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ORIGINAL RESEARCH

CEREBROVASCULAR DISEASE AND STROKE

Antithrombotic Therapy in Patients With Infective Endocarditis

A Systematic Review and Meta-Analysis

Tulio Caldonazo, MD,[a,*] Rita Musleh, MD,[b,*] Alexandros Moschovas, MD,[c] Hristo Kirov, MD,[a] Marcus Franz, MD, PhD,[d] Karl Georg Haeusler, MD, PhD,[e] Gloria Faerber, MD, PhD,[a] Torsten Doenst, MD, PhD,[a] Albrecht Günther, MD, PhD,[b,†] Mahmoud Diab, MD, PhD[a,f,†]

ABSTRACT

BACKGROUND Antithrombotic therapy (ATT) in patients with infective endocarditis (IE) is challenging.

OBJECTIVES The authors evaluated the impact of anticoagulant and antiplatelet therapy on clinical endpoints in IE patients.

METHODS We performed a systematic review and meta-analysis comparing IE patients with prior and/or ongoing use of ATT vs those without any ATT during IE course. Primary outcome was reported in-hospital cerebrovascular events. Secondary outcomes were in-hospital mortality, intracranial hemorrhage (ICH), systemic thromboembolism (ST), and mortality within 6 months.

RESULTS Twelve studies, with a total of 12,151 patients, were included. The primary endpoint was not different comparing 10,115 IE patients with or without prior anticoagulation (OR: 1.10; 95% CI: 0.56-2.17; $P = 0.77$) or comparing 838 IE patients with or without prior antiplatelet (OR: 0.90; 95% CI: 0.61-1.33; $P = 0.61$). In-hospital mortality was lower in IE patients with prior anticoagulation compared to those without (OR: 0.74; 95% CI: 0.57-0.96; $P = 0.03$). There was no difference in reported ICH rates between patients with or without prior anticoagulation (OR: 0.54; 95% CI: 0.27-1.09; $P = 0.09$) or between patients with or without prior antiplatelet (OR: 0.35; 95% CI: 0.11-1.10; $P = 0.07$). The rate of ST was lower in IE patients with prior antiplatelet therapy compared to those without (OR: 0.53; 95% CI: 0.38-0.72; $P < 0.01$).

CONCLUSIONS ATT in IE patients was not associated with higher frequency of cerebrovascular events or ICH. Moreover, we found that the use of anticoagulation was associated with decreased in-hospital mortality and the use of antiplatelets was associated with decreased ST. Due to the limitations of this study, these results should be interpreted cautiously showing the necessity of a randomized setup. (JACC Adv 2024;3:100768) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiothoracic Surgery, Friedrich-Schiller-University, Jena, Germany; [b]Department of Neurology, Friedrich-Schiller-University, Jena, Germany; [c]Department of Thoracic and Cardiovascular Surgery, University Hospital Würzburg, Würzburg, Germany; [d]Department of Cardiology, Friedrich-Schiller-University, Jena, Germany; [e]Department of Neurology, University Hospital of Würzburg (UKW), Würzburg, Germany; and the [f]Department of Cardiac Surgery, Herz-und Kreislaufzentrum, Rotenburg an der Fulda, Germany. *Drs Caldonazo and Musleh are co-first authors. †Drs Günther and Diab are co-senior authors.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ATT = antithrombotic therapy

CVE = cerebrovascular events

ICH = intracranial hemorrhage

IE = infective endocarditis

Infective endocarditis (IE) represents a life-threatening disease with in-hospital mortality rates of approximately 40%.[1,2] Stroke occurs in up to 40% of all cases and mostly occurs as a result of embolization from endocardial vegetation.[3,4] Intracranial hemorrhage (ICH) occurs due to secondary hemorrhagic transformation of embolic stroke or a ruptured mycotic aneurysm in the brain.[5]

In this context, the role of antithrombotic therapy (ATT), such as antiplatelet or anticoagulation therapy, in IE remains controversial.[6] On the 1 side, ATT may be protective against thromboembolic events.[7,8] On the other side, ATT might increase the risk of hemorrhagic transformation or intracerebral hemorrhage.[6] In IE patients with pre-existing indications for ATT, the American IE guidelines recommend continuation of anticoagulant therapy (Class IIb; Level of Evidence: B),[6] while the European IE guidelines, 2015, recommend replacement of oral anticoagulant therapy by unfractionated (UFH) or low-molecular-weight heparin (LMWH) for 1 to 2 weeks under close monitoring (Class IIa; Level of Evidence: C).[9]

We intended with this systematic review and meta-analysis to evaluate the impact of antiplatelet and anticoagulant therapy on cerebrovascular events (CVEs) and major outcomes in IE patients.

METHODS

Ethical approval of this analysis was not required as no human or animal subjects were involved. This review was registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO, CRD42022325953).

SEARCH STRATEGY. We performed a comprehensive literature search to identify contemporary studies reporting short- and mid-term outcomes in IE patients undergoing anticoagulation or antiplatelet therapy. Searches were run on February 2023 and included the following 3 databases: Ovid MEDLINE, Ovid EMBASE, and The Cochrane Library (Wiley). The search strategy for Ovid MEDLINE is available in Supplemental Table 1.

STUDY SELECTION AND DATA EXTRACTION. The study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy. After de-duplication, records were screened by 2 independent reviewers (T.C. and R.M.). Any discrepancies and disagreements were resolved by a third author (A.G.). Titles and abstracts were reviewed against predefined inclusion and exclusion criteria. Studies were considered for inclusion if they were written in English and reported direct comparison between IE patients divided by patients with prior to IE diagnosis and/or ongoing use of ATT (anticoagulation or antiplatelet) vs those without any ATT during IE course. Animal studies, abstracts, case reports, commentaries, editorials, expert opinions, conference presentations, and studies not reporting the outcomes of interest were excluded. The full text was pulled for the selected studies for a second round of eligibility screening. References for articles selected were also reviewed for relevant studies not captured by the original search.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale for observational studies (Supplemental Table 2). Two reviewers (T.C. and R.M.) independently performed data extraction. A third author (A.G.) verified accuracy. The extracted variables included study characteristics (publication year, country, sample size, study design, used medicaments, and outcome definitions) as well as the demographic data and IE characteristics of the patient's population (age, sex, valve involvement, vegetation size, presence of *Staphylococcus* infection, and prior CVE). Patients were considered to be on ATT if they received the medication 6 months before admission or at admission.

