 (%)	Non-survivors N = 20 (%)	*P*
Age, mean ± SD (years)	65.8 ± 15.9	71.1 ± 17.2	0.16
Male sex	57 (68.6)	19 (95)	**0.02**
Comorbidities			
COPD	8 (9.6)	2 (10)	1.0
Coronary artery disease	29 (34.9)	13 (65)	**0.001**
Heart failure	15 (18.0)	5 (25)	0.21
Diabetes	22 (26.5)	2 (10)	0.07
Neurological disease	17 (20.4)	3 (15)	0.73
Cancer	3 (3.6)	3 (15)	0.09
Chronic renal disease	29 (34.9)	15 (75)	**0.002**
Dialysis	1 (1.2)	0	1.0
Chronic liver disease	6 (7.2)	0	1.0
SOT/HSCT	3 (3.6)	0	1.0
Active intravenous drug abuse	4 (4.8)	0	1.0
Affected valve(s)			
Mitral	13 (15.6)	12 (60)	**< 0.001**
Aortic	71 (85.5)	13 (65)	0.06
Tricuspid	1 (1.2)	1 (5)	0.35
Two or more valves	7 (8.4)	1 (5)	0.41
Relapse of IE	18 (21.6)	4 (20)	1.0
Duke classification			
Definite	62 (74.6)	18 (90)	0.2
Possible	21 (25.4)	2 (10)	0.2
Aetiology			
Enterococcal species	14 (16.8)	0	0.06
Streptococcal species	15 (18.1)	0	**< 0.001**
Staphylococcal species	33 (39.7)	19 (95)	**< 0.001**
Other Gram-positive	15 (18.1)	7 (35)	**0.042**
Charlson Comorbidity Index, mean SD	4.2 ± 3.4	5.1 ± 3.1	0.08
Immunosuppressive therapy	3 (3.6)	0	1.0
Source of IE			
Dental	4 (4.8)	0	1.0
SSTI	5 (6.0)	4 (20)	0.07
Intra-abdominal	10 (12.0)	0	0.29
Previous invasive procedure	18 (21.6)	1 (5)	0.11
Positive echocardiogram			
TTE	63 (75.9)	15 (75)	1.0
TEE	71 (85.5)	12 (60)	**0.02**
Cardiac complications			
Perforation or rupture	1 (1.2)	0	1.0
Aneurysm	1 (1.2)	0	1.0
Abscess	30 (36.1)	12 (60)	**0.03**
Fistula	4 (4.8)	9 (45)	**< 0.001**
Prosthesis dislocation	29 (34.9)	12 (60)	**0.03**
New valvular failure	13 (15.6)	10 (50)	**< 0.001**
Other complications			
Peripheral embolism	27 (32.5)	7 (35)	0.79
Peripheral septic thrombophlebitis	1 (1.2)	1 (5)	0.22
Ischaemic stroke	30 (36.1)	16 (80)	**< 0.001**
Persistent bacteraemia	0	3 (15)	**< 0.001**
Worsening renal function	5 (6)	7 (35)	**< 0.001**
Transfer to ICU	1 (1.2)	7 (35)	**< 0.001**
Septic shock	6 (7.2)	13 (65)	**< 0.001**
Treatment-related variables			
DCR	55 (66.2)	6 (30)	**< 0.001**
Surgery for IE	80 (96.3)	9 (45)	**< 0.001**
Time to surgery, mean ± SD (days)	24.1 ± 18.9	26.5 ± 24.3	0.79
Euroscore II mean ± SD	11.1 ± 4.8	11.8 ± 3.3	0.81
Logistic Euroscore, mean ± SD	29.2 ± 23.6	32.3 ± 24.7	0.41
Length of definitive antibiotic therapy, mean ± SD (days)	70.1 ± 29.2	42.1 ± 24.2	**0.03**
Time to definitive therapy, mean ± SD	5.2 ± 3.7	9.1 ± 5.3	**< 0.001**
High-dose daptomycin (≥ 8 mg/kg)	40 (48.1)	2 (10)	**< 0.001**
Outcomes			
New hospital admission for IE complications	1 (1.2)	7 (35)	**< 0.001**
Clinical treatment failure	0	6 (30)	**< 0.001**

