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Real-world evidence of dalbavancin effectiveness as consolidation therapy in infective endocarditis due to *Enterococcus* spp.

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ABSTRACT

Enterococcal endocarditis (EIE) affects elderly patients, with high rates of complications and mortality, and dalbavancin (DBV) exhibits significant antimicrobial activity against most enterococci. However, data are lacking on the use of DBV in EIE. The main objective was to evaluate the outcomes of treatment with DBV in the consolidation therapy of IE by *Enterococcus* spp.

Methods: Spanish-French retrospective observational study of patients with EIE enrolled between November 2016 and June 30, 2022 receiving DBV in consolidation phase and followed for ≥12 months.

Results: Ninety-eight patients were enrolled, 69.4 % male, with mean age of 71.2 (±12.51) years and median Charlson index of 5 (IQR 3–7). Criteria for definite IE were met by 84.7%; 60.2 % had IE on native valve, 26.5 % late prosthetic IE, 8.2 % early prosthetic IE, 2 % cardiovascular implantable electronic-IE (CIE-IE), and 3.1 % CIE-IE and valve. Aortic valve involvement was observed in 66.3 %. *E. faecalis* was isolated in 86.7 %, *E. faecium* in 11.2 %; 32.6 % underwent surgery, and these had a higher cure rate (100 % vs 75.8 %; p = 0.005) and lower mortality (0 vs 13.6 %; p = 0.029). DBV was administered to facilitate discharge in 88.8 %. Total dose was 2500 mg (1500–3000) over 3.5 weeks (2–4). Loss to follow-up was 0 %, relapse rate 8.2 %, 1-year IE-related mortality 3.1 %, and clinical cure rate 81.2 %. Severe adverse events affected 1 % (acute tubular necrosis). Hospital stay was reduced by 21 days (14–28).

Conclusions: DBV appears to be highly effective, safe, and cost-effective as consolidation therapy in patients with IE caused by *Enterococcus* spp., with minimal adverse events.

1. Introduction

Infective endocarditis (IE) remains an uncommon disease but has become more frequent with the aging of the population and the increase in instrumentalization and intracardiac device implantation, alongside improvements in diagnostic methods.[1] These include the wider use of cardiac CT and PET scans and the adoption of modified DUKE diagnostic criteria in clinical practice guidelines.[2] The microbiology of IE has also changed, with *Staphylococcus aureus* becoming the most frequently implicated microorganism and *Enterococcus* spp. becoming one of the most prevalent pathogens after *Staphylococcus* and *Streptococcus* spp.[3] Enterococcal IE (EIE) has also been associated with colonic neoplasms.[4] EIE often affects the aortic valve of elderly people with comorbidities and a history of intraabdominal or urinary infection, and it has been associated with elevated mortality and relapse rates.[5] IE by *E. faecalis* represents 90 % of EIE cases, and the first-choice antibiotic therapy is the combination of ampicillin with ceftriaxone, which is as effective as the combination of ampicillin with gentamicin but less renally toxic, with the capacity to maintain synergy against isolates with high aminoglycoside resistance.[6] The latest European guidelines of the European Society of Cardiology recommend the combination of ampicillin plus ceftriaxone as first-line treatment, on a par with the combination of ampicillin plus gentamicin.[7] The duration of the antimicrobial regimen against EIE can be extended to 6–8 weeks to avoid relapses and associated complications.[8] When available, outpatient parenteral antimicrobial therapy (OPAT) is now possible for stable patients who only need hospitalization for the intravenous administration of antibiotics.[9] Another option for EIE is oral antibiotic therapy, using the combination of linezolid or amoxicillin with rifampicin,[10] although it faces some challenges to ensure adherence and avoid interactions and toxicity.[11] Finally, patients can be treated with a long-acting antibiotic such as dalbavancin (DBV). This lipoglycopeptide is a bactericide that exerts concentration-dependent [AUC/MIC] activity at peptidoglycan level in all Gram-positive microorganisms, including ampicillin-susceptible enterococci. DBV is administered intravenously and acts against both planktonic and biofilm bacteria, having a prolonged half-life (147–258 h [terminal]) and large volume of distribution. It is metabolized by microsomes and does not interact with cytochrome P450, while around 30 % is eliminated by urine and a small percentage by feces, and it has been approved for skin and soft tissue infections (SSTIs).[12] Its pharmacokinetic properties make DBV a highly promising option for the treatment of patients with IE. However, there have been no clinical trials on its effectiveness in these patients, only retrospective cohort series that included a few cases of EIE, which published encouraging results.[13,14]

With this background, our main objective was to conduct a real-life study on the effectiveness and safety of DBV as consolidation treatment in patients with IE due to *Enterococcus* spp. treated by experts in this infection at hospitals in Spain and France. A secondary objective was to explore potential savings yielded by this approach in a comparative pharmacoeconomic study.

2. Methods

Study design: International multicenter, observational, retrospective study of patients hospitalized in Spain and France for EIE who had received at least one DBV dose at hospital discharge under the criteria of the attending physician in a clinical practice setting. Outpatient DVB doses diluted in 5 % glucose saline were administered *via* a peripheral vein over 30–60 min in day hospitals of the participating centers. The Spanish and French researchers were all experts in endocarditis treatment who served in third-level or university hospitals with cardiac surgery or in regional hospitals with reference centers for this surgery.