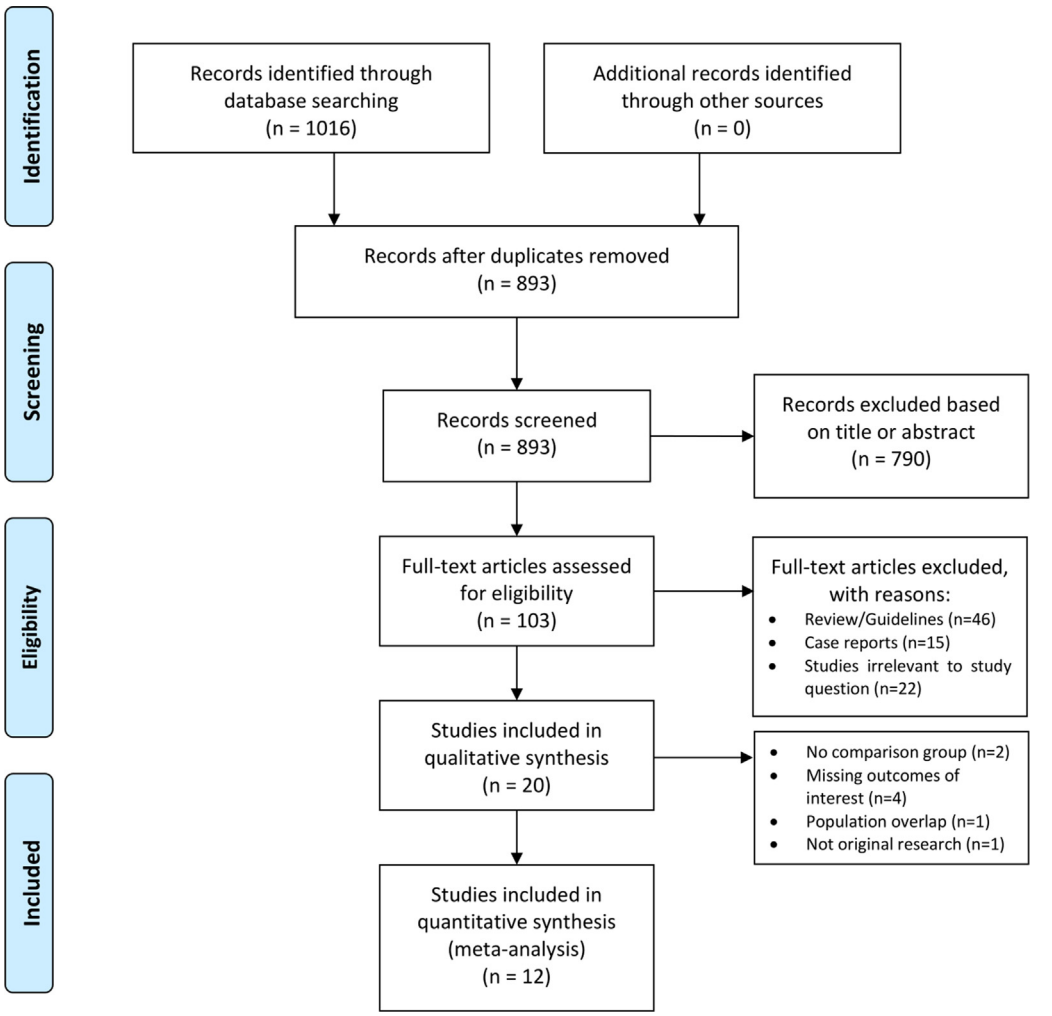
OUTCOME DEFINITIONS. Primary outcome was in-hospital CVEs. CVE included symptomatic ischemic and hemorrhagic strokes, ICH, transient ischemic attacks as well as cerebral infections (meningitis and cerebral abscesses). Secondary outcomes were in-hospital mortality, mid-term mortality (within 6 months), in-hospital ICH, and in-hospital systemic thromboembolism.

Subclinical cerebral events as well as microbleeds were not included in any outcome. CVE definitions for each study are demonstrated in Supplemental Table 3.

STATISTICAL ANALYSIS. Categorical values were analyzed using OR and 95% CIs. An OR >1.00 indicated that the outcome was more frequently present in the anticoagulation/antiplatelet group. Random effects models were used as a primary model. Results were displayed in forest plots. Between-study statistical heterogeneity was assessed with the Cochran Q statistic and by estimating I^2. High heterogeneity was defined as a significance level of $P < 0.10$ and I^2 of at least 50% or more.

Leave-one-out analyses for the primary outcome were performed to assess the robustness of the obtained estimate. All statistical analyses were

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram



performed using R (version 4.1.1, R Project for Statistical Computing) within RStudio and STATA IC17.0 (StataCorp LLC).

RESULTS

STUDY CHARACTERISTICS. A total of 1,016 studies were retrieved from the systematic search, of which 12 met the criteria for inclusion in the final analysis. Figure 1 shows the PRISMA flowchart for study selection. Included studies were observational cohort studies published between 2007 and 2021. Eight studies were retrospective (5 single center and 3 multicenter) and 4 studies were prospective (3 single center and 1 multicenter). Four studies originated from the United States, 2 from Sweden and Denmark, and 1 each from Canada, France, Spain, South Korea, Denmark, and Russia (Table 1 and 2 for details). A total of 12,151 patients were included in the final analysis. The number of patients per study ranged from 34 to 7,621.

PATIENT CHARACTERISTICS. Supplemental Tables 4 and 5 summarize the demographic data and IE characteristics of the patient's population in each study. Overall, 10,152 patients were in the anticoagulation vs no anticoagulation group and 1,999 patients in the antiplatelet vs no antiplatelet group.

