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FULL PAPER

Clinical use of dalbavancin in the Italian SUSANA cohort (SUrveillance of SAfety and outcome of New Antibiotics)

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SUMMARY

The purpose of the study was to evaluate the therapeutic success and adverse events (AEs) of dalbavancin on-label and off-label use in clinical practice. This was a retrospective, observational, multicentre study that enrolled consecutive patients treated with dalbavancin from January 2017 to May 2024 in the Italian SUSANA cohort. Therapeutic success was defined as clinical cure or infection control if chronic suppressive therapy was performed. Risk factors for treatment failure were evaluated using a logistic regression model. A total of 281 patients were enrolled in the study. On-label administration occurred in 162 (57.6%) cases and off-label in 119 (42.6%). The main off-label prescriptions included 29 cases of osteomyelitis and 25 cases of prosthetic joint infections. Dalbavancin was used mainly as empirical therapy (70.4% of cases) in the on-label group, while in the off-label group as targeted therapy for methicillin-resistant *Staphylococcus aureus* (29.4%). The therapeutic success rate was similar in both groups (82.7% on-label versus 84.0% off-label). Only one adverse event caused discontinuation of treatment in the on-label group. In addition, one grade-3 AE was observed in each cohort, without treatment interruption. Dalbavancin was widely used in clinical practice for on-label and off-label indications with a comparable success rate of 82.8% and 84.0%, respectively, and a good safety profile.

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INTRODUCTION

Dalbavancin is a second-generation semi-synthetic lipoglycopeptide antibiotic active against Gram-positive bacteria, with clinical activity in acute bacterial skin and skin structure infections (ABSSSI) demonstrated in the DISCOVER 1 and DISCOVER 2 trials (Jauregui *et al*., 2005; Boucher *et al*., 2014). The bactericidal action of dalbavancin results primarily from inhibition of cell-wall biosynthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits, resulting in bacterial cell death (Anderson, Keating, 2008). The addition of a lipophilic side chain allows dimerization of the molecule and improves the adhesion of dalbavancin to the target site, prolonging its half-life and significantly increasing dosing intervals (Zhanel *et al*., 2010). Dalbavancin has a long elimination half-life of approximately 14.4 days, allowing for weekly or biweek-

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ly doses (Anderson, Keating, 2008; Zhanel *et al*., 2010; Dunne *et al*., 2016). The recommended dose in the adult population is 1500 mg administered as a single infusion of 1500 mg or 1000 mg followed one week later by 500 mg (Jauregui *et al*., 2005; Boucher *et al*., 2014; Dunne *et al*., 2016). This aspect is of particular interest as a strategy for the management of infection in an outpatient setting (Baltin *et al*., 2023) and/or to decrease hospital admission and length of stay, as allowed by outpatient parenteral antimicrobial therapy (OPAT) services (Gatti *et al*., 2021).

Current real-world literature supports the off-label use of dalbavancin to treat invasive Gram-positive infections, especially in cases where prolonged intravenous antibiotic administration is necessary, such as bone and joint infections, bloodstream infections (BSI) and endocarditis (Gatti *et al*., 2021). At present, evidence regarding off-label use of dalbavancin is limited to case series, single-centre observational cohort studies, and small trials focused on osteomyelitis (Gatti *et al*., 2021; Rappo *et al*., 2019; Bouza *et al*., 2018; Morata *et al*., 2022; Hanses *et al*., 2022; Taylor *et al*., 2022; Courjon *et al.*, 2023; De Vito *et al*., 2023; Esposito *et al*., 2024). Current data emphasise the importance of real-world experience in off-label management and dosing regimen, since optimal dosing and frequency remain an open question, especially when therapeutic drug monitoring is not available (Senneville *et al*., 2023; Cooper *et al*., 2021).

Therefore, it is important to assess dalbavancin utilization, safety, and rates of cure in order to optimize treatment and describe real-world scenarios. In the setting of a study aiming to survey the safety of new antibiotics, we evaluated therapeutic success (clinical cure or infection control if chronic suppressive therapy) for on-label and off-label indications in clinical practice.

MATERIALS AND METHODS

We carried out a retrospective, observational, multicentre study that enrolled patients treated with dalbavancin from January 2017 to May 2024 in the Italian SUrveillance of SAfety and outcome of New Antibiotics (SUSANA) cohort, from "Coordinamento Italiano Studio Allergie e Infezione da HIV" (CISAI) study group. The nationwide analysis involved 17 Infectious Diseases (ID) Centres throughout Italy: 7 in Northern, 3 in Middle, 3 in Southern Italy, and 4 from Italian Islands.

Patients included in the study were at least 18 years old and received dalbavancin in hospital and/or in outpatient setting. We recorded demographic characteristics (age, sex at birth, nationality, comorbidities, body mass index (BMI)), Charlson Comorbidity index (CCI), renal biochemistry panel (creatinine and estimated glomerular filtration rate (eGFR) at baseline and after therapy), previous antibiotic therapy, dalbavancin posology regimen, clinical indication, pathogens, clinical outcome, and adverse events (AEs).