Study period: Patients were enrolled between November 2016 and June 30, 2022 and followed up at 12 months after DBV treatment. The study was approved by the ethics committee of the coordinating hospital (HUVN) (CEIm Granada) and by the French Ethics Committee of Infectious Disease (registration number 2023-0509) and complied with the international conference of harmonization and good clinical practice guidelines.

Population: inclusion criteria were age >17 years, diagnosis of IE, microbiological isolation of *Enterococcus* spp. sensitive to DBV [in blood culture, endovascular tissue, cardiovascular implantable electronic devices infectious endocarditis (CIED-IE)], stable condition (no valve or heart failure), requirement for early surgery (i.e., post-DBV administration endocarditis surgery predicted by the attending physician to be unnecessary during the month after hospital discharge), no requirement to remain in hospital other than for intravenous (iv) antibiotics, and prescription by the attending physician of at least one dose of DBV as IE consolidation treatment. Exclusion criteria were DBV administered as suppressive antibiotic treatment, pregnancy, and IE not produced by *Enterococcus* spp. (Fig. 1).

Variables: Variables were gathered from the clinical history of patients in accordance with Spanish Personal Data Protection legislation (3/2018 December 5) and the Digital Rights Guarantee complementary to regulations (EU 2016/679) of the European Parliament and Council (April 27, 2016). The following data were entered in a standardized SPSS database: patient age and sex; days of hospitalization; age-adjusted Charlson index; type of DBV-treated IE [definite/probable, native/prosthetic, early/late, or cardiovascular implantable electronic devices infectious endocarditis CIED-IE); previous/concomitant antibiotic

treatment against the infection; DBV administration date and dose; adverse events related to DBV; diarrhea due to *Clostridioides difficile*; need for surgery during the first 12 months post-discharge with its date; relapse of IE; total 1-year mortality (related and non-related to IE); and loss to follow up. Data were remotely monitored from the coordinating center after the enrolment of all patients.

2.1. Definition of variables

- **IE** was defined according to modified Duke criteria, 2015.[15] IE on prosthetic valve was considered early when observed during the first 12 months post-surgery and late when observed after this period.[16]
- **Microbiological failure** was defined by persistent or recurrent bacteremia during IE treatment[17] or by isolation of the same microorganism in blood cultures from patients after completing antibiotic treatment against IE.
- **IE relapse** was defined by a second IE episode due to the same microorganism within six months of the first episode.[18]
- **Mortality** was defined as in-hospital mortality (death from any cause during hospital stay or first 30 days post-discharge) or mortality at 3- and 12-months post-discharge and was classified as IE-related (e.g., heart failure due to valve dysfunction) or non-IE-related (e.g., cancer).
- **The age-adjusted Charlson index** served to predict the survival of patients at 10 years.[19]
- **Consolidation treatment** was defined by DBV administration as sequential IE treatment rather than first-line therapy.
- **Chronic kidney failure** was defined by creatinine clearance <60 mL/min.
- Suppressive antibiotic treatment was defined by the prolonged use of antibiotics in patients who require surgery for infection control but are not candidates due to high risk or comorbidities; the objective is to control infection and prevent relapse in patients whose IE cannot be completely eradicated by a given course of IE therapy or control.

2.2. Statistical analysis

In a descriptive analysis, qualitative variables were expressed as absolute frequencies, quantitative variables with normal distribution as means with standard deviation, and quantitative variables with non-normal distribution as medians with interquartile range (IQR). The Kolmogorov-Smirnov test was applied to check the normal/non-normal distribution of variables. Bivariate analysis of relapse-related factors used the Chi-square test for qualitative variables, the Student's t-test for quantitative variables with normal distribution, and the Mann-Whitney *U* test for those with non-normal distribution. SPSS 20.0 (IBM plc, Chicago IL) was used for the statistical analyses. $P < 0.05$ was considered significant in all tests.

2.3. Pharmacoeconomic study

The economic impact of the DBV strategy was addressed by comparing the cost with that of other therapies. The two treatments most frequently received before switching to DBV were selected for comparison, i.e., ampicillin (2 g/iv/4 h) + ceftriaxone (2 g/iv/12 h), and daptomycin (10 mg/kg/iv/24 h), applying a weighting to calculate the costs. The costs were obtained from the accounting department in September 2022 (Supplementary Table 4). Costs of microbiological controls and managing therapeutic failures and adverse events were considered to be the same for each treatment. Costs considered for the DBV treatments included the drug price plus costs of consultation with infectious disease specialists and nursing professionals. Costs considered for previous treatments included: weighted drug price + hospital stay for theoretical mean duration of antibiotic coverage with DBV. Finally, the economic impact was expressed as the saving per DBV-treated patient.

3. Results

3.1. Study population

The study included 98 patients with IE. The mean age was 71.2 years; 64.3 % were male; the median age-adjusted Charlson index was 5 (IQR: 3–7); the most frequent comorbidity was chronic kidney failure (43.9 %); 84.7 % had definite IE. The IE type was native (NVIE) in 60.2 %, late prosthetic (late-PVIE) in 26.5 %, early prosthetic in 8.2 %, CIED-IE in 8.2 %, and CIED-IE plus NVIE in 3.1 %; the most frequently affected valve was aortic (66.3 %), followed by mitral (35.7 %), and tricuspid (6.3 %). The most frequent *Enterococcus* species was *E. faecalis* (86.7 %), followed by *E. faecium* (11.2 %), (Table 1).