Patients on ATT were older than patients without ATT. Patients receiving antiplatelet had a higher rate of previous CVEs. The percentage of male patients, IE of aortic/mitral valve, and presence of IE caused by *Staphylococcus* infection were similar in both populations. The indications for anticoagulation involved

TABLE 1 Summary of Included Studies in the Anticoagulation vs No Anticoagulation Group (References Are Reported in the Supplemental Appendix)

First Author	Year of Publication	Country	N	Study Design	Mean Follow-Up	Population Comparability	Used Medication	Reported Outcomes (No. of Events)
Snygg-Martin	2011	Sweden/ Denmark	587 48 ACG 539 No-ACG	Prospective, multicenter	In-hospital data	Adjusted	Vitamin K antagonist	• CVE (ACG: 3; No-ACG: 141) • Mortality (ACG: 5; No-ACG: 68) • ICH (ACG: 1; No-ACG: 13)
Lung	2013	France	120 34 ACG 86 No-ACG	Prospective, single-center	6 mo	Unadjusted	Not reported	• CVE (ACG: 14; No-ACG: 50) • Systemic thromboembolism (ACG: 14; No-ACG: 50)
García-Cabrera	2013	Spain	1,345 241 ACG 1,104 No-ACG	Retrospective, multicenter	1 y	Adjusted	Vitamin K antagonist, UFH, or LMWH	• CVE (ACG: 66; No-ACG: 186) • Mortality (ACG: 85; No-ACG: 316) • ICH (ACG: 22; No-ACG: 38) • Systemic thromboembolism (ACG: 44; No-ACG: 148)
Lee	2014	South Korea	150 51 ACG 99 No-ACG	Retrospective, single-center	In-hospital data	Adjusted	Vitamin K antagonist, UFH, or LMWH	• CVE (ACG: 15; No-ACG: 30) • Mortality (ACG: 13; No-ACG: 16) • ICH (ACG: 5; No-ACG: 4) • Systemic thromboembolism (ACG: 14; No-ACG: 43)
Davis	2020	United States	258 50 ACG 208 No-ACG	Retrospective, single-center	10 wk	Adjusted	Vitamin K antagonist, NOAC, DOAC, UFH, or LMWH	• CVE (ACG: 16; No-ACG: 73) • ICH (ACG: 3; No-ACG: 23)
Pathickal	2020	United States	34 9 ACG 25 No-ACG	Retrospective, single-center	In-hospital data	Unadjusted	Vitamin K antagonist or NOAC	• CVE (ACG: 0; No-ACG:2) • Mortality (ACG: 1; No-ACG: 1) • ICH (ACG: 0; No-ACG: 1) • Systemic thromboembolism (ACG: 2; No-ACG:4)
Klein	2020	Denmark	7,621 209 ACG 7,412 No-ACG	Retrospective, multicenter	3 mo	Adjusted	Not reported	• CVE (ACG: NR; No-ACG: NR)
Koltsova	2021	Russia	37 11 ACG 26 No-ACG	Prospective, single-center	1.5 mo	Unadjusted	Vitamin K antagonist and NOAC	• Mortality (ACG: 3; No-ACG: 6) • Systemic thromboembolism (ACG: 3; No-ACG:10)

ACG = anticoagulation; CVE = cerebrovascular event; DOAC = direct oral anticoagulants; ICH = intracranial hemorrhage; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K oral anticoagulants; NR = not reported; UFH = unfractionated heparin.

atrial fibrillation, previous thrombosis, and the presence of mechanical valve.

PRIMARY OUTCOME. Figure 2A shows the forest plot for in-hospital CVE among 10,115 patients from 7 studies involving IE patients with or without prior anticoagulation. There was no significant difference in in-hospital CVE between IE patients with prior anticoagulation and those without anticoagulation (OR: 1.10; 95% CI: 0.56-2.17; $P = 0.77$). Figure 2B shows the forest plot for in-hospital CVE among 838 patients from 3 studies involving IE patients with or without prior antiplatelet therapy. There was no significant difference in in-hospital CVE rate between IE patients with prior antiplatelet and those without antiplatelet (OR: 0.90; 95% CI: 0.61-1.33; $P = 0.61$).

Supplemental Figure 1 demonstrates the leave-one-out analysis, which confirms the robustness of the main analysis. Supplemental Figure 2 provides the funnel plot, which shows no evident asymmetric configuration reflecting the lack of publication bias.

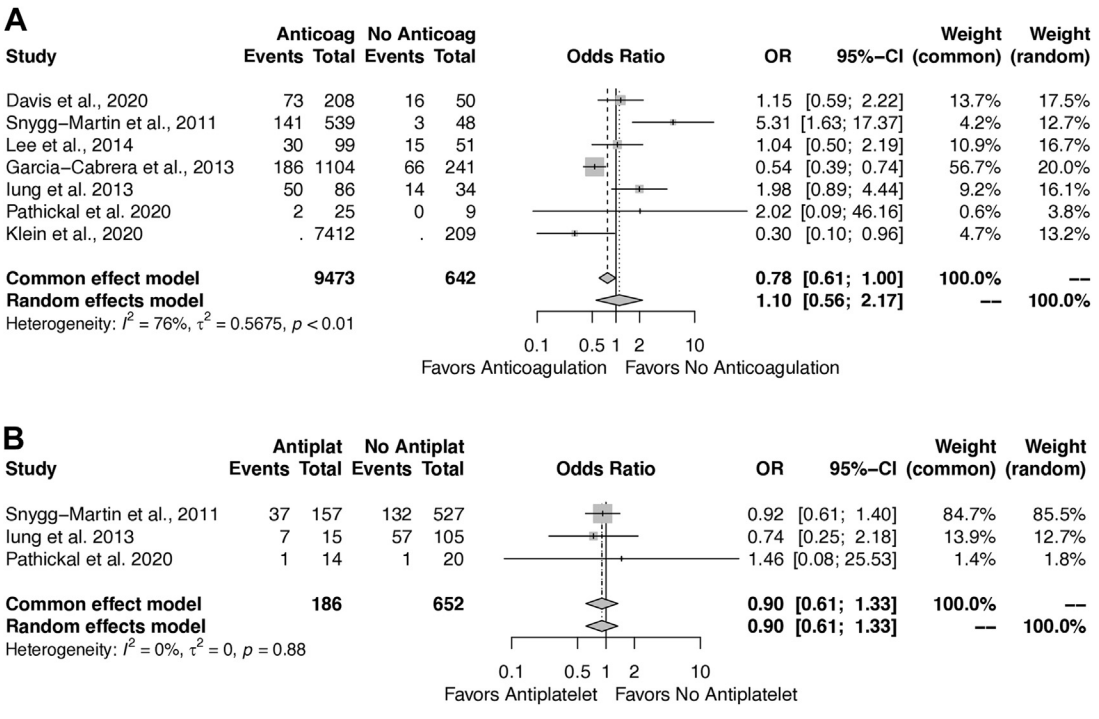
SECONDARY OUTCOMES. Figure 3A presents the forest plot for in-hospital mortality from 5 studies involving 2,328 IE patients with or without anticoagulation. The use of anticoagulation was associated with lower rates of in-hospital mortality (OR: 0.74; 95% CI: 0.57-0.96; $P = 0.03$). Figure 3B shows the forest plot for in-hospital mortality from 3 studies involving 755 IE patients with or without prior antiplatelet. There was no significant difference in in-hospital mortality between IE patients with