The main endpoint of this analysis was therapeutic success for on-label and off-label indications in clinical practice. We defined therapeutic success as clinical cure, specifically the absence of signs and symptoms of infection in a follow-up of at least 30 days after the last dose of dalbavancin, without the need for rescue antibiotic therapy or medical evaluation of index infection. If chronic suppressive therapy was performed, therapeutic success was defined as infection control documented by clinical findings and/or biochemical parameters (blood cell count, C-reactive protein, erythrocyte sedimentation rate). Clinical failure is defined as the clinical evidence of infection progression during the follow-up period. The follow-up period started with the first dose of dalbavancin and ended 30 days after the last dose. Drug safety was also evaluated: AEs were classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (v5.0) of 2017 (US Department of Health and Human Services, 2017).

We considered as on-label indication the prescription of dalbavancin for ABSSSI at 1500 mg or 1000 mg followed by 500 mg after one week. Any use of dalbavancin for ABSSSI with different dose regimens was categorized as an off-label indication, as was the use dalbavancin for conditions other than ABSSSI.

Statistical analysis. Variables were described as frequencies and percentages if categorical, as medians and interquartile ranges (IQR) if continuous. Differences between groups were analysed using the Chi-square (with Fisher correction if necessary) and the Mann-Whitney test, respectively. Risk factors for treatment failure were evaluated using a logistic regression model, where the binary outcome was recovery/treatment failure (the latter defined as clinical failure, AE-related discontinuation, loss to follow-up). All variables associated with the outcome at the univariate analysis (with a $p<0.20$) were included in the multivariate model.

Statistical analyses were performed with SAS/STAT (version 9.4, SAS Institute, Cary, NC, USA).

Ethics Committee. The original study protocol was approved on 24 January 2019 by the coordinating centre Ethics Committee (Brianza EC) and after that by all participating Centres. Written informed consent was obtained from the subjects involved in the study, unless the subjects were deceased or untraceable at the time of data collection. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and by Italian national laws. The amendments were approved on 10 December 2020 by Brianza CE and in April 2024 by the Lombardia 3 Local Ethics Committee.

RESULTS

281 patients were enrolled in the study from January 2017 to May 2024; their baseline characteristics are shown in Table 1. The median age was 65.0 years [IQR 49.0-75.0]; there were 158 (56.2%) males. The median Charlson Comorbidity index was 4 [IQR 1-6] and the most represented comorbidities were cardiovascular diseases (22.4%), diabetes mellitus (17.8%), immunological diseases (11.4%), pulmonary diseases (11.0%), and solid tumours (10.0%). Chronic kidney disease (moderate/severe) was present in 7.8% of the cases. Regarding risk factors for multi-resistant pathogen infections, 10.3% of the patients had surgery in the previous three months, 38.8% had a previous hospitalisation in the last 12 months, and 80.1% of the patients had prior antibiotic treatment in the last three months. As the study population was mainly composed of outpatients, the SOFA score was 0 in most cases (49.1%). Only 5 (1.8%) patients had a SOFA score ≥3. Twenty (7.1%) had a bloodstream infection (bacteremia), defined as one or more pathogen microorganisms detected in the blood.

Overall, on-label administration occurred in 162 (57.6%) cases and off-label in 119 (42.6%), with a higher frequency of bone and joint infections (BJIs), including 29 cases of osteomyelitis, 25 prosthetic joint infections (PJIs), 13 spondylodiscitis, and 8 septic arthritis. Additionally, there were 8 cases of bloodstream and vascular infections and 3 cases of endocarditis, as illustrated in *Figure 1*.

The remaining instances concerned 5 cases of long-term suppressive antimicrobial therapy (SAT) and 28 cases of ABSSSI with an off-label dose. Specifically, long-term suppressive therapy was used in cases where surgeons had ruled out surgical options and opted for conservative treatment instead: chronic osteomyelitis of the femur, left ventricular assist device driveline infection, aortic prosthetic valve endocarditis (PVE) with abscess, aortic and mitral PVE, vascular graft infection (VGI).

Regarding BJIs, 12/75 patients were surgically treated before starting dalbavancin; of these, 10 had a PJI and 2 an osteomyelitis. Overall, PJIs affected hip in 12 cases, knee in 8 cases, elbow in 2 cases, feet in 2 cases (1 ankle and 1 calcaneus), and 1 tibia in one case.

As reported in *Table 1*, the median age of the on-label and off-label cohorts were respectively 65 [IQR 49-76] and 65 [IQR 51-75] (p=0.73); there were 82 (50.6%) males in the on-label group and 76 (73.9%) in the off-label group (p=0.027). The median Charlson Comorbidity index (3.5 [IQR 1-6] on-label versus 4 [IQR 2-6] off-label) was similar (p=0.82) in both cohorts, while risk factors for multi-resistant pathogens infections were slightly different as regards previous hospitalization in the last 12 months with 44 (27.3%) patients in the on-label group and 65 (56.5%) in the off-label group (p<0.0001). Similarly, previous surgeries in the last 3 months were different in both groups, involving 10 (6.3%) patients in the on-label group and 19 (16.7%) in the off-label group (p=0.006). In contrast, the rate of patients who received previous antibiotic treatment was similar in both cohorts (81.1% on-label versus 80.7% off-label, p=0.92).

