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ORIGINAL PAPER

Antithrombotic therapy in infective endocarditis: Long-term clinical outcomes of a retrospective cohort study

Carlotta Posner[1] · Elias Füssl[1] · Firat Koyun[1] · Kostiantyn Kozakov[2] · Henrik Heuer[2] · Florian Hitzenbichler[3] · Jozef Micek[1] · Lukas Krämer[1] · Hiba Daas[1] · Samuel T. Sossalla[4,5] · Lars S. Maier[1] · Kurt Debl[1] · Felix Schlachetzki[6] · Christian Schach[1]

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Abstract

Background Administering antithrombotic therapy (ATT) in patients with infective endocarditis (IE) involves a complex balance of bleeding and thromboembolic risks. Data on outcomes beyond the acute phase remain limited. This retrospective single-center cohort study had two aims: first, to describe the use of anticoagulation during the acute phase of left-sided IE; and second, to examine, without inferring causality, how anticoagulation, as used in routine care, correlated with in-hospital and long-term clinical outcomes, including mortality and neurological events.

Methods ATT in patients with left-sided IE was assessed retrospectively and categorized into two groups: any therapy that included anticoagulation (AC) and therapy without anticoagulation (No-AC). Two observational periods were analyzed: the in-hospital phase and the period beginning 3 months after discharge, when 30% of patients had their ATT modified. Vital and neurological status were obtained by standardized telephone follow-up (mean follow-up time 4.2 ± 3.1 years). Log-rank tests, Kaplan–Meier estimates, Cox regression analyses, and matched analyses were used to explore correlations between ATT and these outcomes.

Results A total of 504 hospitalized patients (mean age 65 ± 13 years, 25% female) with left-sided IE were included. During inpatient treatment, 83 patients (16%) died, with no relevant difference between AC and No-AC groups. During follow-up, patients in the AC group showed a more favorable value for the combined endpoint of mortality and unfavorable neurological function ($P = 0.029$) that was driven primarily by higher survival rates ($P < 0.001$). In Cox regression analyses, higher age, CHA_2DS_2-VA score, EuroSCORE II, Staphylococcus aureus bacteremia, and atrial fibrillation were each linked to a higher hazard of the combined endpoint, whereas AC showed an inverse correlation. Consecutive matched analyses yielded similar results.

Conclusion In this retrospective cohort, anticoagulated patients did not show a higher rate of adverse events during hospitalization and had a lower long-term event rate. These findings represent correlations observed in a non-randomized, single-center setting and may partly reflect differences in underlying risk profiles and treatment selection (confounding by indication and residual confounding). Prospective studies are needed to confirm any causal effects and to define more precisely the role of ATT in patients with IE and elevated cardiovascular risk.

Carlotta Posner and Elias Füssl contributed equally to this work.

✉ Christian Schach
christian.schach@ukr.de

[1] Universitäres Herzzentrum Regensburg, Klinik und Poliklinik für Innere Medizin II, Abteilung für Kardiologie, Universitätsklinikum Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany

[2] Universitäres Herzzentrum Regensburg, Klinik und Poliklinik für Herz-, Thorax- und herznahe Gefäßchirurgie, Universitätsklinikum Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany

[3] Stabsstelle Infektiologie, Universitätsklinikum Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany

[4] Medizinsche Klinik 1, Justus-Liebig-Universität Gießen, Klinikstraße 33, 35392 Gießen, Germany

[5] Abteilung für Kardiologie, Kerckhoff-Klinik GmbH, Ludwigstr. 23, 35390 Bad Nauheim, Germany

[6] Klinik und Poliklinik für Neurologie, Universität Regensburg, Bezirksklinikum Regensburg, Universitätsstraße 84, 93053 Regensburg, Germany

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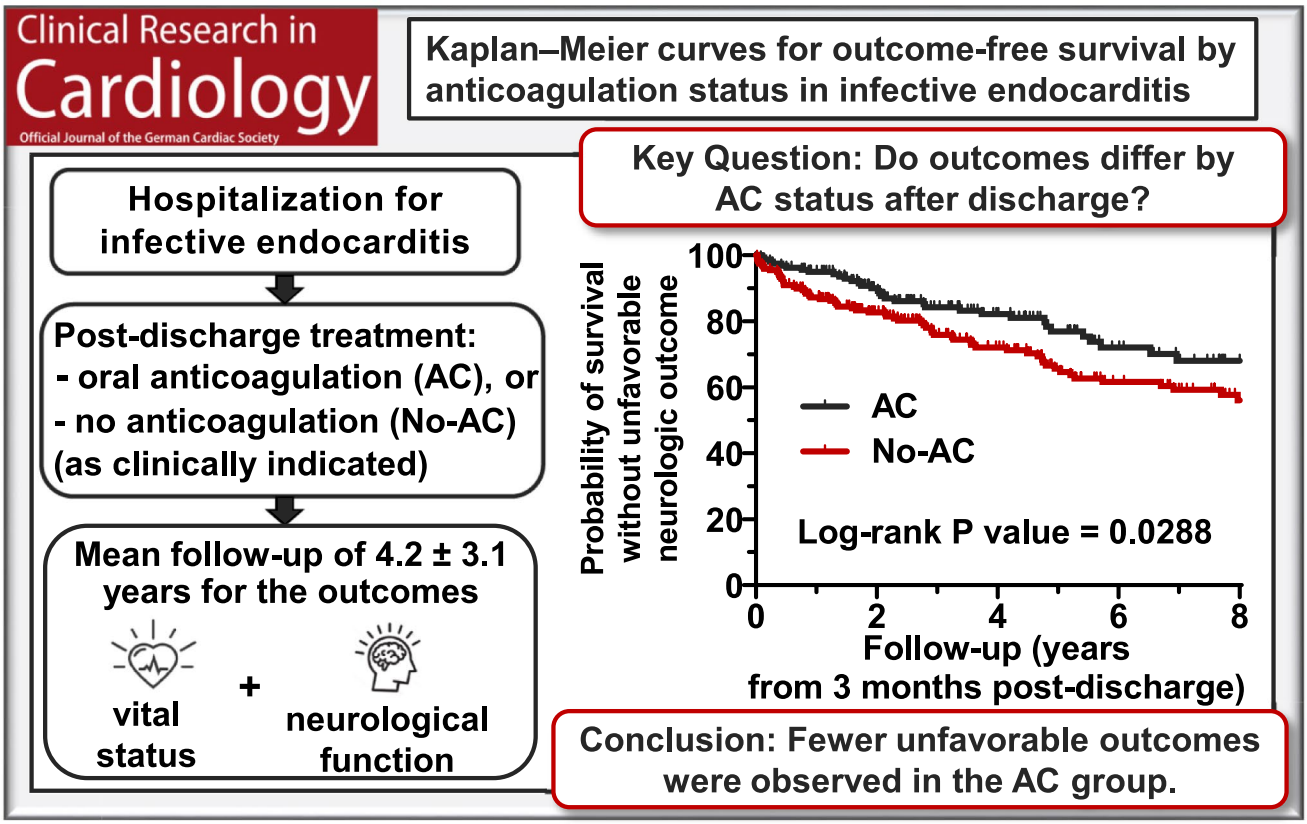
Graphical Abstract