TABLE 2 Summary of Included Studies in the Antiplatelet vs No Antiplatelet Group (References Are Reported in the Supplemental Appendix)

First Author	Year of Publication	Country	N	Study Design	Mean Follow-Up	Population Comparability	Used Medication	Reported Outcomes (No. of Events)
Anavekar	2007	United States	600 125 ATP 475 No-ATP	Retrospective, single-center	6 mo	Adjusted	Aspirin, dipyridamole, clopidogrel, ticlopidine, or combination	• Mortality (ATP: 29; No-ATP: 113) • Systemic thromboembolism (ATP: 15; No-ATP: 132)
Pepin	2009	Canada	241 75 ATP 166 No-ATP	Retrospective, single-center	3 mo	Adjusted	Aspirin, clopidogrel or combination	• Mortality (ATP: 21; No-ATP: 50) • ICH (ATP: 2; No-ATP: 10) • Systemic thromboembolism (ATP: 14; No-ATP: 46)
Anavekar	2011	United States	283 116 ATP 167 No-ATP	Retrospective, single-center	6 mo	Adjusted	Aspirin, dipyridamole, clopidogrel, ticlopidine, or combination	• Mortality (ATP: NR; No-ATP: NR) • Systemic thromboembolism (ATP: 28; No-ATP: 66)
Snygg-Martin	2011	Sweden/ Denmark	684 157 ATP 527 No-ATP	Prospective, multicenter	1 y	Adjusted	Aspirin, aspirin and dipyridamole or clopidogrel	• CVE (ATP: 37; No-ATP: 132) • ICH (ATP: 1; No-ATP: 15) • Mortality (ATP: 28; No-ATP: 67)
Lung	2013	France	120 15 ATP 105 No-ATP	Prospective, single-center	6 mo	Unadjusted	Not reported	• CVE (ATP: 7; No-ATP: 58) • Systemic thromboembolism (ATP: 7; No-ATP: 57)
Pathickal	2020	United States	34 14 ATP 20 No ATP	Retrospective, single-center	30 d	Unadjusted	Aspirin, clopidogrel or combination	• CVE (ATP: 1; No-ATP:0) • Mortality (ATP: 1; No-ATP: 1) • ICH (ATP: 0; No-ATP: 1) • Systemic thromboembolism (ATP: 4; No-ATP: 2)
Koltsova	2021	Russia	37 8 ATP 29 No-ATP	Prospective, single-center	1.5 mo	Unadjusted	Aspirin or clopidogrel	• Mortality (ATP: 4; No-ATP: 5) • Systemic thromboembolism (ATP: 3; No-ATP: 10)

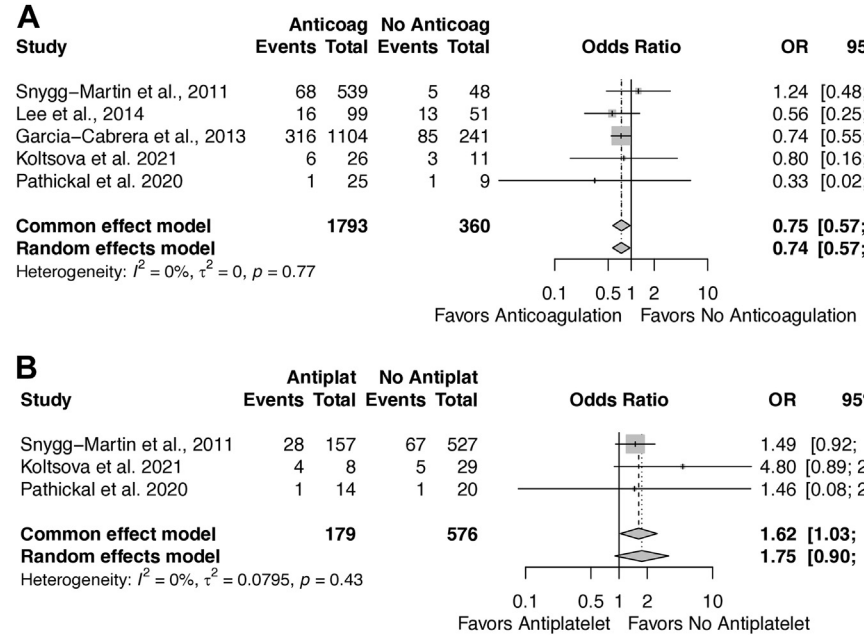
ATP = antiplatelet; CVE = cerebrovascular event; ICH = intracranial hemorrhage; NR = not reported.

FIGURE 2 Meta-Analysis: Primary Outcome: In-Hospital Cerebrovascular Event



Forest plot for in-hospital cerebrovascular events from studies involving anticoagulation (A) and antiplatelet (B) therapy.

FIGURE 3 Meta-Analysis: Secondary Outcome-In-Hospital Mortality



Forest plot for in-hospital mortality from studies involving anticoagulation (A) and antiplatelet (B) therapy.

antiplatelet and those without antiplatelet (OR: 1.75; 95% CI: 0.90-3.39; $P = 0.10$).

Supplemental Figure 3 shows the forest plot for mid-term mortality from 4 studies involving 1,808 IE patients with or without prior antiplatelet. There was no significant difference in mid-term mortality between IE patients with antiplatelet and those without antiplatelet (OR: 1.10; 95% CI: 0.85-1.43; $P = 0.47$). Data were too sparse for an anticoagulation plot.

Figure 4A presents the forest plot for in-hospital ICH from 6 studies involving 2,615 IE patients with or without prior anticoagulation. There was no significant difference in in-hospital ICH between IE patients with anticoagulation and those without anticoagulation (OR: 0.54; 95% CI: 0.27-1.09; $P = 0.09$). **Figure 4B** shows the forest plot for ICH from 3 studies involving 959 IE patients with or without prior antiplatelet. There was no significant difference in in-hospital ICH between IE patients on antiplatelet vs IE patients without antiplatelet (OR: 0.35; 95% CI: 0.11-1.10; $P = 0.07$).