PVE, prosthetic-valve endocarditis; SD, standard deviation; COPD, chronic obstructive pulmonary disease; SOT/HSCT, solid organ transplant/haematopoietic stem cell transplant; IE, infective endocarditis; SSTI, skin and soft-tissue infection; TTE, transthoracic echocardiogram; TEE, transoesophageal echocardiogram; ICU, intensive care unit; DCR, daptomycin-containing regimen



Abbreviations: DCR: daptomycin-containing regimen; NVE: native-valve endocarditis; PVE: prosthetic-valve endocarditis.

Two-drugs regimen: Daptomycin + 1 other antimicrobial

Three-drugs regimen: Daptomycin + 2 other antimicrobials

Fig. 3. Characteristics of the daptomycin-containing regimens (DCRs) used to treat native-valve endocarditis (NVE) and prosthetic-valve endocarditis (PVE).

failure (14% vs. 1.7%, $P = 0.01$) were associated with 30-day mortality, while high-dose daptomycin (≥ 8 mg/kg/day) (22.9% vs. 9.5%, $P = 0.02$), and surgery (57.4% vs. 22%, $P < 0.001$) with survival. In Table 3, IE of the mitral valve (60% vs. 15.6%, $P < 0.001$), staphylococcal aetiology (95% vs. 39.7%, $P < 0.001$), and persistent bacteraemia (15% vs. 0%, $P < 0.001$) were associated with unfavourable outcomes at 30 days, whereas streptococcal aetiology (18.1% vs. 0%, $P < 0.001$), and high-dose daptomycin (≥ 8 mg/kg) (48.1% vs. 10%, $P < 0.001$) with 30-day survival.

The subgroups treated with DCRs vs. non-DCRs are compared in Table 4 (NVE) and Table 5 (PVE). Those whose NVE was treated with a DCR (Table 4) were significantly more likely to have diabetes (41.7% vs. 20%, $P = 0.001$) and less likely to have streptococcal endocarditis (20.2% vs. 36.4%, $P = 0.01$). The DCR-treated NVE patients also had a higher mean Euroscore II (8.8 ± 3.7 vs. 6.7 ± 3.3, $P < 0.001$) than their non-DCR-treated counterparts, as well as higher rates of new valvular failure (21.8% vs. 9.4%, $P = 0.01$), persistent bacteraemia (4.8% vs. 0%, $P = 0.02$), transfer to ICU (8.6% vs. 15.7%, $P = 0.02$), and clinical treatment failure (11.7% vs. 2.7%, $P = 0.03$). As shown in Table 5, DCR-treated PVE patients were also significantly less likely to have streptococcal infections (3.3% vs. 31%, $P < 0.001$). They were also more likely to have staphylococcal endocarditis (67.2% vs. 26.2%, $P < 0.001$) and undergone an invasive procedure prior to diagnosis of IE (26.2% vs. 7.1%, $P = 0.01$). The duration of definitive antibiotic therapy was also shorter among PVE patients treated with DCRs (44.1 ± 22.4 days vs. 71.7 ± 31.2 days, $P = 0.01$). Clinical treatment failure rates were not significantly different in the DCR and non-DCR subgroups of PVE patients, but 30-day mortality was significantly higher in the non-DCR group (38% vs. 6.5%, $P < 0.001$).

Fig. 4 shows 30-day mortality and clinical treatment failure rates for NVE and PVE patients treated with DCRs. The results are presented for subgroups defined by daptomycin dosage (standard vs. high) or by the aetiology of the IE (MRSA, streptococcal, or enterococcal). Compared with high-dose daptomycin, standard-dosage daptomycin regimens were associated with markedly higher 30-day mortality (NVE patients: 26.1% vs. 1.2%; PVE patients: 6.5% vs. 0%) and clinical treatment failure rates (NVE group: 7.1% vs. 1.2%; PVE group: 3.2% vs. 0%). The DCR treatment of streptococcal and MRSA NVE was associated with 30-day mortality rates of 17.8% and 9.5%, respectively. Mortality rates for streptococcal and MRSA PVE were substantially lower.