As expected, the most common bacterial pathogenic agent was *Staphylococcus aureus*. In the on-label group, dalbavancin was used mainly as an empirical therapy (70.4%). In contrast, in the off-label group, it was primarily employed as targeted therapy (72.3%) for *Staphylococcus aureus*, including both methicillin-sensitive *Staphylococcus aureus* (MSSA) (17.7%) and methicillin-resistant *Staphylococcus aureus* (MRSA) (29.4%), as well as Coagulase-negative staphylococci (CoNS) (21.0%). Other Gram-positive bacteria (4.2%) included *Corynebacterium jeikeium, Corynebacterium striatum, Staphylococcus pettenk-*

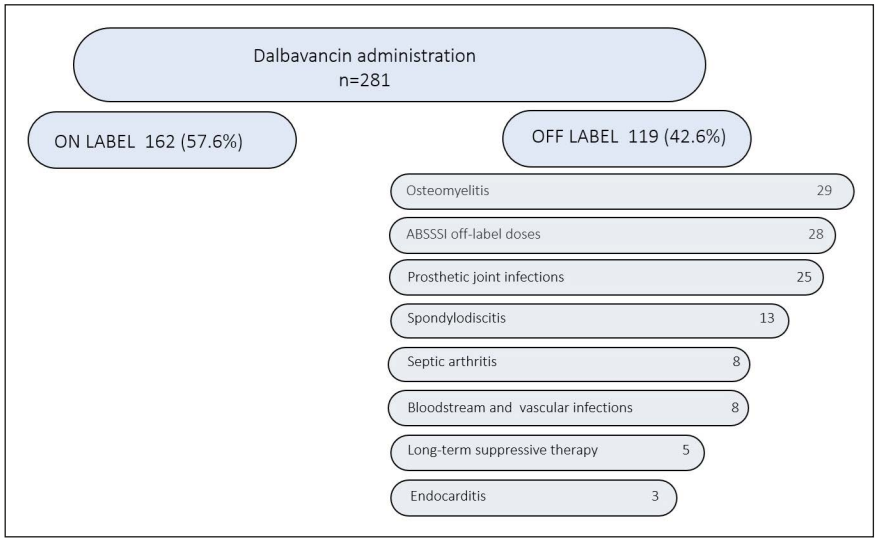

Figure 1
On-label and off-label indications.

oferi, and vancomycin-susceptible *Enterococcus faecium*. These results are presented in *Table* 2.

As illustrated in *Table 2*, heterogeneous dosing administration was used in the off-label group. The standard dosing regimen was the most frequently administered, accounting for 39.3% of cases. The second most common regimen was 1500 mg initially, followed by 1500 mg two weeks later, used in 19.0% of cases. Regarding BJIs, the regimen of 1500 mg on day 1, followed by 1500 mg after one week was the most used (26/42 cases) in the osteomyelitis and spondylodiscitis group. In the PJI cohort, the regimen of 1500 mg on day 1, followed by 1500 mg after one week (12/25 cases) was the most common, followed by the 1500 mg single dose regimen (8/25 cases) and 1500 mg initially, followed by 1500 mg two weeks later (3/25 cases).

As regards association with other antibiotics, in the off-label group dalbavancin was frequently used in combination therapy (34.4% off-label versus 17.3% on-label, p=0.001), mainly with amoxicillin/clavulanate (10.1% off-label versus 3.1% on-label, p=0.02). No other significant difference was found as regards co-administration with other antibiotic drugs, as documented in *Table 2*.

The therapeutic success rate was similar in both groups (82.7% on-label versus 84.0% off-label), while clinical failure was slightly higher in the on-label group (13.6% on-label versus 9.2% off-label, p=0.36). None of these differences were statistically significant. Data from BJI three-month outcome was available for two centres (n=48). The therapeutic success rate was 81.6% in the on-label group (n=136) versus 70.8% of BJIs from the same centres (p=0.07). Patients on SAT with infection control documented by clinical findings and/or biochemical parameters were included in the therapeutic success cohort, as mentioned above. Interestingly, the rate of treatment failure was 6/60 (10.0%) for MSSA; 9/32 (28.1%) for MRSA, 3/31 (9.7%) for CoNS, 3/11 (27.3%) for Other Gram-positive strains, 26/147 (17.7%) in case of no isolates. In our cohort, dalbavancin was administered in 118 (42.0%) elderly patients (age ≥70 years) and 170 (60.5%) comorbid patients with CCI ≥3. The proportion of success was similar in younger people (82.2% elderly group versus 82.0% younger group)