Keywords Infective endocarditis · Antithrombotic therapy · Anticoagulation · Mortality · Neurological outcome · Cox regression

Introduction

Infective endocarditis (IE) is a life-threatening infection of the endocardial surface of the heart, usually caused by bacterial or fungal pathogens [1, 2]. Its incidence has gradually increased since it was first described in the nineteenth century and is currently estimated at 15–80 cases per 1 million inhabitants per year, based on population-based studies [1]. Recent global burden analyses indicate an average annual increase in IE incidence of approximately 1.2% in age-standardized rates [3]. Despite advances in diagnostics and treatment, the prognosis of IE remains poor. Large registries and contemporary reviews report in-hospital mortality rates of 15–20% and 1-year mortality approaching 30–40% [1, 4, 5]. Several countries and global analyses have reported rising or persistently high mortality over recent decades, which may be related to a higher burden of comorbidities and risk factors, increasing antibiotic resistance, an aging population, delayed diagnosis, and the need for complex multidisciplinary care [1, 3, 4].

Neurological complications are among the most frequent and serious manifestations of IE, occurring in approximately 20–40% of patients and substantially worsening prognosis [6, 7]. Up to one-third of patients develop clinically overt cerebrovascular events, and systematic neuroimaging studies have shown acute brain lesions in up to 70–80% of patients, including many without overt neurological symptoms [8–10]. The coagulation system is involved at every stage of the disease process: endothelial injury and local inflammation promote non-bacterial thrombotic vegetations, which serve as a scaffold for bacterial adhesion and vegetation growth and contribute to embolization and valve destruction [11, 12]. This has led to growing interest in the coagulation system as a potential therapeutic target. At the same time, the clinical balance is delicate: antithrombotic therapy (ATT) is used to reduce thromboembolic risk but simultaneously increases the risk of bleeding, requiring individualized decisions.

Despite the clinical relevance of ATT in IE, evidence-based guidance is limited, and current recommendations

remain heterogeneous and often cautious. Major guideline documents emphasize that data on antithrombotic strategies in IE are largely observational, and specific recommendations are based on low levels of evidence [2, 5, 13]. Initiation of anticoagulation (AC) solely for stroke prevention in acute IE is generally discouraged, as available studies have not demonstrated a clear reduction in stroke risk and have raised concerns about intracranial hemorrhage, particularly in patients with neurological complications [2, 6]. Management becomes even more complex in patients who already have indications for AC or antiplatelet therapy, such as mechanical prosthetic valves or coronary artery disease. Several cohort and registry studies suggest that chronic ATT does not consistently reduce the incidence of cerebrovascular events or overall mortality in IE and in some settings may be associated with higher bleeding risk [14, 15]. Consequently, current guidelines offer only limited, largely nonspecific recommendations regarding ATT in IE and emphasize individualized, multidisciplinary decision-making [2, 13]. Experimental and translational data further suggest that endothelial injury and valve damage predispose to IE and may contribute to recurrent disease, raising additional questions about long-term vascular risk and the appropriate duration of ATT in selected patients [16, 17]. Therefore, clinicians face the challenge of balancing potential benefits of AC with the risks of both bleeding and embolism within a context of scarce high-quality evidence and substantial heterogeneity in patient profiles [5, 14].

Against this background, we conducted a retrospective cohort study of patients with left-sided IE. Our aims were twofold: to describe the use and apparent safety of AC during the acute phase of the disease, and to examine how AC, as used in routine clinical practice, correlates with long-term outcomes, specifically mortality and neurological function. Given the ongoing controversy surrounding ATT during and after the active phase of IE and the lack of robust prospective data, this study seeks to provide observational evidence that may help to inform, but not determine, clinical decision-making in this complex patient population.