Table 6 summarises the risk factors associated with 30-day mortality and clinical treatment failure in the overall population, NVE and PVE subgroups. Overall, chronic renal disease, septic shock, and new valvular failure were associated with 30-day mortality, whereas DCR and surgery for IE with survival; surgery for IE was associated with clinical success at the end of therapy, while cardiac complications with clinical treatment failure. Among patients with NVE, surgical treatment of IE was associated with 30-day survival and a reduced risk of treatment failure. In contrast, chronic renal disease at baseline and persistent bacteraemia after IE diagnosis were positively associated with 30-day mortality, and staphylococcal aetiologies were associated with clinical treatment failure. In the PVE subgroup, 30-day mortality was strongly associated with chronic renal disease and new valvular failure following

Table 4
Univariate analysis of DCR-treated and non-DCR-treated subgroups of NVE patients.

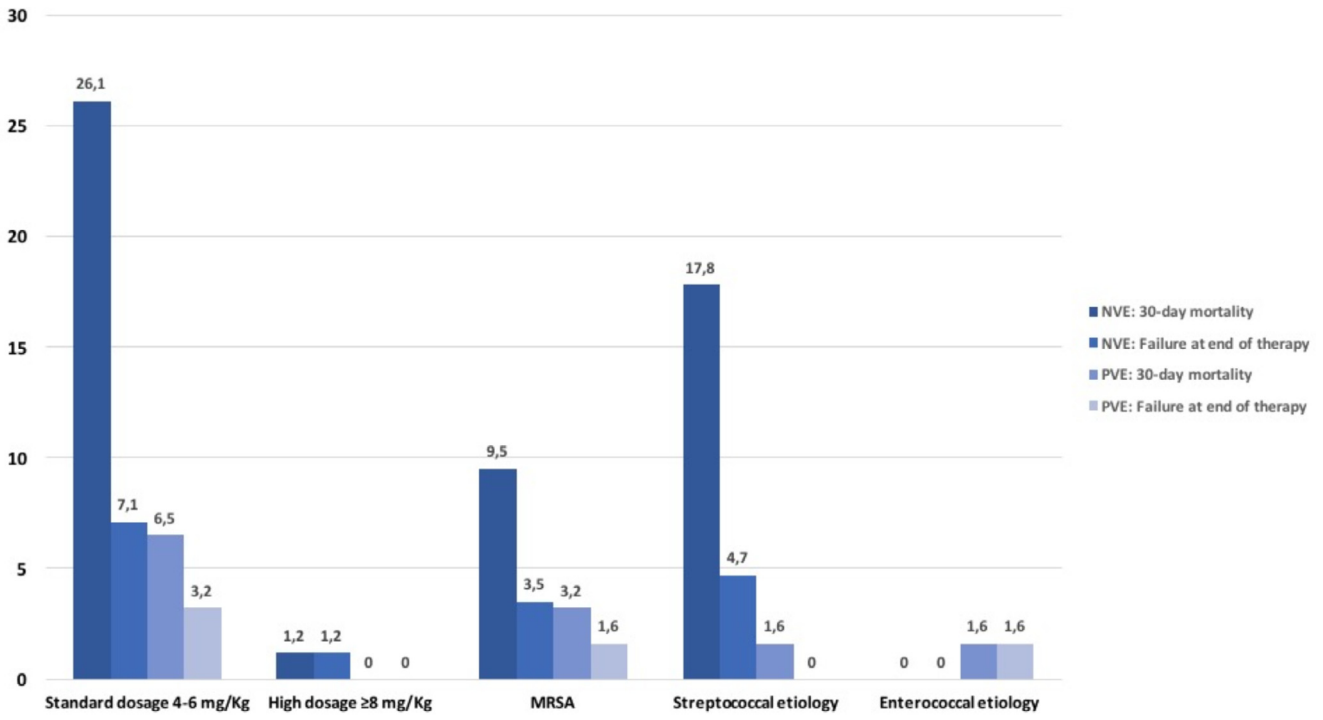
Variables	Non-DCR N = 140 (%)	DCR N = 84 (%)	*P*
Age, mean ± SD (years)	67.2 ± 16.7	67.6 ± 15.2	0.87
Male sex	93 (66.4)	52 (61.9)	0.5
Comorbidities			
COPD	15 (10.7)	7 (8.3)	0.48
Coronary artery disease	24 (17.1)	9 (10.7)	0.07
Heart failure	19 (13.6)	13 (15.5)	0.5
Diabetes	28 (20.0)	35 (41.7)	**0.001**
Neurological disease	12 (8.6)	8 (9.5)	0.6
Cancer	12 (8.6)	11 (13.1)	0.3
Chronic renal disease	40 (28.6)	33 (39.3)	0.1
Dialysis	7 (5.0)	4 (4.8)	1.0
Chronic liver disease	11 (7.9)	5 (6.0)	0.49
SOT/HSCT	0	3 (3.6)	0.09
Active intravenous drug abuse	2 (1.4)	3 (3.6)	0.36
Affected valve(s)			
Mitral	73 (52.1)	37 (44.0)	0.27
Aortic	71 (50.7)	45 (53.6)	0.78
Tricuspid	4 (2.9)	8 (9.5)	0.06
Pulmonary	1 (0.7)	1 (1.2)	1.0
Two or more valves	9 (6.4)	7 (8.3)	0.9
Relapse of IE	3 (2.1)	5 (6.0)	0.15
Duke classification			