Patients received a median total DBV dose of 2500 mg (IQR: 1500–3000 mg) for a median of 3.5 weeks (IQR: 2–4). The most common DBV dosing regimens were loading dose (LD) 1500 mg on day 1 (1d) and 1000 mg every 2 weeks (14d) (27.6 %), followed by a single dose of 1500 mg (22.4 %); an LD of 1000 mg (1d) and 500 mg every week (21.4 %), and doses of 1500 mg (1d) and 1500 mg (14 d) (20.4 %). DBV was

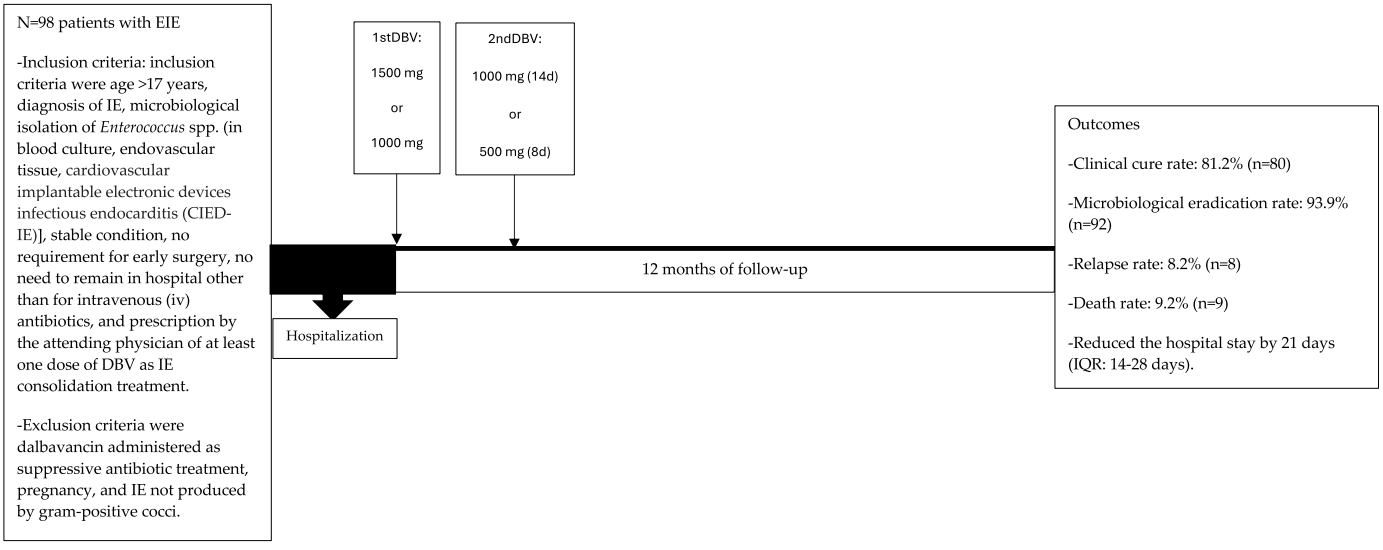

Fig. 1. Study flowchart.

Table 1
Characteristics of study population.

	Overall cohort	NVIE	PVIE CIED-IE	P* values
Number of cases	N = 98	N = 59	N = 39	NA
Age (years), mean (±SD)	71.2 (12.51)	68 (13.4)	75.8 (9.4)	0.003
Male, n (%)	68 (69.4)	43 (72.9)	25 (64.1)	0.356
Charlson index, median (IQR)	5 (3–7)	4 (2.5–6)	5 (4–7.5)	0.032
CKF (clearance <60 mL/min), n (%)	43 (43.9)	19 (32.2)	24 (61.5)	0.004
Hemodialysis, n (%)	6 (6.1)	5 (8.5)	1 (2.6)	0.39
Peritoneal dialysis, n (%)	1 (1.0)	1 (1.7)	0	1
Diabetes mellitus, n (%)	27 (27.6)	11 (18.6)	16 (41)	0.015
Respiratory disease, n (%)	23 (23.5)	15 (25.4)	8 (20.5)	0.57
Neurological disease, n (%)	19 (19.4)	11 (18.6)	8 (20.5)	0.82
HIV infection, n (%)	2 (2.0)	2 (3.4)	0	0.52
Solid organ transplantation, n (%)	4(4.1)	3 (5.1)	1 (2.6)	1
Active neoplasm, n (%)	10 (10.2)	7 (11.9)	3 (7.7)	0.74
Chronic liver disease, n (%)	8 (8.2)	5 (8.5)	3 (7.7)	1
Corticoids/other immunosuppressive, n (%)	11 (11.2)	8 (13.6)	3 (7.7)	0.52
Type of infection, n (%)				
Definite IE	83 (84.7)	52 (88.1)	31 (79.4.9)	0.1
Probable IE	15 (15.3)	7 (11.9)	8(20.5)	
Type of Endocarditis, n (%)				
Native	59 (60.2)			
-Native and prosthetic	3 (5.1)	2 (3.4)	1 (2.6)	1
Late prosthetic	26 (26.5)	3 (11.5)	23 (88.5)	0.12
Early prosthetic	8 (8.2)	0	8 (8.2)	1
CIED-IE	3 (2.0)	0	3 (7.7)	1
-CIED-IE and valve (2 native y 1 Early PVE)	3 (3.1)	2 (3.4)	1 (2.6)	0.56
TAVI, n (%)	8 (8.2)	1 (1.7)	7 (17.9)	0.006
Valve affected, n (%).	N = 96	N=59	N=37	
Aortic	66(64.3)	39 (66.1)	27(73)	0.489
Mitral	35 (35.7)	24 (40.7)	11 (29.7)	0.278
Tricuspid	6 (6.3)	4 (6.8)	2 (5.4)	0.883
Aortic and mitral valves affected by IE, n (%)	11 (11.2)	8 (13.6)	3 (8.1)	0.522
Causative organism, n (%)				
E. faecalis	85 (86.7)	50 (84.7)	35 (89.7)	0.24
E. faecium	11 (11.2)	7 (11.9)	4 (10.3)	
E. casseliflavus	1 (1)	1 (1.7)	0	
E. hirae	1 (1)	1 (1.7)	0	