Methods

Study design and patient population

This single-center registry included patients diagnosed with IE who were treated at the University Hospital Regensburg between 2013 and 2024. After approval by the Ethics Committee of the University of Regensburg (reference # 18–) in 2018, data collection proceeded prospectively. For the present analysis, we included adults (≥ 18 years) with left-sided IE defined according to the modified Duke criteria [18]. Patients were excluded from the follow-up analysis if they declined or were unavailable for telephone follow-up. Clinical data were extracted from the hospital information system (SAP ERP 6.0, Walldorf, Germany) and pseudonymized prior to analysis. The IE diagnosis was based on all available clinical information, including operative reports, histopathological findings, imaging results, laboratory tests, microbiological data, and discharge summaries. Cases were adjudicated according to the modified Duke criteria and reviewed by a clinical committee consisting of cardiologists, cardiac surgeons, microbiologists, and histopathologists. Three observational periods were defined: (1) the in-hospital stay, (2) the period from discharge to 3 months post-discharge, and (3) the follow-up period beginning 3 months after discharge. The 3-month timepoint was chosen because ATT was frequently modified after surgery with biological valve prostheses, according to a class IIa/B recommendation [24]. For each observational period, patients were categorized according to their ATT at the beginning of that period into two groups: no therapy or antiplatelet therapy without anticoagulation (No-AC) and any regimen including anticoagulation (AC).

Echocardiography

All patients underwent transthoracic echocardiography followed by transesophageal echocardiography using either a Philips iE33 or Epiq system (Philips, Hamburg, Germany). Vegetations were defined as distinct, irregular, mobile structures attached to the surface of the affected valve. Vegetation size was measured along the longest axis. An abscess was diagnosed when a well-demarcated area of reduced echogenicity was identified within the valve annulus or adjacent myocardial structures in the context of valvular infection.

Microbiological analysis

Valve cultures and polymerase chain reaction (PCR) testing were performed at the local microbiology laboratory. Blood cultures were obtained from all patients; some initial samples were processed at referring hospitals, whereas additional cultures were performed at the local center using the BD Bactec FX system (Becton Dickinson, Heidelberg, Germany). Antimicrobial susceptibility testing followed established laboratory protocols.

For valve PCR, species identification was performed using broad-range PCR methods accredited according to DIN EN ISO 15189. Amplification targeted the V7–9 variable regions of the 16S rRNA gene for bacteria and the 18S rRNA gene for fungi. Sanger sequencing was carried out on an ABI PRISM® 310 Genetic Analyzer, and sequences were analyzed using the centroid database of the SmartGene Integrated Database Network System.

Assessment of neurological outcome using the modified Rankin Scale

Neurological functional status was assessed using the modified Rankin Scale (mRS), a widely used measure of disability and dependence in daily activities [19]. The mRS ranges from 0 to 6 (0: no symptoms; 6: death), with higher scores indicating more severe disability. In this study, mRS scores were estimated at admission, at hospital discharge, and during telephone follow-up by trained clinicians. Follow-up assessments were used to evaluate long-term functional status and the impact of disease course and complications on daily living.

Statistical analysis

Baseline characteristics are reported as frequencies and percentages for categorical variables and as mean ± standard deviation for continuous variables. Group differences were compared using Student's t-test for continuous variables and the chi-squared test for categorical variables, as appropriate. In-hospital outcomes (embolism and intracerebral bleeding) were analyzed according to anticoagulant use at admission. One-way ANOVA was used to compare mRS values, which was followed by pairwise comparisons. After discharge, the combined endpoint of mortality and unfavorable neurological function, as well as each component separately, was analyzed using log-rank tests and displayed with Kaplan–Meier curves. Cox proportional hazards models were applied to estimate hazard ratios for explanatory variables; the proportional hazards assumption was tested using Schoenfeld residuals. Variables with a P-value < 0.05 in the comparison of clinical characteristics of the follow-up cohort or in Cox regression analyses were included in the matched analysis. To incorporate long-term events while avoiding instability due to sparse data at later timepoints, time-to-event analyses were truncated at 8 years. Statistical significance was defined as a two-sided α level of 0.05. All analyses were performed using Stata version 19 (StataCorp, College Station, TX, USA) and GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

Of the 504 patients included in the in-hospital analyses (25% female; mean age 65 ± 13 years), 116 (23%) received AC at admission. Compared with patients without AC (No-AC), those in the AC group were older and had higher EuroSCORE II and CHA_2DS_2-VA scores. They more frequently had atrial fibrillation (AF) and prosthetic valves and underwent surgery less often; when surgery was performed, operative time was longer in the AC group (Table 1). In the follow-up cohort, patients receiving AC were younger and more often treated surgically, whereas EuroSCORE II and CHA_2DS_2-VA scores were similar between groups. AF remained more prevalent in the AC group. In the in-hospital cohort, 221 biological valves (155 aortic, 66 mitral) and 67 mechanical valves (47 aortic, 17 mitral, 3 pulmonary) were implanted. In the follow-up cohort, 159 biological valves (115 aortic, 44 mitral) and 61 mechanical valves (42 aortic, 16 mitral, 3 pulmonary) were implanted. In the in-hospital cohort, 61 patients with AF were not on AC. Of these, 27 had a history of AF, 9 had a CHA_2DS_2-VA score of 0 or 1, 5 had undergone left atrial appendage closure, 5 declined AC, 8 received individualized treatment because of prior bleeding, and the reason for lacking AC was unknown in 6 patients. In the follow-up cohort, 26 patients with AF were not on AC: 6 had a CHA_2DS_2-VA score of 0 or 1, 9 were considered to have AF only in the context of severe infection, 7 discontinued AC due to bleeding events (3 with a left atrial appendage closure device), 2 declined AC, and the reason was unknown in 2 patients. Fifteen patients had infection of a right-sided valve in addition to left-sided involvement.

Continuous variables are expressed as mean ± SD, categorical variables as n (%). Operative therapy (OP) time is given as cutting/suture time. Abbreviations: AC = anticoagulation; AF = atrial fibrillation; AFlut = atrial flutter; BMI = body-mass index; CHA_2DS_2-VA = congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74; CRP = C-reactive protein; LVEF = left ventricular ejection fraction; WBC = white blood cell count.