Definite	125 (89.3)	72 (85.7)	0.5
Possible	15 (10.7)	12 (14.3)	0.5
Aetiology			
Enterococcal species	19 (13.6)	10 (11.9)	0.83
Streptococcal species	51 (36.4)	17 (20.2)	**0.01**
Staphylococcal species	54 (38.6)	39 (46.4)	0.26
Other Gram-positive species	16 (11.4)	18 (21.4)	**0.04**
Charlson Comorbidity Index, mean ± SD	3.9 ± 3.0	4.5 ± 2.6	0.19
Previous cardiac surgery	8 (5.7)	11 (13.1)	0.08
Immunosuppressive therapy	3 (2.1)	2 (2.4)	0.42
Source of IE			
Dental procedure	5 (10.2)	4 (19.0)	0.43
Urinary tract	6 (12.2)	2 (9.5)	1.0
SSTI	23 (47.9)	11 (52.4)	0.79
Intra-abdominal infection	12 (24.5)	3 (14.3)	0.52
Previous invasive procedure	16 (11.6)	10 (12.0)	1.0
Positive echocardiogram			
TTE	118 (84.9)	69 (83.1)	0.84
TEE	117 (83.6)	67 (79.8)	0.47
Cardiac complications			
Perforation or rupture	9 (6.5)	4 (5.4)	1.0
Aneurysm	2 (1.4)	0	0.23
Abscess	13 (9.3)	11 (13.8)	0.2
Fistula	6 (4.3)	1 (1.2)	0.19
New valvular failure	13 (9.4)	17 (21.8)	**0.01**
Other complications			
Peripheral embolism	68 (48.6)	42 (50)	0.96
Peripheral septic thrombophlebitis	0	1 (1.2)	0.37
Ischaemic stroke	54 (38.6)	29 (34.5)	0.2
Persistent bacteraemia	0	4 (4.8)	**0.02**
Worsening renal function	18 (12.9)	16 (19.0)	0.7
Transfer to ICU	22 (15.7)	24 (28.6)	**0.02**
Septic shock	32 (22.9)	21 (25.0)	0.74
Treatment			
Surgery for IE	71 (50.7)	40 (47.6)	0.68
Time to surgery (days), mean ± SD	37.1 ± 25.8	28.9 ± 21.1	0.46
Euroscore II, mean ± SD	6.7 ± 3.3	8.8 ± 3.7	**< 0.001**
Logistic Euroscore, mean ± SD	12.4 ± 9.4	37.4 ± 1.6	0.07
Duration of definitive antibiotic therapy (days), mean ± SD (days)	64.6 ± 48.1	53.7 ± 47.5	0.2
Time to definitive therapy (days), mean ± SD	6.5 ± 3.7	6.3 ± 3.1	0.9
High-dose daptomycin (≥ 8 mg/kg)	–	48 (57.1)	–
Outcomes			
30-day mortality	27 (19.3)	23 (27.4)	0.18
New hospital admission for IE complications	8 (5.7)	8 (9.5)	0.26
Clinical treatment failure	3 (2.7)	7 (11.7)	**0.03**