Table 1 - *Baseline characteristics of 281 people enrolled in the study.*

Characteristics	*Missing*	*Overall n=281*	*On-label n = 162*	*Off-label n = 119*	*p-value*
Age, years, Median (IQR)	0	65 (49-75)	65 (49-76)	65 (51-75)	0.73
Sex at birth, n (%) Male	0	158 (56.2%)	82 (50.6%)	76 (73.9%)	0.027
Comorbidities, n (%)					
Cardiovascular Disease	0	63 (22.4%)	32 (19.8%)	31 (26.0%)	0.21
Pulmonary disease	4	31 (11.0%)	17 (10.5%)	14 (11.8%)	0.73
Hepatic disease	6	23 (8.2%)	13 (8.0%)	10 (8.4%)	0.90
CNS disease	5	22 (7.8%)	13 (8.0%)	9 (7.6%)	0.91
Solid tumours	5	28 (10.0%)	15 (9.3%)	13 (10.9%)	0.62
Haematological malignancies	2	17 (6.1%)	9 (5.6%)	8 (6.7%)	0.68
Chronic kidney disease (moderate/severe)	4	22 (7.8%)	12 (7.4%)	10 (8.4%)	0.75
Diabetes mellitus	4	50 (17.8%)	26 (16.0%)	24 (20.2%)	0.36
Immunological disease	0	32 (11.4%)	19 (11.7%)	13 (10.9%)	0.84
Charlson Comorbidity index, Median (IQR)	0	4 (1-6)	3.5 (1-6)	4 (2-6)	0.82
Prior surgery (last 3 months), n (%)	8	29 (10.3%)	10 (6.3%)	19 (16.7%)	0.006
Prior antibiotic treatment (last 3 months), n (%)	3	225(80.1%)	129(81.1%)	96 (80.7%)	0.92
Previous hospitalization (last 12 months), n (%)	5	109 (38.8%)	44 (27.3%)	65 (56.5%)	<0.0001
SOFA score	121				
0		138 (49.1%)	62 (38.3%)	76 (63.9%)	
1		13 (4.6%)	5 (3.9%)	8 (6.7%)	
2		4 (1.4%)	1 (0.6%)	3 (2.5%)	
≥3		5 (1.8.%)	1 (0.6%)	4 (3.4%)	0.17
Bacteraemia, n (%)	7	20 (7.1%)	2 (1.2%)	18 (15.1%)	<0.0001
On-label indications, n (%)	0	-			-
ABSSSI			162 (57.6%)	-	
Off-label indications, n (%)				119 (42.6%)	
Osteomyelitis				29	
Spondylodiscitis				13	
Prosthetic joint infection				25	
Septic arthritis				8	
Bloodstream and vascular infections				8	
Long-term suppressive therapy				5	
Endocarditis				3	
ABSSSI off-label doses				28	

SOFA: Sequential Organ Failure Assessment; CNS disease: Central Nerve System disease; ABSSSI: acute bacterial skin and skin structure infections.

Table 2 - *Characteristics of dosing and duration regimen and outcomes for on-label and off-label indications.*

Characteristics	*On-label n = 162*	*Off-label n = 119*	*p-value*
Isolates, n (%)			
MSSA	11 (6.8%)	21 (17.7%)	
MRSA	25 (15.4%)	35 (29.4%)	
CoNS	6 (3.7%)	25 (21.0%)	<0.0001
Others	6 (3.7%)	5 (4.2%)	
None	114 (70.4%)	33 (27.7%)	
Dosing regimen, n (%)			
1500 mg single dose or 1000+500 mg	162 (100%)	33 (39.3%)	
1500 mg every 2 weeks		16 (19.0%)	<0.0001
Others		35 (41.7%)	
Regimen administration, weeks, n (%)			
0	90 (55.6%)	30 (25.4%)	
1	72 (44.4%)	49 (41.6%)	<0.0001
≥2	0	39 (33.0%)	
Association therapy, n (%)	28 (17.3%)	41 (34.4%)	0.001
TMP/SMX	4 (2.5%)	2 (1.7%)	1.0
Rifampicin	1 (0.6%)	5 (4.2%)	0.09
Doxycycline	4 (2.5%)	2 (1.7%)	1.0
Flucloxacillin	3 (1.8%)	1 (1.8%)	0.64
Linezolid	1 (0.6%)	3 (2.5%)	0.31
Amoxicillin/clavulanic acid	5 (3.1%)	12 (10.1%)	0.02
Others	12 (7.4%)	20 (16.8%)	0.01
Treatment outcomes, n (%)			
Recovery	134 (82.7%)	100* (84.0%)	
Failure	22 (13.6%)	11 (9.2%)	
Missing at follow up	6 (3.7%)	7 (5.9%)	0.36
Adverse events	0	1 (0.8%)	

MSSA: Meticillin-Sensitive *Staphylococcus aureus*; MRSA: Methicillin-Resistant *Staphylococcus aureu;* CoNS: Coagulase-negative staphylococci; TMP/SMX: Trimetoprim/sulfametoxazolo. *Five cases of suppressive antibiotic therapy (SAT) were included in the analysis.

and less comorbid subjects (80.0% comorbid group versus 83.8% less comorbid group).

Overall, only one event caused discontinuation of treatment in the off-label group due to maculo-papular rash (grade 2, certain causality). Additionally, one grade 3 event was observed in each cohort without treatment interruption: Stevens-Johnson syndrome in the on-label group and facial oedema in the off-label group (*Table 3*). As both events occurred after dalbavancin 1500 mg single dose infusion, the final outcome was therapeutic success with recovery for both cases.

As listed in *Table 3*, in general, six events occurred in the on-label cohort with likely/possible causality. These included two grade 1 events (hot flashes and vomiting) and four grade 2 events, which comprised one case of dyspnoea and three cases of maculopapular rash. Interestingly, only the case of Stevens-Johnson syndrome led to hospitalisation. The overall rate of AEs was 3.2% (confidence interval 1.7%-6.0%).