Supplemental Figure 4A shows the forest plot for systemic in-hospital thromboembolism from 5 studies involving 1,686 IE patients with or without prior anticoagulation. There was no significant difference in in-hospital systemic thromboembolism between IE patients on anticoagulation and those without anticoagulation (OR: 1.26; 95% CI: 0.69-2.28; $P = 0.45$). Supplemental Figure 4B shows the forest plot for in-hospital systemic thromboembolism from 6 studies involving 1,315 IE patients with or without prior antiplatelet. The use of antiplatelet was associated with lower rates of in-hospital systemic thromboembolism (OR: 0.53; 95% CI: 0.38-0.72; $P < 0.01$).

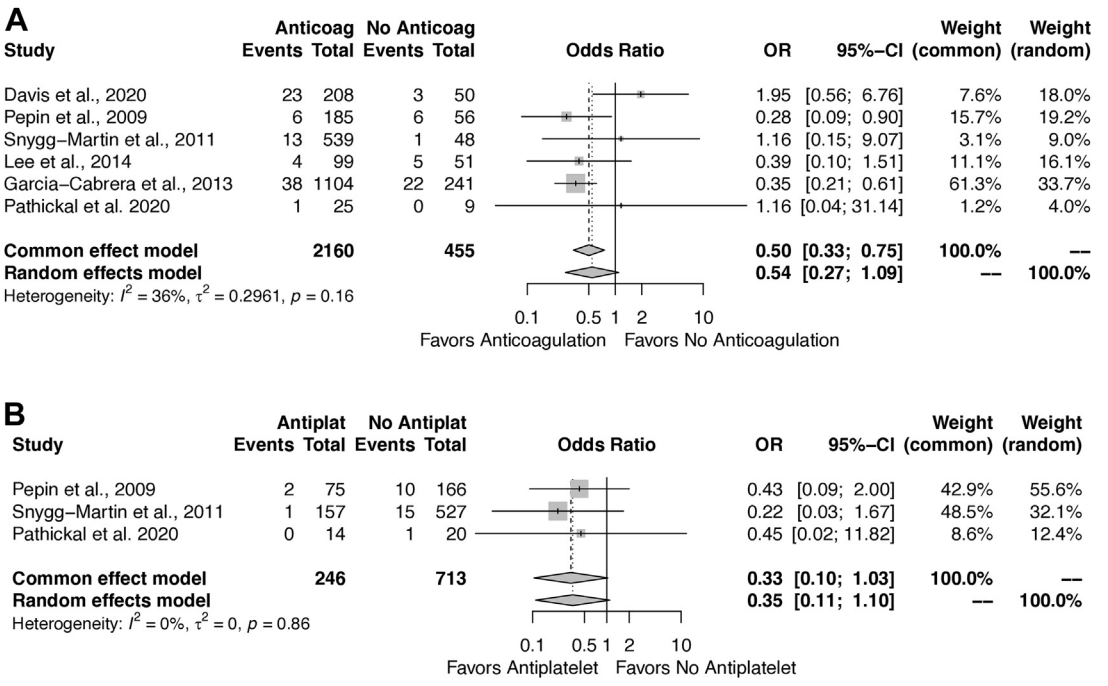
Table 3 and **Central Illustration** outlines the detailed results of the meta-analysis.

DISCUSSION

The results of this meta-analysis suggest that the use of anticoagulants or antiplatelets in IE patients was not associated with higher frequency of CVE or ICH in particular. We found that the use of anticoagulation was associated with decreased in-hospital mortality and the use of antiplatelets was associated with decreased systemic thromboembolism.

ANTIPLATELETS IN PATIENTS WITH IE. The finding that antiplatelet therapy was associated with decreased systemic thromboembolism but not associated with decreased incidence of CVEs may appear controversial. However, as shown in the forest plot for CVEs from studies involving antiplatelet therapy (**Figure 2B**), only 3 of the 6 studies examining the effect of antiplatelet therapy used CVEs as an outcome

FIGURE 4 Meta-Analysis: Secondary Outcome-In-Hospital Intracranial Hemorrhage



Forest plot for in-hospital intracranial hemorrhage from studies involving anticoagulation (A) and antiplatelet (B) Therapy.