DCR, daptomycin-containing regimen**;** NVE, native-valve endocarditis; SD, standard deviation; COPD, chronic obstructive pulmonary disease; SOT/HSCT, solid organ transplant/haematopoietic stem cell transplant; IE, infective endocarditis; SSTI, skin and soft-tissue infection; TTE, transthoracic echocardiogram; TEE, transoesophageal echocardiogram; ICU, intensive care unit

Table 5
Univariate analysis of DCR-treated and non-DCR-treated subgroups of PVE patients.

Variables	Non-DCR N = 42 (%)	DCR N = 61 (%)	*P*
Age, mean ± SD (years)	66.8 ± 16.9	70.1 ± 17.9	0.36
Male sex	27 (64.3)	49 (80.3)	0.1
Comorbidities			
COPD	4 (10.0)	6 (9.8)	0.4
Coronary artery disease	13 (32.5)	29 (47.5)	0.3
Heart failure	5 (11.9)	15 (24.5)	0.08
Diabetes	11 (26.2)	13 (21.3)	0.67
Neurological disease	9 (21.4)	11 (18.0)	0.23
Cancer	1 (2.3)	5 (8.1)	0.1
Chronic renal disease	16 (38.0)	28 (45.9)	0.68
Dialysis	0	1 (1.6)	1.0
Chronic liver disease	2 (4.7)	4 (6.5)	0.3
SOT/HSCT	1 (2.3)	2 (3.3)	1.0
Active intravenous drug abuse	3 (7.1)	1 (1.6)	0.29
Affected valve(s)			
Mitral	11 (26.2)	14 (23.0)	0.81
Aortic	36 (85.7)	48 (78.7)	0.44
Tricuspid	0	2 (3.3)	0.51
Two or more valves	5 (11.9)	3 (4.9)	0.09
Relapse of IE	10 (23.8)	12 (19.7)	0.63
Duke classification			
Definite	36 (85.7)	44 (72.1)	0.16
Possible	6 (14.3)	17 (27.9)	0.08
Aetiology			
Enterococcal species	8 (19.0)	6 (9.8)	0.24
Streptococcal species	13 (31.0)	2 (3.3)	**< 0.001**
Staphylococcal species	11 (26.2)	41 (67.2)	**< 0.001**
Other Gram-positive	10 (23.8)	12 (19.7)	0.2
Charlson Comorbidity Index, mean SD	4.75 ± 2.4	5.3 ± 2.5	0.26
Immunosuppressive therapy	0	3 (4.9)	0.27
Source of IE			
Dental	4 (10.0)	0	**0.02**
SSTI	2 (4.7)	7 (11.4)	0.1
Intra-abdominal	6 (14.3)	4 (6.5)	0.09
Previous invasive procedure	3 (7.1)	16 (26.2)	**0.01**
Positive echocardiogram			
TTE	31 (73.8)	47 (77.0)	0.8
TEE	37 (88.0)	46 (75.4)	0.07
Cardiac complications			
Perforation or rupture	0	1 (1.6)	0.9
Aneurysm	1 (2.3)	0	0.39
Abscess	19 (45.2)	23 (37.7)	0.4
Fistula	5 (11.9)	8 (13.1)	1.0
Prosthesis dislocation	20 (47.6)	21 (34.4)	0.1
New valvular failure	12 (28.5)	11 (18.0)	0.24
Other complications			
Peripheral embolism	12 (28.5)	22 (36.1)	0.69
Peripheral septic thrombophlebitis	0	2 (3.3)	0.52
Ischaemic stroke	16 (38.0)	30 (49.2)	0.58
Persistent bacteraemia	0	3 (4.9)	0.25
Worsening renal function	7 (16.6)	5 (8.2)	0.27
Transfer to ICU	4 (9.5)	4 (6.6)	0.22
Septic shock	4 (9.5)	15 (24.6)	0.07
Treatment-related variables			
Surgery for IE	36 (85.7)	53 (86.8)	0.9
Time to surgery, mean ± SD (days)	26.1 ± 16.9	24.5 ± 23.3	0.82
Euroscore II mean ± SD	11.9 ± 3.8	11.4 ± 4.3	0.59
Logistic Euroscore, mean ± SD	35.0 ± 24.6	31.3 ± 22.7	0.48
Length of definitive antibiotic therapy, mean ± SD (days)	71.7 ± 31.2	44.1 ± 22.4	**0.01**
Time to definitive therapy, mean ± SD	8.4 ± 5.6	8 ± 5.1	0.8
High-dose daptomycin (≥ 8 mg/kg)	–	42 (68.9)	–
Outcomes			
30-day mortality	16 (38.0)	4 (6.5)	**< 0.001**
New hospital admission for IE complications	4 (9.5)	4 (6.6)	0.31
Clinical treatment failure	4 (9.5)	2 (3.3)	0.09