Table 3 - *List of adverse events.*

	Correlation	*Grade CTCAE*	*Sign and symptom*	*Group*	*Site infection*	*Dose schedule*	*Outcome*
1	certain	2	Rash	Off-label	PJI	1500 SD	Interruption
2	likely	3	Edema face	Off-label	ABSSSI	1500 2w	Recovery
3	possible	1	Hot flashes	On-label	ABSSSI	1000+500	Recovery
4	possible	1	Vomiting	On-label	ABSSSI	1500 SD	Recovery
5	likely	2	Rash	On-label	ABSSSI	1500 SD	Failure
6	likely	2	Rash	On-label	ABSSSI	1000+500	Recovery
7	likely	2	Rash	On-label	ABSSSI	1500 SD	Failure
8	likely	2	Dyspnoea	On-label	ABSSSI	1500 SD	Failure
9	likely	3	Stevens Johnson syndrome	On-label	ABSSSI	1500 SD	Recovery

ABSSSI: acute bacterial skin and skin structure infections; PJI: prosthetic joint infections, 1500 SD: 1500 mg single dose; 1500 2w: 1500 mg every two weeks, 1000+500: 1000 mg followed by 500 one week later.

Table 4 - *Treatment outcomes.*

Characteristics	*Success N=234*	*Failure N=47*	*p-value*
Age, years, Median (IQR)	65 (49-76)	64 (49-73)	0.58
Age ≥70, n (%)	101 (43.2%)	17 (36.2%)	0.38
Sex at birth, n (%) Male	132 (56.4%)	26 (55.3%)	0.89
Comorbidities, n (%)			
Cardiovascular Disease	49 (20.9%)	14 (29.8%)	0.20
Pulmonary disease	26 (11.3%)	5 (10.6%)	0.90
Hepatic disease	17 (7.4%)	6 (13.0%)	0.21
CNS disease	17 (7.4%)	5 (10.6%)	0.46
Solid tumours	20 (8.7%)	8 (17.4%)	0.07
Haematological malignancies	13 (5.6%)	4 (8.5%)	0.45
Chronic kidney disease (moderate/severe)	17 (7.4%)	5 (10.6%)	0.46
Diabetes mellitus	40 (17.4%)	10 (21.3%)	0.53
Immunological disease	24 (10.3%)	8 (17.0%)	0.18
Charlson Comorbidity index, Median (IQR)	3 (1-5)	4 (1-7)	0.17
CCI ≥3, n (%)	140 (59.8%)	30 (63.8%)	0.61
Prior surgery (last 3 months), n (%)	22 (9.6%)	7 (15.9%)	0.21
Prior antibiotic treatment (last 3 months), n (%)	185 (80.1%)	40 (85.1%)	0.42
Previous hospitalization (last 12 months), n (%)	94 (41.0%)	15 (31.9%)	0.24
SOFA score			
0	118 (50.4%)	20 (42.6%)	
1	11 (4.7%)	2 (4.3%)	
2	4 (1.7%)	0	0.70
≥3	4 (1.7%)	1 (1.2%)	
Missing	97 (41.4%)	24 (51.1%)	
Bacteraemia, n (%)	20 (8.6%)	0	0.10
Association therapy, n (%)	57 (24.4%)	12 (25.5%)	0.86
Indication, n (%)			
On-label	134 (57.3%)	28 (59.6%)	0.77
Off-label	100 (42.7%)	19 (40.4%)	

CNS disease: Central Nerve System disease; CCI: Charlson Comorbidity index.

As documented in *Table 4*, in the univariate analysis, no significant association was found between the factors analysed and treatment failure.

From the multivariate analyses shown in *Table 5*, it is apparent that no factors were significantly associated with treatment failure. Dalbavancin administration, as expected, was less favourable in MRSA treatment compared to MSSA. Other factors potentially associated with treatment failure included having an immunological disease and each point added to the Charlson Comorbidity Index, although none of these factors showed a statistically significant association.

DISCUSSION

In our cohort, there was a high rate of clinical therapeutic success in both groups, demonstrating the good efficacy of dalbavancin in different types of infection in a real-world scenario. The off-label use of dalbavancin for Gram-positive invasive infections was safe and a reasonable alternative to traditional OPAT in clinical practice.

Our findings were consistent with previous studies reporting a high cure rate and a low rate of side effects in invasive Gram-positive infections (Gatti *et al.*, 2021; Rappo *et al.*, 2019; Bouza *et al.*, 2018; Morata *et al.*, 2022; Hanses *et al.*, 2022; Taylor *et al.*, 2022; Courjon *et al.*, 2023; De Vito *et al.*, 2023; Esposito *et al.*, 2024; Senneville *et al.*, 2023; Cooper *et al.*, 2021). The Italian multicentric cohort described by Esposito *et al.* (2024) has shown that, overall, 50 (50.5%) patients achieved clinical cure during the 30-month study period in the off-label group, which included 99/223 patients (44.4%) (Esposito *et al.*, 2024). The authors described that the most common off-label indications were osteomyelitis, orthopaedic prosthesis-associated infection, and septic arthritis (Esposito *et al.*, 2024). Failure was defined as the lack of lesion healing or infection relapse despite appropriate management and was similar in both groups (4.8% on-label *vs* 3.1% off-label) (Esposito *et al.*, 2024). The authors distinguished failure form relapse, which appeared to have a similar trend (4.8% on-label *vs* 3.1% off-label) (Esposito *et al.*, 2024). In our study, the failure rate appeared higher (13.6% on-label *vs* 9.2% off-label), with no significant differences between the two groups. Altogether, the failure rates comparison is questionable, as in the off-label group heterogeneous infections were included, requiring long-course antibiotic therapy and, in some cases, surgical manage-