Acute outcomes: in-hospital cohort

The length of hospital stay did not differ between the No-AC (33.6 ± 32.9 days) and AC groups (35.4 ± 29.3 days; P = 0.589 (t-test), P = 0.181 (rank-sum test); Supplemental Fig. 1). In-hospital mortality was similar between groups (log-rank P = 0.770). Rates of embolic events and intracerebral bleeding also did not differ between groups (Table 2). Therefore, within the limitations of this observational design, AC at admission did not reveal an obvious safety signal during the acute phase of IE.

Period from discharge until 3 months after discharge

During the period from discharge to 3 months post-discharge, 106 of the 421 discharged patients discontinued AC (Fig. 1). Twelve patients died in the No-AC group and 16 in the AC group. Kaplan–Meier curves did not show a relevant difference in survival between groups (Supplemental Fig. 2).

Table 1 Clinical characteristics of infective endocarditis patients at admission according to their antithrombotic therapy

Variable	*No-AC (n = 388)*	*AC (n = 116)*	*P*	*No-AC (n = 199)*	*AC (n = 159)*	*P*
Observational period	In-hospital			Follow-up		
Age (years)	63.4 ± 13.2	69.3 ± 10.7	**< 0.001**	66.3 ± 13.2	62.7 ± 13.1	**0.011**
Sex, female	92 (24)	35 (30)	0.160	51 (26)	43 (27)	0.762
BMI (kg/m²)	27.5 ± 9.0	28.1 ± 5.8	0.484	27.1 ± 10.3	28.1 ± 6.8	0.270
EuroSCORE II (%)	8.6 ± 11.3	17.8 ± 17.1	**< 0.001**	9.0 ± 11.6	8.3 ± 10.1	0.542
CHA_2DS_2-VA score	2.7 ± 1.6	3.4 ± 1.5	**< 0.001**	2.8 ± 1.7	2.6 ± 1.5	0.219
AF or AFlut	61 (16)	40 (34)	**< 0.001**	26 (13)	46 (29)	**< 0.001**
LVEF < 50%	80 (21)	40 (34)	**0.003**	39 (20)	33 (21)	0.800
Aortic valve	215 (55)	71 (61)	0.269	109 (55)	93 (58)	0.481
Mitral valve	140 (13)	37 (15)	0.731	73 (37)	54 (34)	0.593
Multi-valve	52 (13)	17 (15)	0.731	29 (15)	22 (14)	0.843
Right-sided valve	8 (2)	5 (4)	0.180	4 (2)	3 (2)	0.933
Prosthetic valve	82 (21)	56 (48)	**< 0.001**	52 (26)	41 (26)	0.849
Abscess	77 (20)	25 (22)	0.782	39 (20)	26 (16)	0.457
CRP, initial (mg/L)	87.8 ± 80.2	77.5 ± 79.3	0.225	77.7 ± 72.4	78.9 ± 79.1	0.884
CRP, maximal (mg/L)	175 ± 99	165 ± 94	0.344	162 ± 85	165 ± 89	0.753
Creatinine (mg/dL)	1.56 ± 1.33	1.70 ± 1.50	0.328	1.43 ± 1.19	1.36 ± 0.96	0.549
Causative microorganism	324 (84)	101 (87)	0.120	167 (84)	137 (86)	0.534
Staphylococcus aureus	112 (29)	34 (29)	0.867	57 (29)	41 (26)	0.435
Coagulase-negative Staphyl. species	38 (10)	21 (18)	**0.021**	20 (10)	15 (9)	0.780
Streptococcus species	93 (24)	24 (21)	0.332	44 (22)	47 (30)	0.132
Enterococcus species	42 (11)	15 (13)	0.627	25 (13)	22 (14)	0.794
Others	39 (10)	7 (6)	0.149	21 (11)	12 (8)	0.287
OP during hospitalization	287 (74)	70 (60)	**0.005**	129 (65)	122 (77)	**0.014**
OP time (min)	210 ± 72	246 ± 82	**0.003**	205 ± 66	207 ± 67	0.841

This was confirmed by the log-rank test (P = 0.697) and contingency analysis (P = 0.355). Overall, comparatively few events occurred during this interval, and no clear difference between AC and No-AC groups was observed.

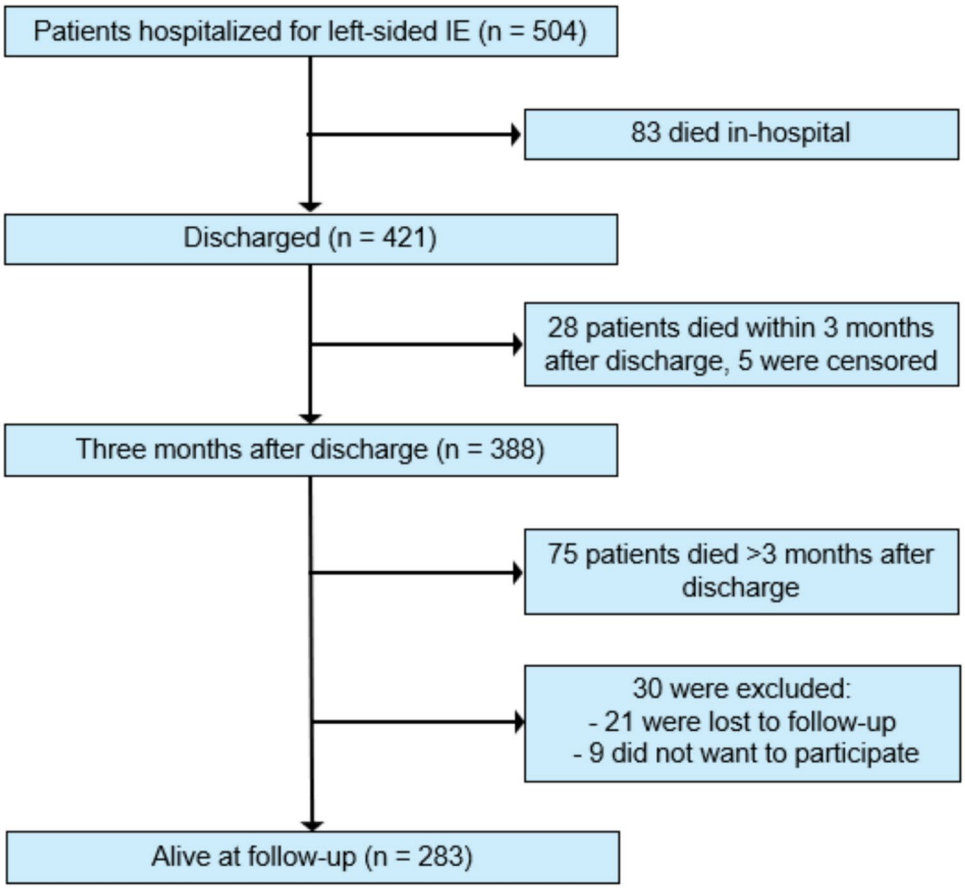
Follow-up period beginning 3 months after discharge