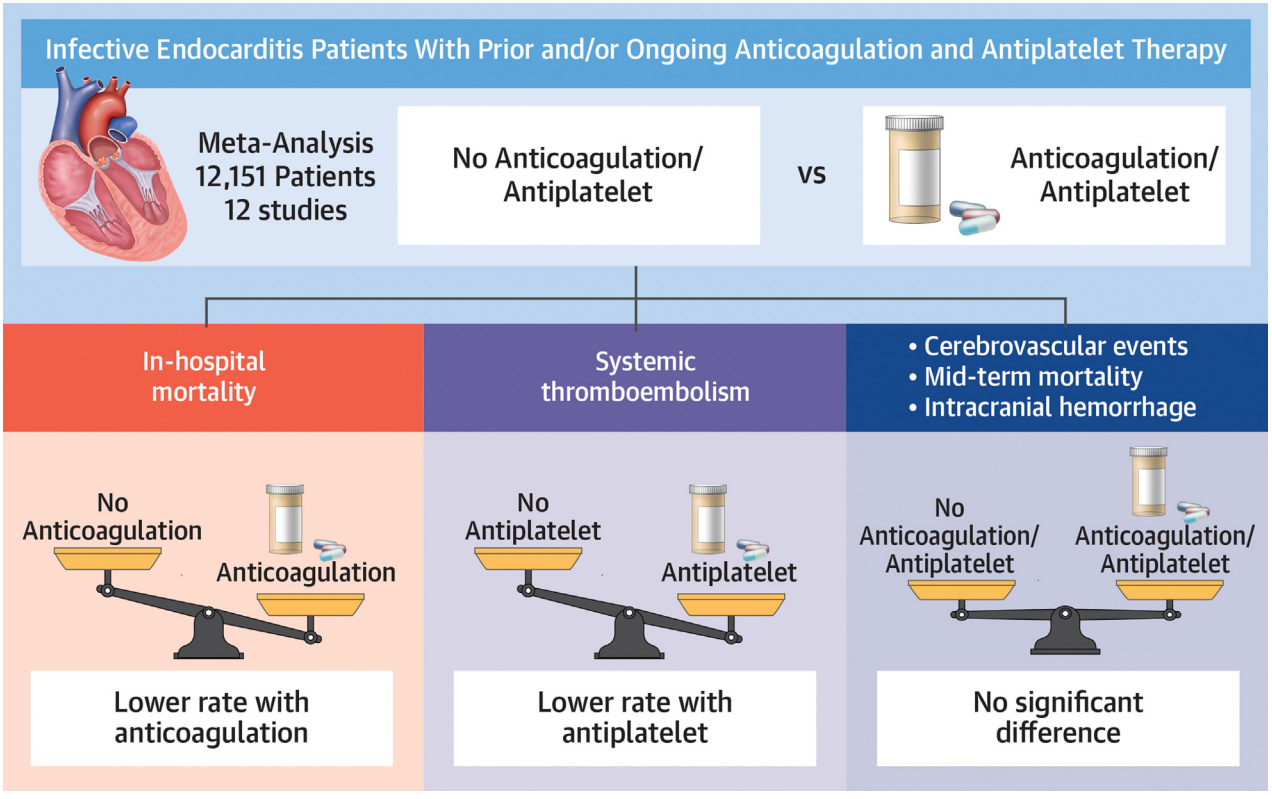
point. In the contrary, all the 6 studies used systemic thromboembolism (which may include cerebral embolism) as an outcome point (Supplemental Figure 4B). In addition, the definitions of CVEs as well as systemic thromboembolism are heterogeneous among different studies. While in the study from Snygg-Martin et al,[10] only symptomatic CVEs (clinical plus radiological) were included, Lung et al[11] included all cerebral lesions (symptomatic or asymptomatic) detected in the systematically performed magnetic resonance imaging. The same applies for systemic thromboembolism; while in the study from Anavekar et al,[12] stroke was the predominant systemic thromboembolism (48%), Pepin et al[13] did not include cerebral embolism in the definition of major embolism. Therefore, based on the finding that antiplatelet therapy was associated with decreased systemic thromboembolism, it is reasonable to assume the same effect on cerebral embolism. However, the most feared deleterious effect of antiplatelet therapy in patients with IE is the development of ICH. All studies included in this meta-analysis

TABLE 3 Outcomes Summary

Outcome	Patient Group Comparison	Number of Studies	N	Effect Estimate OR (95% CI)
Cerebrovascular events (in-hospital)	ACG vs No-ACG	7	10,115	1.10 (0.56-2.17) (P = 0.77)
	ATP vs No-ATP	3	838	0.90 (0.61-1.33) (P = 0.61)
Mortality (in-hospital)	ACG vs No-ACG	5	2,328	0.74 (0.57-0.96) (P = 0.03)
	ATP vs No-ATP	3	755	1.75 (0.90-3.39) (P = 0.10)
Mid-term mortality (within 6 months)	ATP vs No-ATP	4	1,808	1.10 (0.85-1.43) (P = 0.47)
Intracranial hemorrhage (in-hospital)	ACG vs No-ACG	6	2,615	0.54 (0.27-1.09) (P = 0.09)
	ATP vs No-ATP	3	959	0.35 (0.11-1.10) (P = 0.07)
Systemic thromboembolism (in-hospital)	ACG vs No-ACG	5	1,686	1.26 (0.69-2.28) (P = 0.45)
	ATP vs No-ATP	6	1,315	0.53 (0.38-0.72) (P < 0.01)

ACG = anticoagulation; ATP = antiplatelet; NR = not reported.

CENTRAL ILLUSTRATION **Antithrombotic Therapy in Patients With Infective Endocarditis From 12 Studies With in Total 12,151 Patients**



Caldonazo T, et al. JACC Adv. 2024;3(2):100768.

demonstrated that a pre-existing antiplatelet therapy on admission was not associated with increased ICH during hospitalization.[11-17]

Aspirin was the predominant antiplatelet therapy in all these studies (ranging from 86% of patients in 1 study[15] to 98% of patients in another study).[13] The daily dose of aspirin varied between ≤75 mg[15] and 325 mg.[13] Interestingly, the mortality lowering effect of aspirin shown in the study from Pepin et al[13] was the same in patients who received 325 mg daily as well as those who received only 80 mg daily. In the prospective study from Lung et al,[11] systematic magnetic resonance imaging was used to detect cerebral lesions in 120 patients with IE.

Thus, this current meta-analysis demonstrated a potential beneficial effect of pre-existing antiplatelet therapy, mainly aspirin, in reducing systemic embolism, without increasing the risk of ICH in patients with IE. However, the issue regarding the continuation or stopping of antiplatelet therapy in those patients remains uncertain. Pepin et al[13] was the only study that provided information about whether the antiplatelet therapy was continued after admission. In this study, the majority of patients (65 of 75) with prior antiplatelet therapy continued the therapy after the diagnosis of IE. Antiplatelet therapy was associated with lower mortality without increased hemorrhagic strokes.[13] These findings are in accordance with the current American Heart Association Endocarditis Guideline, which recommend continuation of long-term antiplatelet therapy at the time of development of IE, in the absence of bleeding complications (Class IIb; Level of Evidence: B).[6]

Even newly initiated antiplatelet therapy (in patients without pre-existing therapy), after the diagnosis of IE, might be beneficial. In the same study from Pepin et al,[13] 23 (10%) patients started antiplatelet therapy (mainly with aspirin) after the diagnosis of IE. Among those patients, there was a trend toward lower 90-day mortality compared to those

without antiplatelet therapy at all.[13] However, due to the small number of patients in their study, it is not possible to draw a solid conclusion regarding the beneficial effect of initiating aspirin after the diagnosis of IE.