DCR, daptomycin-containing regimen; PVE, prosthetic-valve endocarditis; SD, standard deviation; COPD, chronic obstructive pulmonary disease; SOT/HSCT, solid organ transplant/haematopoietic stem cell transplant; IE, infective endocarditis; SSTI, skin and soft-tissue infection; TTE, transthoracic echocardiogram; TEE, transoesophageal echocardiogram; ICU, intensive care unit



Legend. NVE: native-valve endocarditis; PVE: prosthetic-valve endocarditis; MRSA: methicillin-resistant *Staphylococcus aureus*; DCR: daptomycin-containing regimen.

Fig. 4. Outcomes of daptomycin-containing regimens (DCR)-treated cases of native-valve endocarditis (NVE) and prosthetic-valve endocarditis (PVE) grouped according to infective endocarditis aetiology and daptomycin dosage.

Table 6
Multivariate analysis of risk factors associated with 30-day mortality and clinical treatment failure in overall population, NVE and PVE.

30-day mortality				Clinical treatment failure			
Variables	OR	95% CI	*P*	Variables	OR	95% CI	*P*
OVERALL POPULATION							
DCR	0.32	0.12–0.56	0.02	Surgery for IE	0.31	0.18–0.85	< 0.001
Surgery for IE	0.22	0.09–0.45	< 0.001	Cardiac complications	3.2	1.9–6.9	0.01
Chronic renal disease	3.2	2.1–7.4	< 0.001				
Septic shock	4.2	1.8–9.5	0.01				
New valvular failure	10.2	5.9–22.2	< 0.001				
NVE							
Surgery for IE	0.09	0.03–0.24	< 0.001	Surgery for IE	0.15	0.03–0.78	0.02
Chronic renal disease	4	1.8–8.5	< 0.001	Staphylococcal aetiology	2.7	1.4–11.9	0.01
Persistent bacteraemia	2.1	1.1–3.9	0.01				
PVE							
Chronic renal disease	15.2	1.5–149.2	0.01	Active intravenous drug abuse	16.8	3.6–77.8	< 0.001
Rapid initiation of definitive antibiotic therapy (< 5 days after IE diagnosis)	0.84	0.78–0.91	< 0.001				
DCR	0.41	0.3–0.9	0.01				
New valvular failure	46.8	2.9–751.1	0.007				