Table 5 - *Odds ratios for treatment failure.*

Characteristics	*Crude OR*	*95% CI*	*P*	*Adjusted OR**	*95% CI*	*P*
Age (by 10 years)	0.98	0.82-1.17	0.79			
Age ≥70 years (ref. <70)	0.75	0.39-1.43	0.38			
Sex at birth (ref. M)	1.04	0.56-1.96	0.89			
Comorbidities (ref. N)						
Cardiovascular Disease	1.60	0.80-3.22	0.19	1.46	0.60-3.52	0.40
Pulmonary disease	0.93	0.34-2.57	0.97			
Hepatic disease	1.87	0.70-5.04	0.41			
CNS disease	1.48	0.52-4.24	0.98			
Solid tumours	2.21	0.91-5.38	0.37			
Haematological malignancies	1.57	0.49-5.04	0.98			
Chronic kidney disease (moderate/severe)	1.48	0.52-4.22	0.98			
Diabetes mellitus	1.28	0.59-2.79	0.97			
Immunological disease	1.80	0.75-4.28	0.19	2.12	0.75-5.98	0.15
Charlson Comorbidity index (by 1 point)	1.11	0.99-1.23	0.07	1.06	0.91-1.22	0.45
CCI ≥3 (ref. <3)	1.18	0.62-2.27	0.61			
Prior surgery (last 3 months, ref. N)	1.78	0.71-4.46	0.96			
Prior antibiotic treatment (last 3 months, ref. N)	1.42	0.60-3.38	0.97			
Previous hospitalization (last 12 months, ref. N)	0.67	0.34-1.31	0.96			
SOFA score (ref. 0)						
1	1.07	0.22-5.20	0.96			
2	n.e.		0.96			
≥3	1.48	0.16-13.9	0.95			
Bacteraemia (ref. N)	n.e.		0.10	n.e.		
Associated antibiotics (ref. N)	1.06	0.52-2.19	0.86			
Off-label indication (ref. on-label)	0.91	0.48-1.72	0.77			
Isolates (ref. MSSA)						
MRSA	3.52	1.12-11.04	0.09	4.12	1.26-13.45	0.06
CoNS	0.96	0.22-4.15	0.21	1.14	0.26-5.03	0.30
Others	3.38	0.70-16.26	0.29	3.79	0.73-19.73	0.28
None	1.93	0.75-4.97	0.89	1.68	0.64-4.41	0.58

CNS: Central Nerve System; CCI: Charlson Comorbidity index; MSSA: Meticillin-Sensitive *Staphylococcus aureus*; MRSA: Methicillin-Resistant *Staphylococcus aureus*; CoNS: Coagulase-negative staphylococci; n.e.: not estimable. *Variables associated with the outcome with p<0.20 were included in the multivariate model: cardiovascular disease, immunological disease, CCI as a continuous variable, bacteraemia (with not estimable OR), isolates.

ment. In contrast, in the on-label group, dalbavancin was administered to definitively cure ABSSSI, often after other therapeutic regimens (81.1%), also highlighting infections clinically and therapeutically difficult to manage in this cohort. In general, therapeutic efficacy was difficult to assess and compare between the on-label and off-label cohorts due to the complexity and heterogeneity of cases in both groups, as expected in the real-world context. As documented in other cohorts, the most common off-label dalbavancin administration are BJIs, in particular osteomyelitis and spondylodiscitis (Esposito *et al*., 2024; Lovatti *et al*., 2023; Mazzitelli *et al*., 2022; Cain *et al*., 2021). BJIs represent the most difficult-to-treat infections due to the long treatment course, reduced drug penetration into bone, and the challenge of eradicating bacteria embedded in the biofilm state. In their systematic review, Lovatti *et al*. (2023) concluded that dalbavancin was a valuable option for osteoarticular infections treatment, with 79.3% of patients successfully treated (Lovatti *et al*., 2023). Furthermore, the authors emphasised the significant role of adequate surgical management prior to antibiotic treatment as a determining factor of good outcome (Lovatti *et al*., 2023). Specifically, a surgical source control of the infection site was frequently performed before the use of dalbavancin (110/159, 69.2%) (Lovatti *et al.*, 2023). Our findings were slightly different from those presented, as in the PJI cohort there were only 40% (10/25) patients surgically treated before starting dalbavancin.

Dalbavancin also ensures adherence in circumstances in which oral therapy adherence may be sub-optimal. In this perspective, frailty and comorbidity may influence the therapeutic approach in clinical practice. In our cohort, we prescribed dalbavancin to 118 (42.0%) elderly patients (aged ≥70) and 170 (60.5%) comorbid patients with a CCI ≥3, underlying the use-

ful role of long-acting drugs in these populations. Despite possible alterations in drug pharmacokinetic variables in elderly people, dalbavancin demonstrated a good safety profile with no adverse events in our elderly group, thus confirming the safety profile of this long-acting drug also in a frail and ageing population.