Moreover, antiplatelet therapy has been postulated to affect platelet-bacterial interactions and consequently diminish vegetation growth. This effect has been demonstrated in several experimental studies.[18-22] In a study from Kupferwasser et al,[18] rabbits with *Staphylococcus aureus* IE were given either aspirin or no aspirin (control). The authors found that aspirin was associated with significant decreases in vegetation weight, echocardiographic vegetation growth, vegetation and renal bacterial densities, and renal embolic lesions vs controls.[18] Several other experimental studies supported the efficacy of aspirin in reducing bacterial virulence and vegetation's growth by affecting global regulatory pathways in *Staphylococcus aureus* IE.[19,23,24]

Despite these promising protective effects of aspirin in the setting of IE in experimental and animal settings, its initiation as adjuvant therapy in IE is not recommended by the current American Heart Association guidelines (Class III; Level of Evidence: B).[9] This recommendation is based on the only randomized clinical trial that examined the effect of aspirin (325 mg/day) vs placebo for 4 weeks in 115 IE patients.[25] The authors found that there was no reduction of embolic events (OR: 1.62; 95% CI: 0.68-3.86; $P = 0.29$), but a trend toward a higher incidence of bleeding (OR: 1.92; 95% CI: 0.76-4.86; $P = 0.075$) in patients allocated to the aspirin group. One major limitation of this randomized study is that it included only 31% of its target sample size and therefore the results possibly reflect a type II error (ie, having insufficient statistical power to observe the hypothesized 8.58% aspirin benefit of reducing embolic events).[25]

Furthermore, another analysis[26] also based on the same clinical trial of patients who were excluded from the Multi-Centre Aspirin Trial in Infective Endocarditis because of long-term aspirin use ($n = 84$) compared these patients with the data for patients who were randomized to the placebo arm ($n = 55$). The study found that long-term daily use of aspirin does not reduce the risk of embolic events in patients with endocarditis but may be associated with a higher risk of bleeding ($P = 0.065$).

Additionally, Eisen et al[27] performed a meta-analysis of 9 studies to assess potential benefits of the use of aspirin in IE at the time of diagnosis. Most included studies were observational; 2 studies were randomized controlled trials of aspirin commenced after the diagnosis of IE. The major findings were reduced risk of major systemic emboli in patients either pretreated with aspirin or begun on it at the time of IE diagnosis, as well as a possible trend to increased risk of death and decreased risk of bleeding in aspirin-treated patients. Differences to our findings might be explained by several factors including different inclusion timing of the studies (ours was from 2002 to 2023) and to the different inclusion criteria (we only included patients who are on aspirin therapy for other medical indications and not for the sole indication of IE). Moreover, our meta-analysis included different types of antiplatelet medications; whereas the meta-analysis of Eisen et al[27] was mainly based on examining aspirin. In total, we examined only 4 studies similarly to Eisen et al[27] the other 5 studies did not fulfill our inclusion criteria.

In summary, the positive effect of pre-existing antiplatelet therapy, mainly aspirin, on reduction of major embolism in IE patients demonstrated in this meta-analysis, supported by the promising effects demonstrated in experimental and animal studies regarding the efficacy of aspirin in IE justify the need for further clinical randomized studies.

ANTICOAGULANTS IN PATIENTS WITH IE. The results of the current meta-analysis suggest that prior anticoagulation in patients with IE was associated with lower in-hospital mortality without increased risk of ICH during hospitalization. However, it is still unclear whether to continue or stop anticoagulation in patients with IE who have an indication for anticoagulation (eg, mechanical heart valves). Three of the studies included in this meta-analysis examined this clinically relevant question. In the study from Davis et al, pre-existing anticoagulation (warfarin 54% and heparin 42%) was continued in 27/50 (54%) patients.

There was no significant difference in the rate of stroke, ICH, or mortality at 10 weeks between patients with pre-existing anticoagulation and those without. In addition, none of the patients who continued anticoagulation following admission experienced stroke.[28] In another study, Lee et al[2] examined the effect of anticoagulant therapy on CVEs on admission as well as during hospital stay. Among the 150 patients with IE, 51 were on pre-existing warfarin therapy at admission, while 99 patients did not receive warfarin. On admission, there was no significant difference in the incidence of CVE and mortality between those with or without pre-existing warfarin

therapy. Among the 51 patients with pre-existing warfarin therapy, 38 continued anticoagulation (30 with warfarin and 8 with UFH).

In addition, warfarin was initiated in another 14 patients who were not on pre-existing anticoagulation therapy. The mean international normalized ratio (INR) in patients with warfarin was >2.4 at admission as well as during the first 2 weeks of hospitalization, which reflects a good therapeutic anticoagulation effect. The rates of CVE (13.5% vs 8.2%, $P = 0.303$) and ICH (7.7 vs 2.0, $P = 0.183$) did not significantly differ between patients who continued or newly started anticoagulation after admission (n = 52) and those who stopped or did not have anticoagulation (n = 98).[2]

Snygg-Martin et al demonstrated that among 587 patients with native valve IE, 48 (8%) were on warfarin at admission. Cerebrovascular complications occurred significantly less in patients on pre-existing warfarin therapy compared to those without warfarin (6% vs 26%, $P = 0.006$). The frequency of hemorrhagic complications was 2% in both groups. Warfarin was discontinued within the first few days in 19 (40%) of patients and replaced with LMWH in another 7 patients. Irrespective of what decision was taken reading stopping or continuing warfarin therapy, no CVC occurred in the warfarin group.[8]

Weighting the low risk of continuing anticoagulation therapy in IE patients, as shown in the above quoted studies,[2,8,28] against the well-known risk of major embolism and valve thrombosis, as shown in older studies on non-IE patients with mechanical heart valves who did not receive anticoagulation,[29,30] it may be apparent that continuing the anticoagulation therapy in IE patients with mechanical heart valves in the absence of ICH is more favorable.

Standardized evidence-based protocols for use of antiplatelet and anticoagulant therapies in patients with IE are lacking. The finding that a prior antiplatelet or anticoagulant therapy was associated with lower systemic embolism or in-hospital mortality without increased risk of ICH may set the stage for further randomized studies investigating this important topic.

STUDY STRENGTH AND LIMITATIONS. This is the first meta-analysis, including more than 10,000 patients, to address this clinical relevant issue. The analysis implies the intrinsic limitations of observational retrospective series, including the risk of methodological heterogeneity of the included studies (type of ATT used, demographic data, reported outcome, and follow-up time). In addition, the lack of information on the indications for stopping or continuing the ATT in most of the included studies has to be considered a major limitation of this meta-analysis. Information on individual patient data is also missing in our study resulting in limited information on correct time points of events.

CONCLUSIONS

The results of this meta-analysis suggest that the use of anticoagulants or antiplatelets in IE patients did not affect the incidence of CVE in general or ICH particularly. Moreover, we found that the use of anticoagulation was associated with decreased in-hospital mortality and the use of antiplatelets was associated with decreased systemic thromboembolism. Due to the limitations of this study, a randomized setup investigating this relevant clinical issue is necessary.