OR, odds ratio; CI, confidence interval; NVE, native-valve endocarditis; IE, infective endocarditis; PVE, prosthetic-valve endocarditis; DCR, daptomycin-containing regimen

IE diagnosis, whereas rapid initiation of definitive antibiotic therapy and use of a DCR were associated with survival at 30 days. For PVE patients, clinical treatment failure was positively associated with active intravenous drug abuse.

Table 7 shows the risk factors associated with 30-day mortality and clinical treatment failure in the subsets of NVE and PVE patients treated with DCRs. Among NVE patients treated with DCRs, 30-day mortality was associated with streptococcal aetiology, persistent bacteraemia, standard rather than high-dose daptomycin, a Charlson Comorbidity Index > 2, and the development of septic shock, whereas clinical treatment failure was associated with the onset of cardiac complications. In the PVE group, cardiac complications were associated with 30-day mortality. Surgical treatment of PVE was associated with a lower risk of death, and rapid initiation of definitive antibiotic therapy was associated with a reduced risk of treatment failure.

4. Discussion

This large single-centre study prospectively analysed the use of daptomycin for treating Gram-positive NVE and PVE. The findings support previous observations that high daily dosages of daptomycin (≥ 8 mg/kg) are associated with better outcomes than currently approved dosages (4–6 mg/kg). They also highlight the

Table 7
Multivariate analysis of risk factors associated with 30-day mortality and clinical treatment failure in DCR-treated patients with NVE or PVE.

30-day mortality				Clinical treatment failure			
Variables	OR	95% CI	*P*	Variables	OR	95% CI	*P*
NVE							
Streptococcal aetiology	1.5	1.2–2.8	0.03	Cardiac complications	3.4	1.8–12.1	0.001
Persistent bacteraemia	7.29	1.4–69.4	0.01				
Standard-dose daptomycin (4–6 mg/kg/day)	2.2	1.91–4.56	0.02				
Charlson Comorbidity Index > 2	2.2	1.5–4.6	0.02				
Septic shock	5.6	2.3–13.7	< 0.001				
PVE							
Cardiac complications	2.3	1.8–12.4	0.002	Rapid initiation of definitive antibiotic therapy (< 5 days of IE diagnosis)	0.31	0.1.2–0.65	0.001
Surgery for IE	0.1	0.02–0.87	0.03				

DCR, daptomycin-containing regimen; OR, odds ratio; CI, confidence interval; NVE, native-valve endocarditis; PVE, prosthetic-valve endocarditis; IE, infective endocarditis

favourable impact on the outcome of PVE (which is notoriously difficult to treat) with rapid initiation of a definitive regimen that includes daptomycin.

Overall, DCR was independently associated with 30-day survival; specifically, in NVE patients treated with DCRs, streptococcal aetiologies, persistent bacteraemia, approved rather than high-dose daptomycin, Charlson Comorbidity Index, and septic shock were all associated with 30-day mortality. For PVE patients, the data support the utility of a combined approach consisting of cardiac surgery plus prompt initiation of a definitive antimicrobial regimen that includes daptomycin, which was associated with better survival and lower rates of clinical treatment failure. Kornberger et al. have reported high clinical success rates (87%) with daptomycin in patients with Gram-positive infections after cardiac surgery [17]. In contrast, the development of cardiac complications related to the infection was associated with death.