CKF: Chronic kidney failure; TAVI**: Transcatheter Aortic Valve Implantation. NVIE: native valvule IE; PVE: prosthetic valvular endocarditis, CIED-IE: cardiovascular implantable electronic devices infectious endocarditis; p*>0.05 significance.

administered to facilitate discharge in 88.8 % of cases. Thirty-two patients (32.6 %) underwent surgery for IE, which was before DBV administration in 29 (90.6 %) (Table 2). The operated subjects were younger (66.6 ± 12.1 vs 73.4 ± 12.2y; p = 0.011), predominantly male (81.3 vs 18.7 %; p = 0.015), with lower Charlson index [IQR: 3(2–5) vs 5 (4–7); p = 0.001)], definite IE (96.9 vs 78.8 %; p = 0.021), and NVIE (84.4 vs 48.5 %; p = 0.001) (Table S1).

Before receiving DVB, the initial antibiotic regimen against IE was combined therapy in 83 patients (80.6 %) for a median of 19.5 days (IQR: 4–13). A second treatment regimen was administered to 35 (35.7 %) patients and was a combined therapy in 40 % of these for a median of 20 days (IQR:12–28). The most frequently administered antimicrobial was ampicillin (81.6 %), followed by ceftriaxone (69.4 %) and daptomycin (34.7 %), for a median of 22.5 days (15–34.3). Table 2

Table 2
Treatments received according type of IE.

	Overall cohort	NVIE	PVIE CIED-IE	P* values
Number of cases	N = 98	N = 59	N = 39	NA
Heart Surgery, valve replacement, and/or device extraction, n (%)	32 (32.6)	27 (45.8)	5 (12.8)	0.001
- Surgery before DBV administration	29 (90.6)	25 (92.6)	4 (80)	0.41
-Surgery after DBV administration	3 (9.4)	2 (7.4)	1 (20)	
Antibiotic treatment before DBV, n (%)	98 (100)	59 (100)	39 (100)	
1st antibiotic treatment, n (%):				0.52
- Combined	79 (80.6)	51 (86.4)	28 (71.8)	
- Median days of administration (IQR)	19.5 (12–28)	18 (12–28)	18 (10.8–33	0.073
2nd antibiotic treatment, n (%):				0.7
- Combined	35 (35.7)	23 (38.9)	12 (30.1)	0.26
- Median days of administration (IQR)	20 (12–28)	19 (10.5–27)	17 (12–30)	
3rd antibiotic treatment, n (%)				
- Combined	6 (6.1)	4 (6.7)	2 (5.1)	1
- Median days of administration (IQR)	15 (14–42)	14 (4–17)	14 (5–27)	
Previous antibiotics, n (%)				
Ampicillin	80 (81.6)	48 (81.4)	32 (82.1)	0.93
Ceftriaxone plus ampicillin	68 (69.4)	40 (67.8)	28 (71.8)	0.67
Daptomycin	34 (34.7)	21 (35.6)	13 (33.3)	0.82
Ceftaroline plus daptomycin	4 (4.1)	2 (3.4)	2 (5.1)	1
Linezolid	8 (8.2)	5 (8.5)	3 (7.7)	1
Vancomycin	9 (9.2)	6 (10.2)	3 (7.7)	0.68
Amoxicillin	11 (11.2)	7 (11.9)	4 (10.3)	1
- - Monotherapy	6 (54.5)	4 (57.1)	2 (50)	1
- - Combined with Ceftriaxone	5 (45.5)	3 (42.8)	2 (50)	1
Median days of antibiotic treatment before DBV (IQR)	22.5 (15.0–34.25)	23 (15-33-5)	22(25–40)	0.41
Reason for DBV administration, n (%)				
Facilitation of discharge	87 (88.8)	54 (91.5)	33 (84.6)	0.16
Failure of previous treatment	2 (3.0)	1 (1.7)	1 (2.6)	
Adverse event/Renal failure	4 (3.1)	3 (5.1)	1 (2.6)	
Other	5 (5.1)	1 (1.7)	4 (10.3)	
Initial DBV dose, n (%)				
750 mg	3 (3.1)	1 (1.7)	2 (5.1)	0.51
1000 mg	24 (24.5)	16 (27.6)	8 (20.5)	
1500 mg	71 (72.4)	42 (71.2)	29 (74.4)	
Median total DBV dose (mg) administered (IQR)	2500 (1500–3000)	2000 (1500–3000)	3000 (2000–3000)	0.002
Median duration (in weeks) of DBV administration (IQR)	3.5 (2–4)	2(2–4)	4(2–5)	0.001
Most frequent DBV regimens, n (%)				
1000 mg (1 d), 500 mg every week	21 (21.4)	11 (18.6)	10 (25.6)	0.21
1000 mg (1 d)	5 (5.1)	5 (8.5)	0	
1500 mg (1 d)	22 (22.4)	16(27.1)	6 (15.4)	
1500 mg (1 d), 1000 mg every (14 d)	27 (27.6)	17 (28.8)	10 (25.6)	
1500 mg (1d), 1500 mg every (14 d)	20 (20.4)	9 (15.3)	11 (28.2)	
Other regimens	3 (31.6)	1 (1.7)	2 (5.1)	