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ADDRESS FOR CORRESPONDENCE: Dr Tulio Caldonazo, Department of Cardiothoracic Surgery, University of Jena, Am Klinikum 1, 07747 Jena, Germany. E-mail: tulio.caldonazo@med.uni-jena.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ATT in patients with IE is challenging. On the one side, ATT may be protective against thromboembolic events. On the other side, ATT might increase the risk of hemorrhagic transformation or intracerebral hemorrhage. In IE patients with pre-existing indications for ATT, the American guidelines recommend continuation of anticoagulant therapy, while the European guidelines recommend replacement of oral anticoagulant therapy by UFH or LMWH for 1 to 2 weeks under close monitoring.

TRANSLATIONAL OUTLOOK: Based on a study-level analysis, the use of anticoagulants or antiplatelets in IE patients was not associated with higher frequency of CVE or ICH in particular. To avoid potential confounders, this clinical issue needs to be investigated in a randomized setup.

REFERENCES

1. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169:463–473.

2. Lee SJ, Oh SS, Lim DS, Hong SK, Choi RK, Park JS. Usefulness of anticoagulant therapy in the prevention of embolic complications in patients with acute infective endocarditis. *BioMed Res Int*. 2014;2014:254187.

3. Cahill TJ, Baddour LM, Habib G, et al. Challenges in infective endocarditis. *J Am Coll Cardiol*. 2017;69:325–344.

4. Bonaros N, Czerny M, Pfausler B, et al. Infective endocarditis and neurologic events: indications and timing for surgical interventions. *Eur Heart J Suppl*. 2020;22:M19–M25.

5. Vanassche T, Peetermans WE, Herregods MC, Herijgers P, Verhamme P. Anti-thrombotic therapy in infective endocarditis. *Expert Rev Cardiovasc Ther*. 2011;9:1203–1219.

6. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.

7. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation*. 2013;127:2272–2284.

8. Snygg-Martin U, Rasmussen RV, Hassager C, Bruun NE, Andersson R, Olaison L. Warfarin therapy and incidence of cerebrovascular complications in left-sided native valve endocarditis. *Eur J Clin Microbiol Infect Dis*. 2011;30:151–157.

9. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128.

10. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. *Clin Infect Dis*. 2008;47:23–30.

11. Iung B, Tubiana S, Klein I, et al. Determinants of cerebral lesions in endocarditis on systematic cerebral magnetic resonance imaging: a prospective study. *Stroke*. 2013;44:3056–3062.

12. Anavekar NS, Schultz JC, De Sa DD, et al. Modifiers of symptomatic embolic risk in infective endocarditis. *Mayo Clin Proc*. 2011;86:1068–1074.

13. Pepin J, Tremblay V, Bechard D, et al. Chronic antiplatelet therapy and mortality among patients with infective endocarditis. *Clin Microbiol Infect*. 2009;15:193–199.

14. Anavekar NS, Tleyjeh IM, Anavekar NS, et al. Impact of prior antiplatelet therapy on risk of embolism in infective endocarditis. *Clin Infect Dis*. 2007;44:1180–1186.

15. Snygg-Martin U, Rasmussen RV, Hassager C, Bruun NE, Andersson R, Olaison L. The relationship between cerebrovascular complications and previously established use of antiplatelet therapy in left-sided infective endocarditis. *Scand J Infect Dis*. 2011;43:899–904.

16. Pathickal SM, Park TE, Sharma R. Clinical outcomes associated with the use of anticoagulant and antiplatelet agents in patients undergoing treatment for infective endocarditis: a pilot study. *Clin Ther*. 2020;42:1828–1838.

17. Koltsova EM, Sorokina MA, Pisaryuk AS, et al. Hypercoagulation detected by routine and global laboratory hemostasis assays in patients with infective endocarditis. *PLoS One*. 2021;16:e0261429.

18. Kupferwasser LI, Yeaman MR, Shapiro SM, et al. Acetylsalicylic acid reduces vegetation bacterial density, hematogenous bacterial dissemination, and frequency of embolic events in experimental Staphylococcus aureus endocarditis through antiplatelet and antibacterial effects. *Circulation*. 1999;99:2791–2797.

19. Nicolau DP, Freeman CD, Nightingale CH, et al. Reduction of bacterial titers by low-dose aspirin in experimental aortic valve endocarditis. *Infect Immun*. 1993;61:1593–1595.

20. Hannachi N, Habib G, Camoin-Jau L. Aspirin effect on Staphylococcus aureus-platelet interactions during infectious endocarditis. *Front Med*. 2019;6:217.

21. Hannachi N, Ogé-Ganaye E, Baudoin JP, et al. Antiplatelet agents have a distinct efficacy on platelet aggregation induced by infectious bacteria. *Front Pharmacol*. 2020;11:863.

22. Lerche CJ, Christophersen LJ, Goetze JP, et al. Adjunctive dabigatran therapy improves outcome of experimental left-sided Staphylococcus aureus endocarditis. *PLoS One*. 2019;14:e0215333.

23. Kupferwasser LI, Yeaman MR, Nast CC, et al. Salicylic acid attenuates virulence in endovascular infections by targeting global regulatory pathways in Staphylococcus aureus. *J Clin Invest*. 2003;112:222–233.

24. Nicolau DP, Marangos MN, Nightingale CH, Quintiliani R. Influence of aspirin on development and treatment of experimental Staphylococcus aureus endocarditis. *Antimicrob Agents Chemother*. 1995;39:1748–1751.

25. Chan KL, Dumesnil JG, Cujec B, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. *J Am Coll Cardiol*. 2003;42:775–780.

26. Chan KL, Tam J, Dumesnil JG, et al. Effect of long-term aspirin use on embolic events in infective endocarditis. *Clin Infect Dis*. 2008;46:37–41.

27. Eisen DP, McBryde ES. An association between aspirin use in human cases of infective endocarditis and reduced systemic embolism is shown in meta-analysis of observational studies. *J Infect Dis*. 2015;212 4:673-674.

28. Davis KA, Huang G, Petty SA, Tan WA, Malaver D, Peacock JE Jr. The effect of preexisting anticoagulation on cerebrovascular events in left-sided infective endocarditis. *Am J Med*. 2020;133:360-369.

29. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89:635-641.

30. Stein PD, Alpert JS, Copeland J, Dalen JE, Goldman S, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest*. 1995;108:371s-379s.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.