During the extended follow-up (mean 4.2 ± 3.1 years; median 3.5 years, interquartile range 1.7–6.6), we observed differences between groups in the combined endpoint of mortality and unfavorable neurological outcome (Graphical Abstract). Patients receiving AC had a lower probability of reaching the combined endpoint compared with those without AC. In multivariable Cox regression analysis, older age, higher EuroSCORE II, higher CHA_2DS_2-VA score, Staphylococcus aureus bacteremia, and AF/AFlut were each linked to a higher hazard of the combined endpoint. AC showed an inverse correlation with the combined endpoint (hazard ratio 0.45, 95% CI 0.23–0.88; Table 3). The difference in the combined endpoint was driven by mortality (Fig. 2). Time-to-event analysis did not show a relevant difference in unfavorable neurological outcome between groups (P = 0.465). Figure 3A depicts a significant increase in mRS scores over the observational period, whereas Fig. 3B shows similar proportions of patients with unfavorable neurological outcome in both groups, suggesting no clear difference in neurological function. For this analysis, patients with an mRS score of 6 (death) were excluded because mortality was evaluated separately.

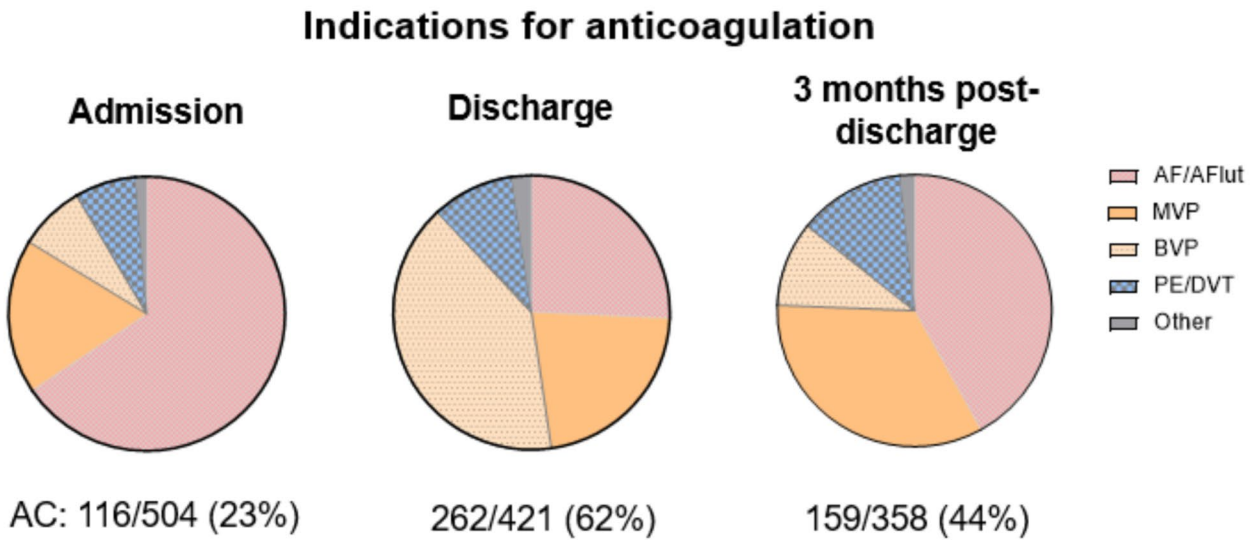
Matched analyses and cardiovascular risk

In matched analyses, we explored adjusted differences in the combined endpoint between AC and No-AC groups. Variables that differed significantly between groups in baseline characteristics (Table 1) or in the Cox regression model (age, EuroSCORE II, CHA_2DS_2-VA score, Staphylococcus aureus bacteremia, operative therapy, and AF/AFlut) were included in the models. Across regression adjustment, nearest-neighbor matching, and propensity-score matching,

A


Patients hospitalized for left-sided IE (n = 504)
83 died in-hospital
Discharged (n = 421)
28 patients died within 3 months after discharge, 5 were censored
Three months after discharge (n = 388)
75 patients died >3 months after discharge
30 were excluded:
- 21 were lost to follow-up
- 9 did not want to participate
Alive at follow-up (n = 283)

B


Indications for anticoagulation
Admission
Discharge
3 months post-discharge
AF/AFlut
MVP
BVP
PE/DVT
Other
AC: 116/504 (23%)
262/421 (62%)
159/358 (44%)