NVIE: native valvule IE; PVIE: prosthetic valvular IE, CIED-IE: cardiovascular implantable electronic devices IE; p*>0.05 significance.

summarizes the results for the remaining variables.

There were differences according to the type of IE (NVIE *vs.* PVIE/CIED-IE). Patients with NVIE were younger (68 ± 13.4 years *vs.* 75.8 ± 9.5 years; p = 0.003), had a lower Charlson index [4 (2.5–6) vs 5 (4–7.5), p = 0.032], better renal function (clearance <60 ml/min: 32.2 *vs.* 61.5 %, p = 0.004); were operated on at a higher rate (45.8 *vs.* 12.8 %, p = 0.001), and received lower doses of total DBV (2000 mg vs 3000 mg, p = 0.002) (Tables 1 and 2).

3.2. Outcomes

During the 12-month follow up, eight patients had an IE relapse (8.2 %), and nine patients died (9.2 %) (Table 3). Two of the deaths were directly attributable to IE: one from refractory heart failure at 10 days after DBV administration (surgery prescribed but not performed due to the patient's clinical status), and the other from massive brain hemorrhage at day 37 of antibiotic treatment, having received a single dose of DBV (Table S2). Seven of the deaths (7.1 % of sample) were for non-related causes at a median of 57 days (IQR: 26–180 days) (Table 3).

A clinical cure of IE was recorded in 80 patients (81.2 %) and microbiological eradication, with negative blood culture, in 92 (93.9). DBV treatment reduced the hospital stay by 21 days (IQR:14–28 days). Table 3 lists the results for remaining variables. There were no differences in clinical outcomes according to the type of endocarditis, although they differed according to the receipt of cardiac surgery; subjects who underwent the indicated operation had a lower mortality (0 *vs.* 13.6 %; p = 0.029), higher clinical cure rate (100 *vs.* 75.8 %; p = 0.005) and lesser relapse rate (0 *vs.* 12.1; p = 0.05) (Table 4).

3.3. Analysis of factors related to IE relapse

In bivariate analyses, IE relapse-related risk factors were a late prosthetic IE (62.5 % vs 23.3 %; p = 0.029) and the non-receipt of endocarditis surgery (device explant or valve replacement) (0 % vs 35.6 %; p = 0.05) because a cure was considered possible by antibiotic therapy alone (Table 5).

Table 3
Outcomes according type of IE.

	Overall cohort	NVIE	PVIE CIED-IE	p* values
Number of cases	N = 98	N = 59	N = 39	NA
Clinical cure, n (%)	80 (81.2)	49 (83.1)	31 (79.5)	0.2
Mortality, n (%)	9 (9.2)	7 (11.9)	2 (5.2)	0.31
IE-related death, n (%)	2 (2)	2 (3.4)	0	0.52
- During hospitalization	0	0	0	
- After discharge at <40 days	2 (100)	2 (3.4)	0	
Non-IE-related death, n (%)	7 (7.1)	5 (8.5)	2 (5.1)	0.69
- Traumatic brain injury	1 (14.3)			
- Sepsis related to kidney transplant	2 (28.6)			
- Unknown cause	3 (42.3)			
- Advanced oncological disease	1 (14.3)			
- Median (IQR) days after DBV treatment for IE non-related deaths	57 (26–180)			
Relapse, n (%)	8 (8.2)	2 (3.4)	6 (15.4)	0.056
Microbiological cure, n (%)		N = 57	N = 36	
- Negative blood cultures after DBV	92 (93.9)	57 (100)	35 (97.2)	0.39
Hospital stay reduction, (days), median (IQR)	21(14–28)	14 (14–28)	28 (14–29)	0.116
Loss to follow up, n (%)	0	0	0	

NVIE: native valvule IE; PVIE: prosthetic valvular IE, CIED-IE: cardiovascular implantable electronic devices IE; p*>0.05 significance.

Table 4
Outcomes according to the surgery.