The current findings support the use of daptomycin at doses of ≥ 8 mg/kg/day for both NVE and PVE. Doses higher than those currently approved by the Federal Drug Administration have frequently been advocated based on the pharmacodynamic rationale that such doses are warranted for treating high-inoculum, high-mortality infections such as endocarditis. However, the observational studies conducted thus far to evaluate the efficacy and safety of higher daptomycin dosages have included limited numbers of patients with IE [8,13,14]. It is believed that this is the first study to show that daily doses of ≥ 8 mg/kg are associated with lower mortality than approved doses (4–6 mg/kg) when treating Gram-positive NVE and PVE. Moreover, DCR was associated with high mortality in the current NVE patients whose infections were streptococcal, which is consistent with previous reports of acquired in vitro and in vivo daptomycin resistance in Viridans streptococcal infections treated with the drug [18-19]. Conversely, daptomycin displayed good efficacy in treating enterococcal NVE and PVE, and the findings suggest that for NVE caused by these organisms, even single-drug therapy with daptomycin is associated with lower 30-day mortality than non-DCRs.

In the current NVE patients, staphylococcal aetiologies (especially MRSA) were the most important predictor of clinical treatment failure, especially when non-DCRs were used. Vancomycin is currently the standard treatment for IE known or suspected to be caused by an MRSA strain. However, concerns have been raised regarding the renal toxicity of this approach [20], and there have also been many reports of clinical treatment failure. In a retrospective study, when MRSA strain showed MIC > 1, patients treated with daptomycin were reported with a lower rate of mortality and persistent bacteraemia, compared with vancomycin [13,21]. Several case series and reports have documented experiences with higher-than-approved doses of daptomycin (8–12 mg/kg/day) for left-sided endocarditis [22,23]. High-dose daptomycin has also been proven to be beneficial in in vitro studies in which there was enhanced killing and decreased emergence of resistance in simulated *S. aureus* and enterococci endocarditis vegetations in an in vitro pharmacokinetic/pharmacodynamic model treated with 8–12 mg/kg of daptomycin, compared with dosages of 6 mg/kg [24,25]. Additionally, since enterococcal isolates typically have higher daptomycin MICs than other Gram-positive organisms (0.5–4 mg/L vs. 0.25–1 mg/L), patients with these serious infections may require higher dosages of daptomycin for optimal treatment [26].

Although randomised trial data are lacking, the results of large retrospective studies indicate that high-dose daptomycin is both safe and effective [22,27]. In the current study population, none of the patients treated with DCRs experienced major adverse events (AEs) necessitating a change of therapy. In their analysis of 102 cases of IE treated with high-dose daptomycin, Durante-Mangoni et al. identified 47 major AEs – most involving mild myotoxicity or peripheral eosinophilia – but no daptomycin-related deaths [9]. European Cooperation in Research and Education data on real-world use of daptomycin in Gram-positive infections revealed clinical success rates of 90% among IE patients who received daptomycin at doses > 6 mg/kg/day, compared with 61.5% for those receiving 4 mg/kg/day and 86.1% in those treated with 6 mg/kg/day [28]. Six (3%) of the patients experienced daptomycin-related AEs. Therapeutic drug monitoring might be useful for minimising AEs, which is an important goal in critically ill patients with increased renal clearance, those with altered renal function, or those on continuous renal replacement therapy [29-31].

Limitations of this study were its single-centre nature and short follow-up period. Despite these shortcomings, data confirm the use of daptomycin in PVE at higher-than-approved dosages and show that such doses are also associated with reduced mortality in NVE patients, as compared with approved-dosage DCRs. The drug displayed good efficacy in the treatment of staphylococcal and enterococcal forms of IE, but its benefits in patients with streptococcal NVE were less clear, as reported by others. Overall, surgery was associated with better 30-day survival and lower rates of clinical treatment failure, confirming the well-known benefits of the combined approach to the treatment of IE. This real-life clinical experience provides useful information for clinicians regarding the management of these difficult-to-treat infections.

Declarations

Funding

None.

Competing Interests

None.

Ethical Approval

18/IRB_BASSETTI_18.

All authors have seen and approved the manuscript: AR, MP and MB conceived and designed the study; FG, MI and EG performed data collection; AR analysed data; AR and MB wrote the manuscript.

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