◂**Fig. 1** Patient and study flow. (**A**) Flowchart of infective endocarditis (IE) patient inclusion and follow-up. Between discharge and 3 months post-discharge, 33 patients were censored or died. Three months after discharge, 106 of 358 patients (30%) had discontinued anticoagulation (AC). Thirty patients were excluded from the follow-up analysis (21 lost to follow-up, 9 declined participation). (**B**) Indications for AC at the start of each observational period (admission, discharge, and 3 months post-discharge). Abbreviations: AF = atrial fibrillation; AFlut = atrial flutter; BVP = biological valve prosthesis; DVT = deep vein thrombosis; MVP = mechanical valve prosthesis; PE = pulmonary embolism

the estimated difference (labeled as average treatment effect, ATE, and average treatment effect among the treated, ATET, according to statistical convention) in the probability of the combined endpoint between AC and No-AC ranged from −0.17 to −0.28 (Table 4). In other words, within this observational cohort, patients receiving AC had an approximately 17–28 percentage point lower probability of the combined endpoint over 8 years of follow-up after accounting for measured covariates. These estimates describe adjusted differences between groups and should not be interpreted as causal treatment effects.

Because thromboembolic stroke is a major concern in patients with AF and the CHA_2DS_2-VA score is widely used for risk stratification, we also evaluated its performance—together with EuroSCORE II—in the broader IE population, including patients in sinus rhythm. Patients with a CHA_2DS_2-VA score ≥ 5 or a EuroSCORE II ≥ 6 had markedly higher rates of the combined endpoint of mortality and unfavorable neurological outcome (log-rank $P < 0.001$ for both). In this cohort, higher CHA_2DS_2-VA and EuroSCORE II values therefore identified a subgroup of patients with particularly unfavorable long-term outcomes, irrespective of the presence of AF.

Discussion

In IE, the management of ATT remains clinically important but controversial, and clinical practice varies widely. In this single-center retrospective cohort, we examined how AC, as used in routine care, correlated with mortality and neurological function during hospitalization and long-term follow-up. Because treatment allocation was not randomized and confounding by indication was likely, these findings are descriptive and do not allow causal inference. Within these constraints, we did not observe an increase in in-hospital adverse events among patients receiving AC, and during long-term follow-up, patients on AC showed lower rates of the combined endpoint of mortality and unfavorable neurological outcome. These observations are hypothesis-generating and should be interpreted with caution.

In-hospital outcomes

Cerebral lesions and microembolic findings on MRI are frequent in IE, often without overt neurological symptoms. A prospective cohort by Cooper et al. reported acute brain lesions in up to 80% of patients with left-sided IE, whereas only 25% had clinical stroke symptoms [8]. That study, however, did not examine the impact of AC on these MRI findings. An MRI-based study of 120 patients with left-sided IE found that ischemic brain lesions correlated with vegetation size and Staphylococcus aureus infection, but not with prior AC use [20]. In the same study, cerebral microbleeds were linked to prosthetic valve infection rather than to AC. More recent observational data suggest that AC may correlate with lower in-hospital mortality in IE, [15] but its relevance for silent cerebral embolization remains unclear. In our cohort, in-hospital mortality, embolic events, and intracerebral bleeding did not differ between patients with and without AC at admission. Within the limits of sample size and observational design, AC appeared to be tolerated in carefully selected patients. However, given the substantial embolic and bleeding risks in this population, decisions to continue or discontinue AC during hospitalization should remain individualized and reserved for situations in which clinical circumstances clearly justify a change.

Follow-up period

Evidence regarding ATT after discharge in IE is sparse and heterogeneous. Observational studies of antiplatelet therapy have reported conflicting results, with some suggesting increased mortality (e.g. Snygg-Martin et al.) and others, such as Anavekar et al., finding no clear difference in outcomes [21, 22]. Registry and cohort studies consistently show that neurological complications during the acute phase of IE are linked to worse short- and long-term prognosis [23, 24]. Patients with neurological involvement at baseline have higher mortality and poorer functional outcomes years after discharge, but most studies do not systematically report ATT use after hospitalization. In this context, our study contributes additional observational data. During long-term follow-up, patients receiving AC had lower mortality and a lower rate of the combined endpoint than patients without AC. These correlations may reflect differences in underlying cardiovascular risk profiles and treatment patterns among patients selected for continued AC rather than a direct effect of AC itself. The strong correlations of both CHA_2DS_2-VA and EuroSCORE II with mortality and the combined endpoint support the importance of overall cardiovascular risk in this setting. CHA_2DS_2-VA and EuroSCORE II were originally developed for different clinical indications, yet they share several key variables (such as age, diabetes, and

Table 2 In-hospital outcomes according to antithrombotic therapy

Outcome	*No-AC (n = 388)*	*AC (n = 116)*	*P*
Embolic event	209 (54)	69 (59)	0.286
≥ 2 sites	41 (11)	8 (7)	0.242
Site of embolism			
Brain	115 (30)	27 (23)	0.181
Spleen	54 (14)	14 (20)	0.609
Kidney	31 (8)	11 (9)	0.610
Liver	5 (1)	2 (2)	0.725
Mesentery	7 (2)	3 (3)	0.596
Eye	12 (3)	4 (3)	0.848
Extremity	17 (4)	5 (4)	0.974
Coronary	4 (1)	2 (2)	0.546
Other	10 (3)	5 (4)	0.335
Intracerebral bleeding	38 (10)	18 (16)	0.085
Light to moderate	25 (6)	11 (9)	0.265
Severe	13 (3)	7 (6)	0.194

AC = anticoagulation, other abbreviations as in Table 1

prior cardiovascular events) and can be viewed as markers of global cardiovascular vulnerability [25, 26]. One possible interpretation of our findings is that IE may unmask or amplify pre-existing cardiovascular risk, and that patients with higher risk scores are more often maintained on AC and more closely monitored, which remains speculative. However, alternative explanations—such as selection of more stable patients for continuing AC, survival bias, differences in follow-up intensity, and unmeasured comorbidities—are at least as plausible. Therefore, it cannot be determined from the present data whether AC modifies long-term risk after IE.