	Overall cohort	No surgery	Surgery	p* values
Number of cases	N = 98	N = 66	N = 32	NA
Clinical cure, n (%)	80 (81.2)	50 (75.8)	32 (100)	0.005
Mortality, n (%)	9 (9.2)	9 (13.6)	0	0.029
IE-related death, n (%)	2 (2)	2 (3)	0	1
Non-IE-related death, n (%)	7 (10.6)	7 (10.6)	0	0.092
Relapse, n (%)	8 (8.2)	8 (12.1)	0	0.05
Microbiological cure, n (%)	N = 93	N = 64	N = 29	1
Negative blood cultures after DBV	92 (98.9)	63 (98.4)	29 (100)	
Hospital stay, (days), median (IQR)	21(14–28)	22 (16–38)	35.5 (25–39.5)	0.005
Loss to follow up, n (%)	0	0	0	

Table 6 shows the eight patients who relapsed.

3.4. Adverse events

Acute tubular necrosis was observed in one patient (1 %). No other adverse events were reported. There was no case of infection by *Clostridioides difficile*.

3.5. Pharmacoeconomic study

The cost of DBV per patient and day was 3115.31 €, and the median DBV regimen duration was 3.5 weeks. The cost of usual IE treatments in hospital for 3.5 weeks, considering a weighted cost of 29.8 €/day, was calculated as 14,182.83 €/per patient. The total saving generated by treatment with DBV was calculated as 11,067.52 € per patient (Table 7). Estimated prices for antibiotics, hospital stay, and medical and nursing care can be found in Table S4.

4. Discussion

This study, which focuses on DBV use in enterococcal endocarditis, highlights the good efficacy and tolerability of DBV as an alternative consolidation treatment. The patients in the study were elderly, mostly male, with major comorbidities. More than one-half of IEs were on native valve and one-third on prosthetic valve. Left valves were more frequently involved, especially the aortic valve. *E. faecalis* was the most frequently isolated microorganism. These findings are comparable to previously published epidemiologic data on EIE.[5] The DBV regimen was not uniform in our cohort, being predominantly a loading dose of 1500 mg followed by 1000 mg every two weeks. The DBV dose was higher in cases of prosthetic *versus* native valves (3000 vs. 2000 mg) to cover a longer period of time (4 vs. 2 weeks), based on real-life studies of DBV against IEs.[20] A recently published expert review of available evidence on the use of DBV recommended optimizing its administration beyond currently authorized doses.[21]

The overall mortality rate was 9.2 %, the IE-related mortality rate was low (2 %), and the relapse rate was 8.2 %. Late-PVIE and the non-performance of surgery were risk factors for a relapse. Relapses are frequent in EIE, as exemplified by a French multicenter retrospective study (n = 14 hospitals) of 279 individuals with *E. faecalis,* which described a similar relapse rate (9.3%) and found surgery during treatment to be a protective factor against one-year relapse and death.[22] An international collaborative study led by the University of California in 2005 reported a mortality rate of around 11 % for EIE, which was associated with a better prognosis in comparison to IE caused by *S. aureus.*[23] However, numerous studies have reported an elevated mortality rate for EIE, which was around 30 % in the study by Martínez-Marcos FJ et al., who had administered antibiotic treatments with vancomycin plus aminoglycoside or ceftriaxone plus ampicillin in

Table 5
Bivariate analysis of risk factors related to IE relapse.

	Relapse N = 8	No relapse N = 90	p*
Age (years), mean (±SD)	72.1 (14)	71 (12.5)	0.82
Sex (Male), n (%)	8 (100)	60 (66.7)	0.102
Charlson index, median (IQR)	5 (4–9.5)	5 (3–6)	0.357
Chronic kidney failure (clearance <60 mL/min), n (%)	4 (50)	39 (43.3)	0.73
Diabetes mellitus, n (%)	1 (12.1)	26 (28.9)	0.439
Respiratory disease, n (%)	1 (12.5)	22 (24.4)	0.676
Neurological disease, n (%)	1 (12.5)	18 (20)	1.000
HIV infection, n (%)	0 (0.0)	2 (2.2)	1.000
Solid organ transplantation, n (%)	0 (0.0)	4 (4.4)	1.000
Active neoplasm, n (%)	2 (25)	8 (8.9)	0.188
Chronic liver disease, n (%)	2 (25)	6 (6.7)	0.128
Corticoids/other immunosuppressive drugs in previous month, n (%)	1 (12.5)	10 (11.1)	1.000
Concomitant infection, n (%)	2 (25)	22 (25)	1
TAVI, n (%)	0 (0.0)	8 (9.0)	1.000
Valve affected, n (%)			
- Mitral	2 (25)	33 (36.7)	0.706
- Aortic	5 (62.5)	61 (69.3)	0.702
- Tricuspid	1 (12.5)	5 (5.7)	0.781
- Aortic -mitral	0	11 (12.5)	0.591
Type of IE, n (%):			
NVIE	2 (25.5)	57 (63.3)	0.056
Early-PVE	1 (12.5)	7 (7.8)	0.507
Late-PVE	5 (62.5)	21 (23.3)	0.029
CIED-IE	0 (0.0)	3 (3.3)	1
CIED-IE device and valve	0 (0.0)	3 (3.3)	1
Mitral and aortic valve affected, n (%)	0	8 (9.8)	1
E. faecalis	7 (87.5)	78 (86.7)	0.678
E. faecium	1 (12.5)	10 (11.1)	
Other	0 (0.0)	2 (2.2)	
Heart Surgery, valve replacement, and/or device extraction previous DBV	0	32 (35.6)	0.05
Related-death, n (%)	1 (12.5)	1 (1.1)	0.157
Concomitant antibiotic treatment with DBV	0	13 (14.4)	0.592
Previous antibiotics, n (%)			
Ampicillin in monotherapy	2 (25)	11 (12.2)	0.286
Ceftriaxone plus Ampicillin	4(50)	64 (71.1)	0.244
Daptomycin	1 (12.5)	32 (36.7)	0.256
Ceftaroline plus daptomycin	0 (0)	4 (4.4)	1
Linezolid	0 (0)	8 (8.9)	1
Vancomycin	1 (12.5)	8 (8.9)	0.551
Amoxicillin in monotherapy	2 (25)	4 (4.4)	0.074
Amoxicillin combined with ceftriaxone	0	5 (5.5)	0.22
Adverse event	1 (11.1)	0 (0.0)	0.092