In our study, there were different treatment regimens in the off-label group with respect to dose and number of dalbavancin administration, duration and type of partner drugs, reflecting the heterogeneous therapeutic approaches of different centres, as generally observed in a clinical context. In our clinical practice, the degree of drug administration heterogeneity was greater in the first years after the drug was marketed. However, recent years have seen a trend towards standardization and similar therapeutic strategies among the Italian centres involved in the study.

This trend is probably related to pharmacokinetic and pharmacodynamic analysis investigated by recent available studies (Dunne *et al.*, 2015; Cojutti *et al.*, 2022; Thomas *et al.*, 2020), especially regarding osteoarticular infections. Dunne *et al.* (2015) described that regimens of 1500 mg on day 1 and 1500 mg on day 8 may be associated with better clinical outcomes in osteomyelitis (Dunne *et al.*, 2015). Similar trends have been reported by Cojutti *et al.* (2022), which demonstrated that the two-dose regimen of 1500 mg on day 1 and day 8 showed efficacy against *S. aureus* BJIs for up to 5 weeks, dependent on renal function (Cojutti *et al.*, 2022). Data from Thomas *et al.* (2020) highlighted the efficacy of the 3000 mg regimen over a 4-week period in off-label indications (Thomas *et al.*, 2020). Based on these data, an expert review panel suggested that therapeutic drug monitoring (TDM) is recommended for more than 6 weeks of dalbavancin therapy and/or in cases of renal failure. In these scenarios, TDM should be initiated between day 28 and day 35 to guide the timing of the next dose of dalbavancin (Senneville *et al.*, 2023). In our cohort, most dosing schedules were managed without TDM, as only few institutions have recently implemented its use in their routine. Our findings confirm those of these earlier studies (Dunne *et al.*, 2015; Cojutti *et al.*, 2022; Thomas *et al.*, 2020), since the regimen of 1500 mg, followed by 1500 mg after one week was the most common in the BJIs. Therefore, in the BJIs group, clinical success could be correlated with the use of the dalbavancin posology regimens which follow the optimal pharmacokinetic models. However, in this study, the impact of the type and timing of surgery on the outcome was not analysed.

Our analysis showed that dalbavancin was prescribed mainly as a consolidation therapy in both groups, as most of the patients (81.1% on-label versus 80.7% off-label) received previous antibiotics. This therapeutic approach is in line with the findings of Mazzitelli *et al.* (2022), who reported their experience using dalbavancin for MRSA spondylodiscitis after a 2-week course of in-hospital vancomycin therapy as the initial treatment (Mazzitelli *et al.*, 2022). In this setting, the use of long-acting drugs, such as dalbavancin, is attractive because it contributes to a shorter hospital stay, a decrease in treatment-related costs, and a better patient quality of life (Baltin *et al.*, 2023; Gatti *et al.*, 2021; Lovatti *et al.*, 2023; Mazzitelli *et al.*, 2022).

Dalbavancin was frequently used for ABSSSI empirical treatment (70.4% cases), as its good efficacy in this setting and its favourable management aspects probably influenced clinicians to choose a long-acting drug requiring a single-dose administration. The advantages that dalbavancin provides in the management aspects related to drug administration emerged in our multivariate analyses. In this cohort, MRSA is the most detected pathogen (29.4%) in the off-label group. Overall, 9 patients (28.1%) with MRSA strains experienced treatment failure. Dalbavancin demonstrated excellent antibacterial and bactericidal activity in vitro against representative strains belonging to the major epidemiologically diffused phenotypes of *S. aureus*, including MRSA (Sweeney *et al.*, 2017; Bongiorno *et al.*, 2020). In our experience, the efficacy of dalbavancin appeared to be poor with regard to MRSA compared with MSSA, but many confounding aspects must be considered in a real word context. The correlation between MRSA isolation and treatment failure could be interpreted as the results of the clinical characteristics of patients with an off-label MRSA infection, such as previous prior surgery and concomitant bacteriemia, but also previous hospitalizations and CCI. Parameters that statistically differ between on-label and off-label cohorts, but also those without statistically significant differences, could play an important role in clinical practice in defining the clinical complexity and severity of patients with an MRSA infection. In their systematic review on the use of dalbavancin in BJIs, Lovatti *et al.* (2023) similarly concluded from their data that MRSA was prevalently isolated in people with unfavourable outcomes (80%) (Lovatti *et al.*, 2023). The authors emphasized the role of synergistic in vitro activity of dalbavancin in combination with other antimicrobials, such as linezolid, ceftaroline, and rifampin, in reducing MIC for MRSA (Lovatti *et al.*, 2023). The authors also highlighted the limited real-world experience with combination therapy for BJIs (Lovatti *et al.*, 2023).