Although this study was not designed to clarify mechanisms, the results underline the need for prospective research on long-term cardiovascular risk after IE. Structural valve damage, endothelial dysfunction, persistent inflammation, and other factors may contribute to excess risk after the acute episode [27, 28]. Future studies incorporating imaging, biomarkers, and detailed functional assessments (e.g. disability scales or cognitive testing) could help to disentangle these mechanisms. Given the well-known bleeding risks of long-term AC, including intracerebral hemorrhage, continuation of AC after discharge in IE survivors should remain cautious, individualized, and closely monitored. Future prospective registries and randomized trials should systematically document post-discharge indications for AC, specific agents, duration, adherence, bleeding events, and neurological outcomes to better inform clinical practice.

Taken together, our data suggest that AC is frequently required in selected IE patients because of concomitant conditions (e.g. prosthetic valves or AF). In this cohort, AC did not reveal an obvious safety signal during the acute phase and correlated with more favorable long-term outcomes. However, these findings are observational, may be influenced by confounding by indication and selection bias, and should not be interpreted as evidence that AC itself improves prognosis. They primarily highlight the need for rigorous prospective studies specifically addressing antithrombotic strategies in IE survivors.

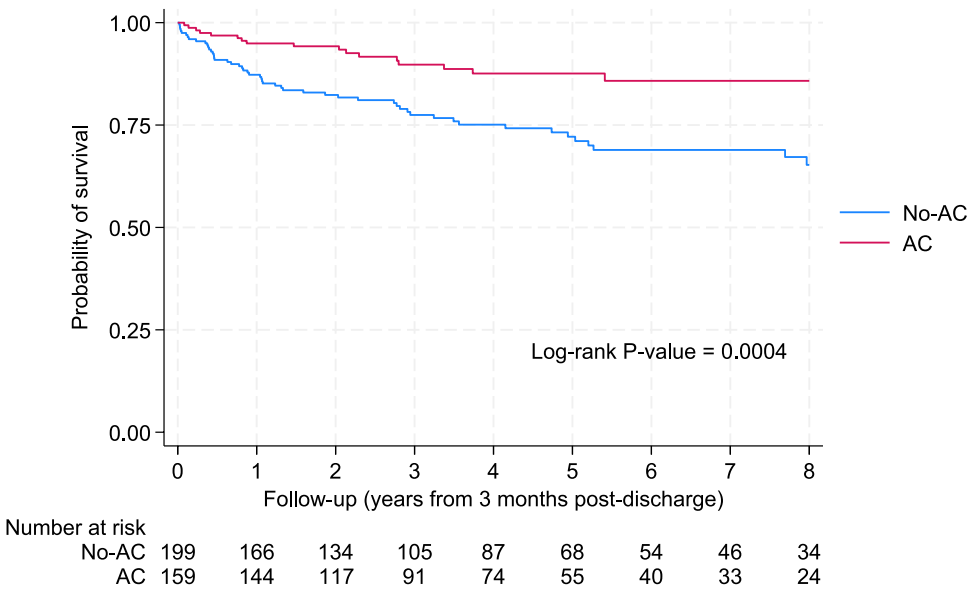


Fig. 2 Kaplan–Meier curves for all-cause mortality in patients with left-sided IE, stratified by anticoagulation (AC vs No-AC) at the beginning of the follow-up period

Table 3 Cox regression analysis of explanatory variables and the combined endpoint (mortality and unfavorable neurological function) over 8 years of follow-up

Variable	*Estimate*	*95% CI*	*|Z|*	*P*
Age (years)	1.053	1.013 to 1.095	2.61	**0.009**
Sex, female	0.763	0.381 to 1.528	−0.76	0.445
BMI (kg/m²)	1.031	0.992 to 1.070	1.55	0.122
EuroSCORE II	1.025	1.002 to 1.043	2.11	**0.035**
CHA_2DS_2-VA score	1.263	1.011 to 1.579	2.05	**0.040**
Creatinine (mg/dL)	1.193	0.926 to 1.538	1.36	0.172
CRP, initial (mg/L)	0.999	0.994 to 1.004	−0.47	0.636
CRP, maximal (mg/L)	1.001	0.997 to 1.005	0.46	0.649
Blood culture with Staph. aureus	2.483	1.343 to 4.592	2.90	**0.004**
Vegetation size (mm)	0.994	0.952 to 1.038	−0.27	0.789
LVEF < 50%	0.949	0.616 to 1.461	−0.24	0.813
Abscess	0.810	0.345 to 1.850	−0.50	0.617
Embolism	1.214	0.667 to 2.210	0.64	0.525
AF or AFlut	2.234	1.135 to 4.399	2.33	**0.020**
Operative therapy	1.536	0.761 to 3.098	1.20	0.230
Anticoagulation	0.452	0.233 to 0.879	−2.34	**0.019**

ATT = antithrombotic therapy, *CI* = confidence interval, *CRP* = C-reactive protein, other abbreviations as in Table 1