p* = significance, OR = odds ratio, CI = confidence interval.
NVIE: native valvule IE; PVE: prosthetic valvular endocarditis, CIED-IE: cardiovascular implantable electronic devices infectious endocarditis; p*>0.05 significance.

strains with low gentamycin-resistance percentages.[24] Various factors may explain the lower mortality rate in the present study, including technological advances in cardiovascular surgery, the higher proportion of patients undergoing surgery,[25] and the prescription of a combination of fast-acting bactericides (ampicillin + ceftriaxone) during the acute phase of IE (<10 % received vancomycin). Furthermore, the administration of DBV in consolidation phase permitted earlier discharge, thereby reducing the health risks associated with prolonged hospitalization, including infections, falls, and functional impairment. In the EURO-ENDO cohort of 3116 patients, with left-valve EI involvement in 78.6 % of cases and epidemiologically comparable to the present series, the performance of early surgery when required was associated with a lower mortality rate, finding that its non-performance was due to high surgical risk.[26]

In the present study, the main reason for DBV administration was to facilitate discharge, reducing the hospital stay and associated costs and lowering the risk of nosocomial complications. In this line, the ENHANCE clinical trial in patients with SSTIs found that DBV treatment reduced their hospital stay, improving their work productivity and capacity for daily life activities.[27] Similar findings were observed in real-life studies of patients with bacteremia and endocarditis treated with this lipoglycopeptide.[28] A retrospective multicenter cohort study of adult patients with IE due to gram-positive cocci (GPC) compared DBV (n = 22) as sequential treatment *versus* standard of care therapy (n = 47), finding a similar effectiveness and shorter hospital stay, especially in patients with EIE.[29] A clinical trial in patients with SSTIs also reported that DBV administration improved the quality of life of patients, who described greater satisfaction and comfort in comparison to conventional treatment.[30]

The sole adverse effect was acute tubular necrosis in one patient, which was not directly related to the receipt of DBV. Despite receiving a median of 2500 mg DBV, with a half-life of around four weeks, no patient suffered from diarrhea due to *C. difficile*. This intravenously administered lipoglycopeptide has a high level of binding to plasmatic proteins and a very large volume of distribution in intracellular fluid. It is eliminated slowly, in part by the kidney, with little intra- or interindividual variability in its linear pharmacokinetics and no pharmacokinetic interactions, and it needs no dose adjustment in patients with mild or moderate kidney failure, hemodialysis, liver failure, or advanced age.[12] DBV therefore offers multiple benefits as an antibiotic in elderly polymedicated patients with comorbidities, such as patients with EIE. Regarding the impact on the endogenous microbiota observed with most antibiotics, DBV was found to have no effect on normal gut microflora in healthy individuals, with no changes in counts of *Enterococci*, *E. coli, Lactobacilli, Clostridioides*, or *Bacteroides* and no emergence of DBV-resistant aerobic or anaerobic bacteria.[31] This represents a theoretical advantage of DBV, given that current antibiotics of choice against EIE (ampicillin + ceftriaxone or vancomycin + gentamicin) have been associated with gut microflora disorders, dysbiosis, and the development of resistant strains in the microbiota.[32,33] An *in vitro* study reported significantly lower MIC50 and MIC90 values against *C. difficile* for DBV than for vancomycin (0.016 *vs.* 0.38 and 0.03 *vs.* 3.5, p < 0.001), although the authors called for clinical trials to verify the usefulness of DBV against this species.[34]

Finally, outpatient treatment with DBV for the last month of IE proved to be a cost-effective strategy in select patients, in agreement with previous findings that DBV is an option for the off-label treatment of infections by GPC, facilitating the early discharge and outpatient management of patients.[35,36]

The study is limited by its retrospective observational design, by the reduced number of clinical events (relapses or death), hampering robust risk factor analysis; and by the heterogeneity of DBV administration, restricting the extrapolation of our findings. However, it is the first investigation specifically designed to analyze the outcomes of DBV as consolidation treatment in patients with EIE. Additional strengths include its large sample size and its collaborative and international scope, with the participation of hospitals from two European Union countries. Further studies are warranted to compare the effectiveness of the combination of ampicillin + ceftriaxone *versus* DBV to treat IE by *Enterococcus* spp.