In our study, dalbavancin was frequently used as combination therapy in the off-label group, mainly with amoxicillin/clavulanate. These results differ slightly from those reported by Lovatti *et al.* (2023), which showed that only a quarter (24%) of the patients received antimicrobial drugs together with dalbavancin for osteoarticular infections, suggesting

that dalbavancin alone is generally considered a reliable monotherapy option for BJIs (Lovatti *et al.*, 2023). In *in vitro* assays, dalbavancin demonstrated a synergistic effect with beta-lactam antibiotics (Xhemali *et al.,* 2019) and linezolid (Aktas, Derbentli, 2017). Data presented by Cacopardo *et al*. showed that dalbavancin, when used as a combination therapy for patients with ABSSSI, was not superior to monotherapy. On the contrary, combination regimens represented a useful option in BJI or subacute/chronic intravascular infections with no possibility of device removal (Cacopardo *et al*., 2022). The authors suggested rifampin, beta-lactams, fluoroquinolones, doxycycline, and trimethoprim/sulfamethoxazole as potential partner drugs, according to synergistic tests, patient profile, and type of infection (Cacopardo *et al.*, 2022). In our real-world experience, combination therapy in the on-label group was adopted mainly as consolidation therapy in difficult-to-cure ABSSSI. More studies are needed to assess the relevance of combination therapies in difficult-to-treat infections for on-label and off-label indications.

Dalbavancin was well tolerated, and only one patient interrupted treatment due to adverse effects in the off-label group (maculopapular rash, grade 2, certain causality). A grade 3 event was observed in each cohort without treatment interruption, as both AEs occurred after dalbavancin single dose complete infusion. The final outcome was therapeutic success in both cases. This finding highlights the excellent safety profile of dalbavancin, as documented in both randomized clinical trials and observational studies investigating on and off-label indications (Jauregui *et al*., 2005; Boucher *et al*., 2014; Gatti *et al.,* 2021; Esposito *et al.,* 2024). In a critical reappraisal of real-world use of dalbavancin for off-label indications, Gatti *et al.* confirmed the excellent safety profile, as in their study the overall proportion of AEs ranged from 0% to 13% and serious AEs ranged from 0.0% to 2.9% (Gatti *et al.*, 2021).

The strength of this study includes its real-world setting, which may be helpful in accumulating evidence about the role of dalbavancin use in clinical practice, and in describing the real-life Italian scenario. To our knowledge, this multicentre retrospective study is the largest Italian real-world study on the use of dalbavancin for both on-label and off-label indications. However, this study has several limitations. Retrospective design and relatively small sample size limited the statistical power comparing treatment regimens. Furthermore, although similar in the two cohorts, previous antibiotic therapy could have influenced the outcome evaluation. This is particularly true for the BJIs group, in which the type and timing of the previous surgery could also have influenced the outcome. Finally, the methodological decision to standardize the follow-up time to compare the two groups may have led to a possible overestimate of therapeutic success in the off-label group, particularly in the BJIs subgroup, as these infections require a longer follow-up time. In their systematic review on the use of dalbavancin in BJIs, Lovatti *et al.* (2023) highlighted that clinical success within 4 weeks of the end of treatment was higher compared to the outcome after 4 weeks (84.3% *vs* 77.4%, respectively) (Lovatti *et al.,* 2023). Failure due to persistent infection (13.5% within 4 weeks *vs* 9.1% after 4 weeks) and failure due to relapse (0.7% within 4 weeks *vs* 7.3% after 4 weeks) also differed in the two groups (Lovatti *et al.,* 2023). These limitations highlight the need to investigate dalbavancin in specific randomised control trials for each type of infection to minimize confounding.

CONCLUSIONS

The study provided useful information on the indications and administration of dalbavancin in routine clinical practice in Italy. In our setting, dalbavancin was widely used for on-label and off-label indications, with a success rate of 82.7% and 84.0%, respectively, and a good safety profile. Specifically, dalbavancin was used mainly as a consolidation therapy in association with other oral antibiotic molecules. Our results are in line with the growing body of published real-world cohorts documenting the good efficacy and safety of dalbavancin for off-label indications in Gram-positive invasive infections requiring a long course of antibiotic therapy. In this scenario, dalbavancin represents a suitable option in the outpatient setting, since it may decrease length of stay in hospital and contribute to cost savings. Further research is expected to support the currently available results in different sub-populations, not yet fully investigated.

Ethics approval and consent to participate

The original study protocol was approved on 24 January 2019 by the coordinating centre Ethics Commit tee (Brianza EC) and after that by all participating Centres. Written informed consent was obtained from the subjects involved in the study, unless the subjects were deceased or untraceable at the time of data collection. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and by Italian national laws. The amendments were approved on 10 December 2020 by Brianza CE and in April 2024 by the Lombardia 3 Local Ethics Committee.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of A. Manzoni Hospital (transmittal letter: 11 March 2019; date of approval: 24 January 2019).

Clinical trial number
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, S.T., upon reasonable request.

Competing interests
The following authors served as consultant or advisory board member and/or received speaker's fees and/or received research grants for their institutions, outside the present work: G.V.D.S. from Gilead Sciences and ViiV Healthcare; P.M. from Gilead Science, ViiV Healthcare, Janssen and Merck Sharp & Dohme; P.B. from Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme; D.F. from Gilead Science, ViiV Healthcare, Janssen and Merck Sharp & Dohme. The other authors declare that they have no competing interests.

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Conceptualization: S.T., E.R., P.B., G.V.D.S.; methodology: S.T. and E.R.; formal analysis: E.R., S.T., G.V.D.S.; investigation: S.T., E.R., P.B., G.V.D.S.; data curation: all the authors; writing - original draft preparation: S.T., E.R., G.V.D.S.; writing - review and editing: all the authors; supervision: P.B. F.L and G.V.D.S. All authors have read and agreed to the published version of the manuscript.

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