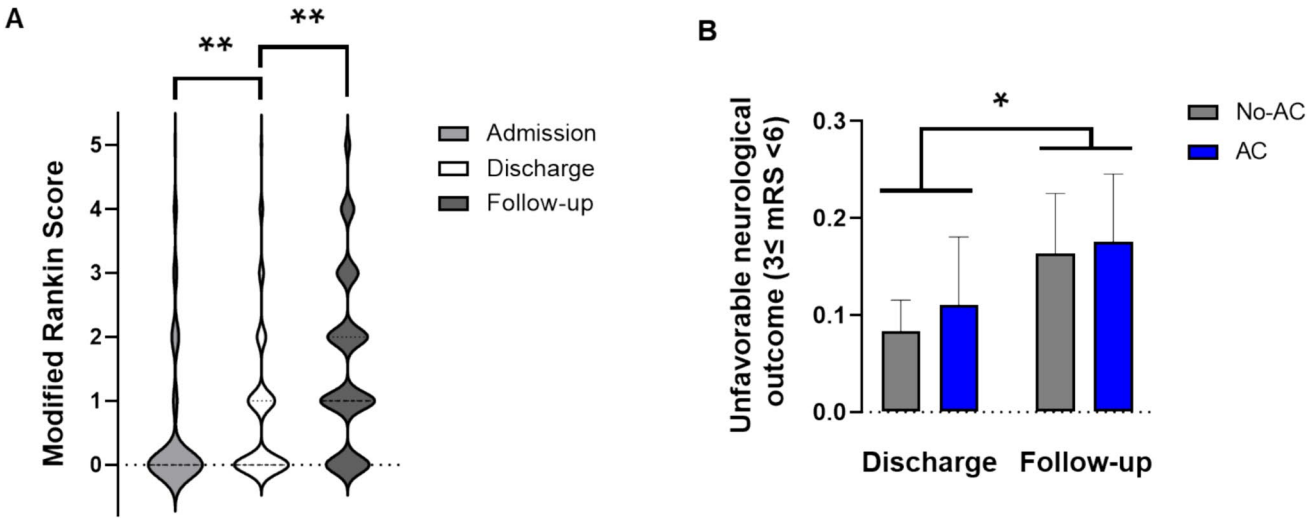


Fig. 3 Neurological outcomes measured with the modified Rankin Scale (mRS). (**A**) Violin plots depicting the distribution of mRS scores at admission, discharge, and follow-up. (**B**) Bar graphs showing the proportion of patients with unfavorable neurological outcome (mRS 3–5) at discharge and at follow-up, stratified by AC vs. No-AC. * indicates $P < 0.01$; ** indicates $P < 0.0001$

Strengths and limitations

This study has several strengths. It includes a comparatively large cohort of patients with left-sided IE treated at a tertiary care center, with systematic long-term follow-up extending well beyond hospital discharge. Neurological outcomes were assessed using the modified Rankin Scale, providing standardized information on functional status that is often underreported in IE cohorts. Multiple analytic approaches—including Cox regression and matched analyses—were used to explore the robustness of the observed correlations.

Important limitations must also be acknowledged. First, the retrospective, single-center design inherently limits generalizability and precludes any causal inference. All results should be viewed as correlations and as hypothesis-generating. Second, treatment exposure was classified into AC versus No-AC, regardless of specific antiplatelet

Table 4 Matched analyses estimating adjusted differences in the combined endpoint (mortality and unfavorable neurological function) between patients with and without anticoagulation

Model	*Coefficient*	*95% CI*	*|Z|*	*P*
Regression adjustment				
ATE	−0.200	−0.334 to −0.066	−2.93	0.003
ATET	−0.194	−0.319 to −0.068	−3.02	0.002
Nearest-neighbor matching				
ATE	−0.212	−0.376 to −0.048	−2.54	0.011
ATET	−0.277	−0.465 to −0.090	−2.89	0.004
Propensity-score matching				
ATE	−0.166	−0.302 to −0.030	−2.38	0.017
ATET	−0.248	−0.390 to −0.105	−3.41	0.001

ATE = average treatment effect, *ATET* = average treatment effect among the treated

regimens, leading to heterogeneity within groups and potential misclassification of the true antithrombotic strategy. Third, confounding by indication and selection bias are major concerns. Patients receiving AC may differ systematically from those who do not (e.g., with respect to frailty, bleeding risk, comorbidities, and physician judgment). Despite multivariable adjustment and matching, unmeasured and residual confounding cannot be excluded. Furthermore, some data were obtained from telephone follow-up, which may introduce recall bias and limit the precision of neurological assessments. The study may also be underpowered to detect differences in rare events such as intracerebral bleeding. Finally, temporal changes in surgical techniques, antimicrobial regimens, and antithrombotic strategies over the study period may have influenced outcomes.

Overall, this study should be regarded as an exploratory, hypothesis-generating analysis that underscores the need for prospective studies to better characterize the long-term impact of ATT in survivors of IE.

Conclusion

For patients diagnosed with IE, ATT is of particular interest because of the delicate balance between preventing embolic events and increasing the risk of bleeding. In this retrospective single-center cohort, AC did not appear to increase adverse events during the acute phase of the disease. During long-term follow-up, patients who received AC had lower all-cause mortality, whereas neurological outcomes were similar.

These findings describe correlations observed in routine clinical practice and must not be interpreted as evidence of a causal or directional effect of AC. Treatment allocation was not randomized and was likely influenced by patient characteristics and clinicians' risk assessment, introducing confounding by indication, selection bias, and residual confounding despite statistical adjustment. Therefore, our data cannot prove that AC per se reduces mortality after IE. Prospective, ideally randomized studies are needed to clarify causal relationships and to define more precisely the role of AC in secondary prevention after IE.

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Data availability To protect patient privacy, the data are not publicly available, but may be made available upon reasonable request.

Declarations

Institutional review board statement The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Regensburg, Germany (approval number 18–925-101; approved March 2018).

Informed consent statement The requirement for written informed consent was waived by the Institutional Review Board based on the Bavarian Hospital Act.

Conflicts of interest All authors declare no competing interests relevant to this study.

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