Table 6
Description of patients who relapsed.

N	Sex	Age	Type of IE	CI	Bacteria	Surgery requirement	Previous antibiotic to DBV	Reason DVB prescription	Cause and day of relapse	Death
1	M	83	NVIE	10	*E. faecalis*	no	Ceftriaxone 4g/24 plus Ampicillin 12g/24h (17 d)	Facilitation of discharge	- severe valvular insufficiency and heart Failure – 10 days	Yes (Death related to IE)
2	M	79	Late-PVIE	4	*E. faecalis*	no	Ceftriaxone 2g/24h plus Ampicillin 12g/24h (12 d)	Facilitation of discharge	- severe valvular insufficiency – 4 months	No
3	M	85	Late-PVIE	4	*E. faecalis*	Yes (Surgery was indicated but was not performed previous to DBV because of the patient's age, situation, comorbidities)	Ceftriaxone 2g/24h plus Ampicillin 12g/24h (42 d)	Facilitation of discharge	- severe valvular insufficiency – 1 month	No
4	M	80	Late-PVIE	6	*E. faecalis*	no	Amoxicillin 12g/24h plus Ceftriaxone 2g/24h (15d)	Failure of previous treatment	8 months	No
5	M	74	Late-PVIE	10	*E. faecium*	no	Teicoplanin 900mg/24h (42 d)	Failure of previous treatment and facilitation of discharge	- Recurrent bacteremia – 12 months	Yes (Death related to IE)
6	M	64	NVIE	4	*E. faecalis*	no	Vancomycin 3g/24h (28d) + Gentamycin 240 mg (1d)	Facilitation of discharge	Bacteremia due to E. faecalis – 3 months	No
7	M	42	Late-PVIE	0	*E. faecalis*	no	Amoxicillin 9g/iv/24h + gentamycin 240 mg (17 d)	To ensure adherence, the patient was a parenteral drug addict.	- Early relapse with new vegetation on tricuspid valve of 17 mm – 17 days	No
8	M	70	Early-PVIE	9	*E. faecalis*	no	1- Amoxicillin 12g/iv/24 (9d) 2- Daptomycin 10 mg/kg/iv/24h + Piperacillin/Tazobactam 4g/iv/6h (12d)	Facilitation of discharge	- Recurrence of left shoulder arthritis – 6 months	No

M: male, W: women, CI: Charlson index, NVIE: native valvule IE; PVIE: prosthetic valvular IE; CIED-IE: cardiovascular implantable electronic devices IE; *S. aureus-MS*: *S. aureus* Methicillin-Sensible; p*>0.05 significance.

Table 7
Pharmacoeconomic analysis.

Treatment strategy	Medication cost	Specialist consultation	Nurse consultation	Total
3.5 weeks covered with 2500 mg DBV	2150.65 €	892.75 €	71.92 €	3115.31 €
Control strategy	Medication cost	Hospital stay (3.5 weeks)		Total
3.5 weeks of hospital stay	661.28 €	13,521.55 €		14,182.83 €
Difference between DBV and. Control strategy	Medication cost	Consultations and stay		Difference per patient
	1489.37 €	−12,556.89 €		−11,067.52 €

5. Conclusions

DBV appears to be effective, safe, and cost-effective as consolidation therapy in patients with EIE, with minimal adverse events.

CRediT authorship contribution statement

Carmen Hidalgo-Tenorio: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Svetlana Sadyrbaeva-Dolgova:** Visualization, Validation, Software, Data curation. **Eduardo Aparicio-Minguijón:** Visualization, Validation, Software. **Arístides Alarcón:** Visualization, Validation, Software. **Antonio Plata:** Visualization, Validation, Software. **Francisco Javier Martínez Marcos:** Visualization, Validation, Software. **Beatriz Álvarez-Álvarez:** Visualization, Validation, Software. **Belén Loeches:** Visualization, Validation, Software. **Benedetta Varisco:** Visualization, Validation, Software. **Agustín Estévez:** Visualization, Validation, Software. **Carmen Herrero:** Visualization, Validation, Software. **Francesc Escrihuela-Vidal:** Visualization, Validation, Software. **Lucia Boix-Palop:** Visualization, Validation, Software. **Yvon Ruch:** Visualization, Validation, Software. **Florent Valour:** Visualization, Validation, Software. **Nahéma Issa:** Visualization, Validation, Software. **Pauline Thill:** Visualization, Validation, Software. **Sophie Nguyen:** Visualization, Validation, Software. **Samantha Poloni:** Visualization, Validation, Software. **Romain Millot:** Visualization, Validation, Software. **Nathan Peiffer-Smadja:** Visualization, Validation, Software. **Timothée Boyer-Chammard:** Visualization, Validation, Software. **Kevin Diallo:** Visualization, Validation, Software. **Romaric Larcher:** Visualization, Validation, Software. **Jose M. Miró:** Writing – review & editing, Visualization, Validation, Supervision, Software. **David Luque-Paz:** Writing – review & editing, Visualization, Validation, Supervision, Software.

Declaration of competing interest

The authors declare no conflicts of interest relevant to the manuscript submitted to the Journal.

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Appendix A. Supplementary data

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